Upper Airway Dysfunction in Obstructive Sleep Apnea and its Relationship to Laryngopharyngeal Reflux and Postoperative Morbidities in Cancer of the Oral Cavity and Cancer of the Oropharynx

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ABSTRACT:

Obstructive sleep apnea (OSA) is a disease process characterized by collapse of the upper airway during periods of sleep leading to the cessation airflow despite persistent respiratory efforts. The aim of this research project is to investigate for associations and correlations between OSA and other clinical entities using two separate prospective studies. The initial objective was to evaluate the prevalence of laryngopharyngeal reflux (LPR) in patients with OSA. LPR was present in 26/28 (93%) of OSA patients. Moreover, there were significant correlations between LPR and OSA severity (eg. $r = 0.57$, $p = 0.001$). The second objective of this research study was to determine the prevalence of OSA in patients with cancer of the oral cavity and oropharynx, and to correlate the presence of OSA and the occurrence of postoperative morbidities. OSA was present in 76% of patients. Overall, postoperative complications were observed in 67% of OSA and 25% of non-OSA patients, although this difference was not yet significant ($p = 0.27$, Fisher exact test).

SUMMAIRE:

L'apnée obstructive du sommeil (AOS) est un syndrome caractérisé par un affaissement des voies aériennes supérieures pendant certaines périodes du sommeil, causant la cessation du flux respiratoire en dépit d'efforts persistants pour respirer. Le but du présent projet de recherche est d'établir les associations et corrélations existant entre l'AOS et d'autres entités cliniques à l'aide de deux études prospectives distinctes. L'objectif initial est d'évaluer chez les patients atteints d'AOS : la prévalence du reflux gastro-laryngé (RGL). Un RGL était présent chez 26/28 des patients atteints d'AOS. Des corrélations significatives ont été établies entre les sévérités du RGL et de l'AOS (ex. : r=0,57, p=0,001). Le deuxième objectif de la présente étude est de déterminer la prévalence d'AOS chez les patients avec un cancer de la cavité buccale et de l'oropharynx, et d'établir des corrélations entre la présence d'AOS et l'occurrence de morbidités post-opératoires. L'AOS était présente chez 76% des patients. Les complications post-opératoires ont été observées chez 67% des patients avec l'AOS et 25% des patients sans AOS. L'analyse statistique a démontré que les résultats n'étaient pas significatifs (p = 0.27, Fisher exact test).

ABBREVIATIONS

AHI	Apnea-Hypopnea Index
AR	Arytenoid
CVA	Cerebrovascular Accident
EST	Endoscopic Sensory Testing
GERD	Gastroesophageal Reflux Disease
HTN	Hypertension
ICU	Intensive Care Unit
LAR	Laryngeal Adductor Reflex
LPR	Laryngopharyngeal Reflux
NS	Not Significant
OP	Oropharynx
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
REM	Rapid eye movement stage of sleep
RFS	Reflux Finding Score
SaO_2	Oxygen saturation
SE	Standard Error
TNF-α	Tumour Necrosis Factor Alpha
TNM	Tumour, Node, Metastasis
TST	Total sleep time
UES	Upper Esophageal Sphincter
VP	Velopharynx

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CHAPTER I: INTRODUCTION

1.1 Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a disease process characterized by collapse of the upper airway during sleep leading to the cessation airflow despite persistent respiratory efforts. These episodes of obstruction occur repeatedly throughout sleep. The resulting progressive asphyxia develops and causes an arousal.[1,2] The occlusion is corrected almost instantaneously and the subjects returns to a state of sleep.

OSA has been reported to affect 4% to 9% of males and 1% to 4% of females in the general population.[3-7] This disorder is now considered to represent a major public health problem.[5,8,9] In the past 3 decades, considerable strides have been made in understanding the pathophysiology and adverse effects of OSA.[4,5] There have also been significant improvements in detecting OSA through innovations in polysomnographic techniques as well as advances in medical and surgical treatment options. There are multiple morbidities which result from the sleep fragmentation and hypoxic state associated with OSA.[1,2]

1.2 Pathophysiology

Despite the prevalence of OSA, many aspects of the pathophysiology remain poorly understood. Research has been centered around both systemic and local factors that may predispose individuals to developing sleep apnea. Recent advances have focused on both anatomic factors and alterations in the integrated neuromuscular function of upper airway structures which contribute to airway collapse during sleep.[10,11] Anatomical factors associated with OSA include obesity, abundance of soft tissues in the upper airway, craniofacial anomalies, hypopharyngeal and laryngeal edema and sensory denervation secondary to LPR, and airway obstruction secondary to the mass effect of neoplasms.[6,10-18] At the cellular level, an increase in the inflammatory cytokine tumour necrosis factor alpha (TNF-α) has been uncovered in the serum of patients with OSA.[19] Whether the local upper airway tissues are responsible for secreting the TNF-α has not yet been determined. Nonetheless, it has been postulated that an accumulation of this inflammatory cytokine in tissues of the upper airway may partly explain the muscle dysfunction associated with OSA.

1.3 Cellular Markers of OSA

1.3.1 TNF-α

TNF-α is an inflammatory cytokine. Increases in circulating TNF-α has been reported to correlate with measures of disease severity in OSA patients.[19,20] In addition to promoting edema formation, inflammatory mediator release can also have direct effects on muscle function. TNF-α release from macrophages has been implicated as an etiologic factor in mediating nerve damage in inflammatory neuropathy.[21,22]

Studies have reported that TNF-α has a direct effect on reducing upper airway muscle force-generating capacity.[23,24] An example stems from research involving isolated skeletal muscles with impairment of excitation-contraction coupling secondary to the presence of TNF-α.[25] Superoxide and nitric oxide have both been implicated in skeletal muscle dysfunction.[26-29] Studies have shown that TNF-α may indirectly contribute to the muscle dysfunction by stimulating the generation of both superoxide and nitric oxide. Nitric oxide synthase is primarily implicated in the augmented nitric oxide production associated with TNF-α.[30]

1.4 OSA and Laryngopharyngeal Reflux

Laryngopharyngeal reflux occurs when gastric secretions pass through the upper esophageal sphincter and into the larynx and hypopharynx. The larynx and hypopharynx are vulnerable to the refluxate, since they do not have the same innate protective barriers as the esophagus. Thus minimal exposure can lead to laryngopharyngeal reflux disease and its associated morbidities.

Laryngopharyngeal reflux (LPR) is common in the North American adult population, being estimated to affect up to 35% of the population over 40 years of age.[31] This condition has recently been recognized to be distinct from gastro-esophageal reflux disease (GERD), based on both characteristic differences in double probe (simultaneous pharyngeal and esophageal) pH recordings, and clinical features.[31,32] Symptoms commonly associated with LPR include dysphonia, throat clearing, vocal fatigue and

cough.[33] LPR has also been linked to more substantial morbidities including laryngospasm, arytenoid fixation, laryngeal stenosis, and glottic carcinoma [13,34-36]

These clinical manifestations of LPR are attributable to inflammation of the laryngopharyngeal mucosa which result from repeated exposure to acid and pepsin.[13,31-36] While double-probe pH monitoring is considered to be the gold-standard for the identification of LPR, it has been shown that the diagnosis can reliably be established using an endoscopic scoring algorithm, the reflux finding score (RFS), which quantifies the extent and severity of hypopharyngeal and laryngeal mucosal inflammatory changes which are characteristic of this disorder.[37]

Progress has also been made at identifying risk factors for LPR, which include age over 60 years, obesity, cigarette smoking and heavy alcohol consumption.[5,12,15,38-40] It is of note that these risk factors clearly also predispose patients to OSA. Given this, together with the anatomic effects of LPR on upper airway calibre due to irritation, edema and inflammation of the soft tissues as well as alterations in sensory nerve function, an increase in the prevalence of sleep apnea among patients with laryngopharyngeal reflux disease would be anticipated.

Recent work has identified a mucosal sensory impairment in the oropharynx, velopharynx and larynx of OSA patients using endoscopic sensory testing (EST).[14,15] Correlations between the severity of the laryngeal sensory impairment and apnea severity strongly suggest that this sensory impairment plays a role in the pathophysiology of OSA.

Further studies support the concept that upper airway inflammation contributes to this altered sensory function.[16,17]

Aviv and co-workers previously reported that laryngeal sensation is impaired in patients with LPR, and that treatment of LPR results in improved sensory function.[18] While previous studies have shown that GERD is prevalent among patients with OSA, there has been no previous evaluation of LPR in this patient population.[41]

1.5 OSA and Cancer of the Oral Cavity and Oropharynx

Patients with cancer of the oral cavity often undergo surgery and/or radiation therapy for cure or as a mode of palliation. The tumour node metastasis (TNM) stage of the malignancy dictates the treatment regimen. It is not uncommon for these patients to undergo extensive surgical resections of the oral cavity or oropharynx, necessitating microvascular free flap reconstruction and tracheotomy. In addition to the TNM stage, the patients health status in terms of comorbidities is evaluated when deciding on a treatment plan.

It is anticipated that sleep apnea is a comorbidity that is prevalent in patients with malignancies of the oral cavity and oropharynx. There are many factors that predispose this group of cancer patients to OSA. Cancer of the oral cavity and oropharynx and OSA have many common etiologic factors including age over 60 years, cigarette smoking and heavy alcohol consumption.[5,12,15,38-40] As a result of the anatomic effects on upper airway calibre resulting from primary malignancies as well as potential alterations in neuromuscular functional relationships of upper airway structures due to the presence of

neoplasms, an increase in prevalence of OSA among patients with primary head and neck malignant tumours is anticipated.

Friedman et al determined the prevalence of OSA in patients treated for head and neck malignancies to be 92%.[6] Interestingly, the prevalence of OSA prior to surgical intervention in patients with cancer of the head and neck has not been evaluated in a systematic fashion. A link between head and neck cancer and OSA may be of considerable potential importance in terms of perioperative morbidity at the time of surgical intervention. There is a rapidly growing body of evidence linking OSA to cardiopulmonary complications including hypertension, cardiac arrhythmias, myocardial infarction, pulmonary hypertension, congestive heart failure, and cerebrovascular events.[3,42-47] Thus the detrimental effects of untreated OSA places patients in a sub-optimal preoperative state of health resulting in a potentially greater postoperative risk for morbidities and mortalities.[42,44]

Treatment of the OSA may be warranted prior to surgery since these preoperative cardiopulmonary conditions often improve as the sleep apnea resolves.[48-60] According to Meoli et al, perioperative control of the airway, postoperative monitoring, and care with medications is essential at avoiding airway complications following surgery.[53] Esclamado et al determined that 13% (18/135) of patients with OSA undergoing surgery developed perioperative complications of which 77% (14/18) were airway problems and 5% (1/18) were cardiac related (arrhythmia).[58] Finally, Rennotte et al conclude that nasal CPAP be administered to patients with OSA in the perioperative period after respiratory complications (respiratory arrest) developed in patients who failed to receive treatment.[60]

1.6 Rationale

Based on findings during endoscopic sensory testing in OSA patients, it is hypothesized that LPR is prevalent among OSA patients, and that this contributes to impaired laryngeal sensation in these patients, which in turn may contribute to the pathophysiology of OSA.[14] Moreover, the presence of OSA in patients with cancer of the oral cavity and oropharynx may place this group at an increased postoperative risk for cardiopulmonary morbidities. The aim of the present study was therefore to systematically evaluate the prevalence of LPR in consecutive patients with OSA using the reflux finding score, and to assess the relationships between the finding of LPR and the severity of both upper airway sensory impairment and OSA. Also to evaluate the prevalence of OSA in patients with cancer of the oral cavity and oropharynx and to assess its relationship to postoperative cardiopulmonary morbidities.

1.7 Objectives

The objective of this research study is to uncover associations involving OSA and other clinical entities. There are 2 distinct disease entities that are investigated. The aim of the first part of the study was to determine the prevalence of LPR among 34 consecutive patients referred for suspected OSA, and to assess the relationship between LPR, upper airway sensory impairment and the severity of OSA. The second objective of this research study involves determining the prevalence of OSA in patients with cancer of the oral cavity and oropharynx scheduled for primary surgical resection. In addition, to correlate the presence of OSA and the occurrence of postoperative morbidities in this patient population.

CHAPTER II: MATERIALS AND METHODS

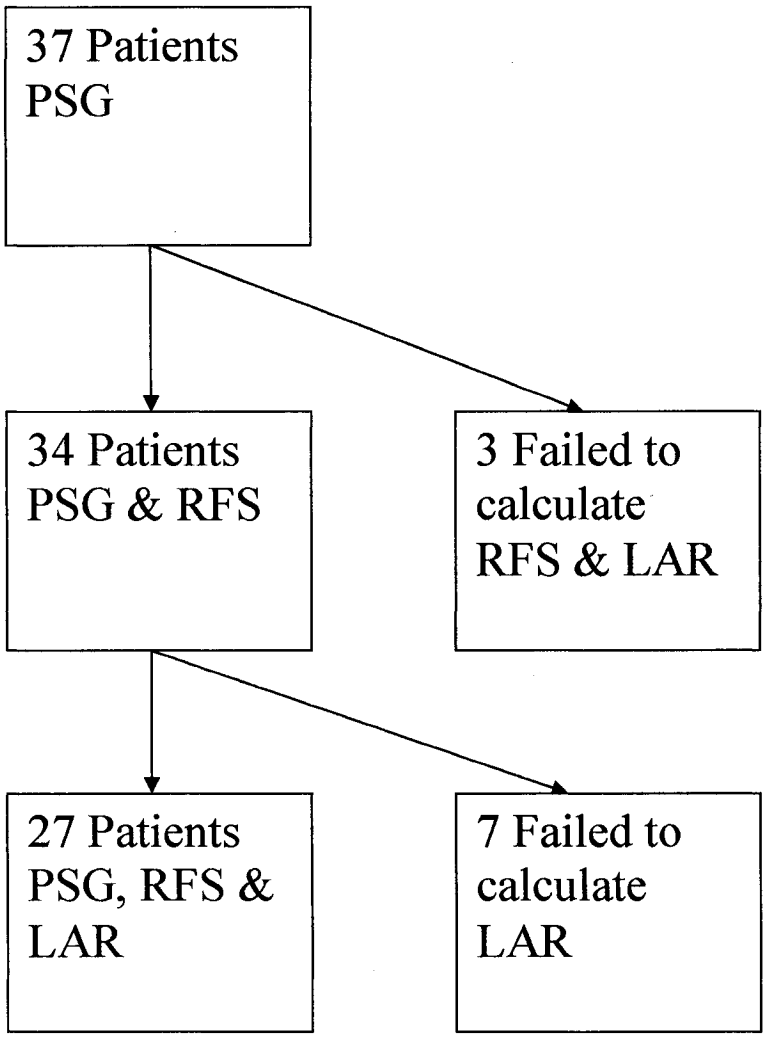
2.1 Study Design

Patients were recruited from the Jewish General Hospital, Royal Victoria Hospital, and St. Mary's Hospital. Consecutive patients were approached and informed consent was obtained prior to including an individual in the study. The research study obtained full scientific and ethical approval from the review boards at each institution (see chapter VI).

2.1.1 Laryngopharyngeal Reflux and Upper Airway Sensory Testing

Thirty-seven patients suspected of having OSA were recruited for confirmation of sleep apnea as well as for assessment of laryngopharyngeal reflux and upper airway sensory impairment in a prospective and blinded manner. Recruitment of subjects was conducted completely independent of any symptoms suggestive of laryngopharyngeal reflux to avoid any selection bias. Patients were expected to undergo polysomnography (PSG), upper airway pulse endoscopic sensory testing (EST) of the laryngeal adductor reflex (LAR) and aryepiglottic fold sensation, and assessment of LPR using the RFS. Thirty-four patients completed both PSG and LPR testing. Twenty-seven patients completed PSG, LPR, and endoscopic sensory testing (Figure 1). Patients on continuous positive airway pressure or taking anti-reflux medications were excluded from the study, as were patients under the age of 18 years old. A questionnaire was used to determine patients' smoking and alcohol consumption histories. The study was approved by the Research Ethics Boards of the participating hospitals, and written informed consent was obtained from each subject.

Figure 1- Patient Grouping



PSG = Polysomnography
RFS = Reflux Finding Score
LAR – Laryngeal Adductor Reflex

2.1.2 Cancer of the Oral Cavity and Oropharynx

Seventeen patients with primary malignant tumours of the oral cavity and oropharynx were recruited for this aspect of the study. Consecutive patients were approached for participation in the study if it was determined that their malignancy was amenable to primary surgical resection. Recruitment of subjects was conducted completely independent of any symptoms suggestive of obstructive sleep apnea or other sleep complaint to avoid any selection bias. Patients with a tracheotomy prior to surgery were excluded from the study, as were patients with malignancies of the head and neck spreading secondarily to the oral cavity or oropharynx, such as nasopharyngeal carcinoma and supraglottic carcinoma. A chart review was conducted to determine patients' smoking, alcohol consumption, and cardiopulmonary histories. The tumours were measured by radiologists specialized in head and neck oncology using computed tomographic images enhanced with intravenous contrast in the axial, coronal, and sagittal planes.

2.2 Diagnosis of OSA

Complete overnight diagnostic polysomnography was performed using the Suzanne (Melville, Tyco, Ottawa) portable recording system. Studies were conducted in the patient's home, with set-up of the apparatus and verification of signals conducted by a trained technologist in the evening, followed by unattended recording through the night. The signals recorded included standard electroencephalographic leads (C4-A1/C3-A2), bilateral electrooculogram, chin and anterior tibialis electromyograms, pulse oximetery, airflow via nasal pressure cannula and oronasal thermistor, thoracoabdominal movements

via piezo bands, body position via mercury position sensor and sound via a microphone taped to the lateral aspect of the neck.

The polysomnographic data was downloaded to a personal computer and scored manually by trained, experienced polysomnographic technologists with review by an expert physician. Sleep-wake state was defined according to standard criteria.[61] An obstructive apnea was defined as an episode of cessation of airflow lasting at least 10 seconds with persistent respiratory effort, and an obstructive hypopnea as a discrete episode of reduction in airflow with inspiratory flow limitation on the nasal cannula pressure signal lasting > 10 seconds with associated desaturation > 2% or arousal defined according to American Sleep Disorders Association criteria.[62] The apnea-hypopnea index (AHI) defined as the number of apneas and hypopneas per hour of sleep, was the primary polysomnographic outcome measure. A diagnosis of OSA was made on the basis on an AHI value $\geq$ 15 events per hour. A diagnosis of OSA requiring treatment was made on the basis of an AHI value $\geq$ 20 events per hour.

2.3 Laryngopharyngeal Reflux Testing

2.3.1 Reflux Finding Score[37]

Laryngopharyngeal reflux was assessed using the reflux finding score. Each patient underwent a standardized videotaped upper airway flexible fiberoptic nasolaryngoscopy using the Pentax® FNL 10ap flexible laryngoscope with the Olympus® OPV F2 video attachment. The recordings were viewed and scored on a JVC® 32 inch television screen. Two investigators blinded to OSA and sensory status determined the RFS for each patient independently. The results from both scorers were

tested for agreement and the mean score was used in the calculations (Figure 2). An RFS > 7 was considered as significant for LPR.

The reflux finding score is a reliable predictor of LPR when compared to double-probe pH monitoring. Calculating the reflux finding score is less expensive, less time consuming, and easier for patients to tolerate than pH probe. Scoring of laryngeal inflammation and irritation may in fact be a more physiologically relevant measure than pH measurements (Figure 3).

Figure 2 - Inter-Scorer Agreement

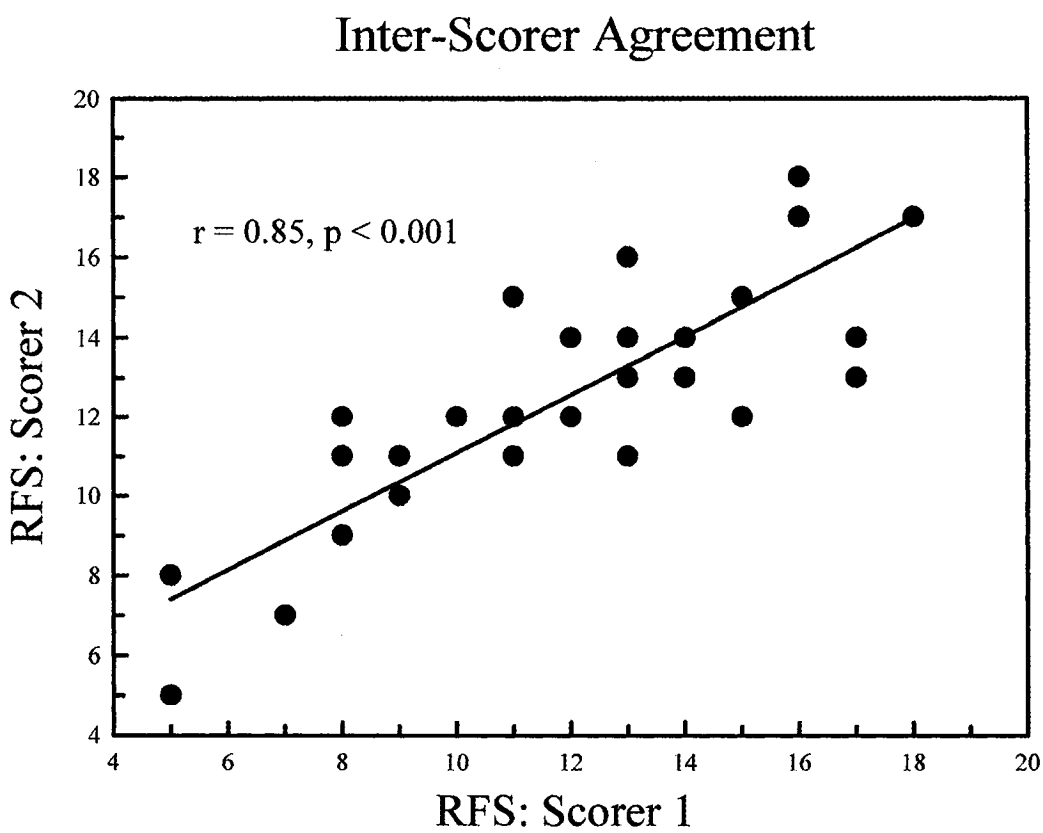


Figure 3 - Reflux Finding Score

Sign	Definition	Score
Laryngeal Erythema/Hyperemia	2 = arytenoids 4 = diffuse	____
Vocal Fold Edema	1 = mild 2 = moderate 3 = severe 4 = polypoid	____
Diffuse Laryngeal Edema	1 = mild 2 = moderate 3 = severe 4 = obstructing	____
Ventricular edema	2 = partial 4 = complete	____
Subglottic edema	0 = absent 2 = present	____
Posterior commissure hypertrophy	1 = mild 2 = moderate 3 = severe 4 = obstructing	____
Granuloma/Granulation tissue	0 = absent 2 = present	____
Thick Mucus	0 = absent 2 = present	____

2.3.2 Endoscopic Sensory Testing

Upper airway sensory testing was performed using the endoscopic air pressure pulse technique. The Pentax® FNL 10ap flexible laryngoscope with the Olympus® OPV F2 video attachment was used with the AP 4000 air pulse stimulator. Incremental pressure pulses 2 – 10 mm Hg were used until the LAR was stimulated. True and sham pulses were both employed. Sensory detection threshold was considered positive if the reflex was positively detected for 4 out of 5 pulses. The degree of sensation measured at the aryepiglottic folds was performed in a similar manner. The amount of air pressure needed was considered as the subjects score (2-10). A patient failing to have a positive reflex or sensation at the maximum setting was scored as 11.

2.4 Cancer of the Oral Cavity and Oropharynx

2.4.1 Determination of Prevalence

The apnea-hypopnea index was calculated for all 17 patients within 2 to 14 days of the surgery. Patients with an AHI value $\geq$ 20 events per hour were considered as positive for having OSA requiring treatment.

2.4.2 Measures of Postoperative Morbidity

The hospital charts of all subjects were reviewed by an investigator unaware of the subject's OSA status to determine the postoperative course for the period up to 60 days following surgical intervention. Values for the following variables were determined for each patient: length of stay in the intensive care unit (ICU) or monitored setting, hours on a ventilator, and number of cardiopulmonary and other OSA related postoperative complications. Intensive care unit stay greater than 24 hours and the need for mechanical ventilation were considered to be surgical morbidities. Cardiopulmonary complications were defined as newly diagnosed arrhythmias requiring medical treatment, myocardial infarction, cerebrovascular events, hypoxemia, pulmonary edema, pleural effusion, and pneumonia.

2.5 Statistical Analysis

AHI, RFS, LAR, and sensation at the level of the aryepiglottic folds were compared for associations by calculating the correlation coefficient. Outcome variables for the patients with cancer were compared between the obstructive sleep apnea and non-OSA groups using an unpaired t-test in the case of normally distributed continuous variables, and the Mann-Whitney rank-sum test for non-normally distributed variables. Categorical comparisons in a two-by-two format were made using the Fisher exact text. Statistical calculations were made using SigmaStat software (Jandel, XX). A value of $p < 0.05$ was used for statistical significance.

CHAPTER III: RESULTS

3.1 Laryngopharyngeal Reflux

Subjects:

There were 26 males and 8 females enrolled in the study. For the group overall, the mean age was 43.9 ± 2.4 (SE) years and the mean body mass index was 26.5 ± 0.8 kg/m^2. For the subjects with OSA (n= 29) these values were 45.4 ± 2.3 years and 27.2 ± 0.8 kg/m^2.

Polysomnographic findings:

The polysomnographic recordings were of high quality, and were adequate for diagnosis in all subjects. Sleep and respiratory data for the group overall and for subjects with OSA are shown in Table 1. AHI values ranged from 7.5 to 108.1 events per hour. Given that the subjects recruited had been referred for polysomnography in the clinical context of suspected OSA, a majority (29/34) were found to have an AHI ≥ 15 events per hour. This therefore represents a prevalence for OSA in this subject group of 85%. In that the small size of the non-OSA group (5 subjects) does not allow for meaningful comparisons between the two groups, the primary focus of the analysis below is on the OSA group (Figure 4).

Air pulse endoscopic sensory testing findings:

Sensory threshold values were obtained in all subjects for the oropharynx, and while the video recording was adequate in all subjects for RFS scoring, several were unable to tolerate the EST procedure sufficiently to allow determination of sensory

thresholds via the trans-nasal approach. Thus sensory detection thresholds were determined at the VP and AR in 28 subjects, and LAR thresholds were determined in a total of 29. Sensory threshold data and LAR values are shown in Table 2 and in Figures 5 and 6 below. As we described previously, there was strong correlation between AR sensory and LAR thresholds ($r = 0.86$, $p < 0.0001$).[14] There was also a significant correlation between sensory thresholds at the OP and VP ($r = 0.46$, $p < 0.03$), while neither of these correlated with laryngeal sensory measures. The sensory threshold values for OSA subjects were considerably elevated compared with those in normal non-snoring controls previously evaluated in our laboratory.[14,15]

Laryngopharyngeal reflux assessment findings:

The video recordings of the larynx were of high quality, and were adequate for diagnosis in all 34 subjects. There was very close correlation between the independent values from the two scorers, with a correlation coefficient $r = 0.85$ ($p< 0.001$). The mean difference between RFS for scorer 1 vs. 2 was only 0.8 ± 0.3 units, and for OSA patients there was 100% concordance regarding the diagnosis of LPR. Of the 34 subjects, 30 were found to have a mean RFS > 7, yielding a prevalence of LPR in this subject group of 88%. The prevalence of LPR in subjects with OSA was 93% (26/28). Mean RFS values for the group overall are shown in Table 2, with the values ranging from 5 to 17.5. RFS Scores from OSA subjects are also shown in Table 2 and in Figure 4 and 5 below.

Relationships between LPR, apnea severity and upper airway sensory function:

For patients with OSA, there was a significant correlation between the severity of LPR and OSA severity as reflected in the AHI (Figure 4). There was also a slightly

weaker but still significant correlation between RFS scores and the nadir SaO_2 for the night ($r = -0.38$, $p < 0.05$). These findings therefore point to a strong relationship between LPR as reflected in the RFS score, and apnea severity.

There were also significant relationships between RFS scores and upper airway sensory function. RFS correlated strongly with LAR values (Figure 5) as well as with AR sensory threshold values ($r = 0.46$, $p < 0.03$). Of note, if the outlier subject (upper left corner of Figure 5) was removed from the calculations, these correlations become considerably stronger, with $r = 0.70$, $p < 0.0001$ for RFS vs. LAR, and $r = 0.62$, $p < 0.002$ for RFS vs. AR sensory threshold. In contrast to the findings at the larynx, there were no significant correlations between RFS and sensory measures at the OP or VP. Thus LPR appears to be strongly related to laryngeal, but not oropharyngeal or velopharyngeal sensory dysfunction.

As recently described for the OSA subject cohort, significant correlations between laryngeal but not OP or VP sensory function and apnea severity were observed (Figure 6).[14]

Table 1 – Sleep and Respiratory Variables

	All Subjects *(n=34)*	**OSA Subjects** *(n=29)*
Sleep Variables		
Total Sleep Time *(h)*	5.9 ± 0.3	6.0 ± 0.3
Sleep Efficiency *(%)*	76.8 ± 2.4	76.5 ± 2.6
Microarousal Index *(#/h)*	34.4 ± 3.6	36.4 ± 3.8
Stage 1 *(% TST)*	6.7 ± 1.1	7.2 ± 1.1
Stage 2 *(% TST)*	57.1 ± 2.8	57.8 ± 2.9
Stage 3 &4 *(%TST)*	15.4 ± 1.6	14.3 ± 1.6
REM *(% TST)*	20.8 ± 1.2	20.7 ± 1.3
Respiratory Variables		
AHI *(events/h)*	35.2 ± 4.0	39.2 ± 3.9
Apnea Index *(events/h)*	12.4 ± 3.8	10.7 ± 3.7
Hypopnea Index *(events/h)*	22.0 ± 2.2	23.9 ± 2.2
Mean Event Duration *(s)*	15.9 ± 0.8	16.7 ± 0.8
Minimum SaO_2 *(%)*	86.7 ± 1.5	85.8 ± 1.5

(Values are Mean ± SE)

Table 2 – Sensory Thresholds

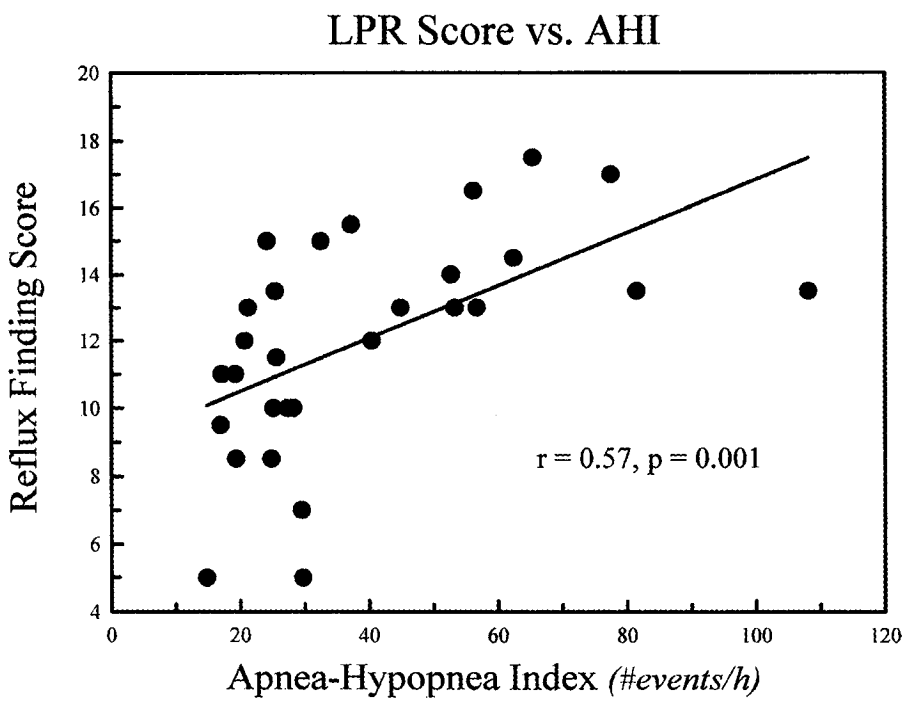
Sensory Thresholds	**All Subjects** *(n=34)*	**OSA Subjects** *(n=29)*
Oropharynx *(mm Hg)*	5.3 ± 0.6	5.4 ± 0.6
Velopharynx *(mm Hg)*	9.5 ± 0.5	9.6 ± 0.5
Larynx *(mm Hg)*	7.4 ± 0.6	7.6 ± 0.6
LAR Threshold *(mm Hg)*	6.2 ± 0.5	6.4 ± 0.5
RFS Values	11.6 ± 0.6	12.0 ± 0.6

(Values are Mean ± SE)

3.1.1 LPR and OSA

There were significant positive correlations between the severity of laryngopharyngeal reflux (RFS) and apnea severity measures. It was determined that 93% of subjects with OSA had LPR. A direct correlation exists between RFS and AHI ($r = 0.57$, $p = 0.001$).

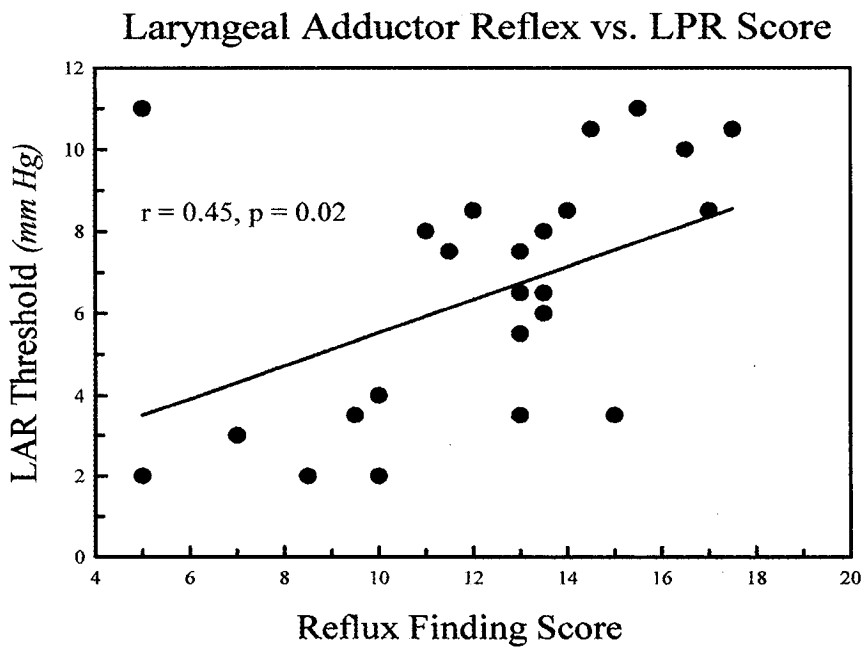
Figure 4 – Relationship Between LPR and AHI



3.1.2 LPR and Upper Airway Sensation

There were significant positive correlations between the severity of laryngopharyngeal reflux (RFS) and laryngeal sensory measures ($r = 0.45$, $p = 0.02$).

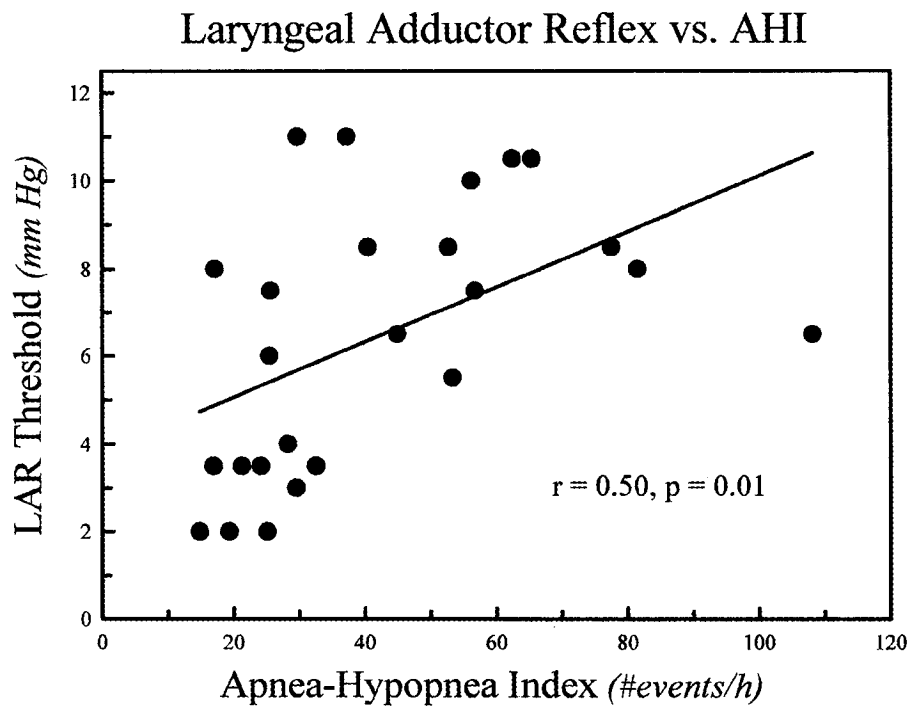
Figure 5 - Relationship Between LAR and LPR



3.1.3 OSA and Upper Airway Sensation

There were significant positive correlations between both LAR and subjective laryngeal sensory thresholds and apnea-hypopnea index ($r = 0.50$, $p = 0.01$).

Figure 6 - Relationship Between LAR and AHI



3.2 Cancer of the Oral Cavity and Oropharynx

There were 14 males and 3 females enrolled in this part of the study. The majority of these subjects (88%) had a history significant for smoking, alcohol abuse, or cardiopulmonary comorbidities. The mean age was 64 ± 2.1 years, ranging from 42 to 76. The mean body mass index was 26.7 ± 2.3 kg/m^2 ranging from 16.5 to 37.4 (Table 3).

Table 3 - Subject Characteristics

Subject	Age/Gender	BMI (kg/m^2)	Social Habits	Cardiopulmonary History
1	69 male	32.4	Alcohol	Hypercholesterolemia
2	58 male	24.3	Alcohol / Smoker	None
3	76 male	23.7	Alcohol / Smoker	HTN, CVA
4	65 male	20.9	Smoker	None
5	59 male	30.6	Alcohol / Smoker	None
6	64 male	28.7	Smoker	Coronary Artery Disease
7	42 female	26.6	None	None
8	66 male	30.7	Alcohol / Smoker	HTN, Hypercholesterolemia
9	59 male	26.6	Alcohol / Smoker	Hypercholesterolemia
10	67 female	21.5	None	None
11	76 male	37.4	None	HTN, Hypercholesterolemia
12	62 female	16.5	Smoker	HTN
13	62 male	24.4	Alcohol / Smoker	None
14	69 male	30.8	Alcohol / Smoker	HTN
15	68 male	21	Alcohol / Smoker	HTN
16	51 male	28.8	Smoker	HTN, Hypercholesterolemia
17	70 male	28.8	None	HTN

HTN: Hypertension
CVA: Cerebrovascular Accident

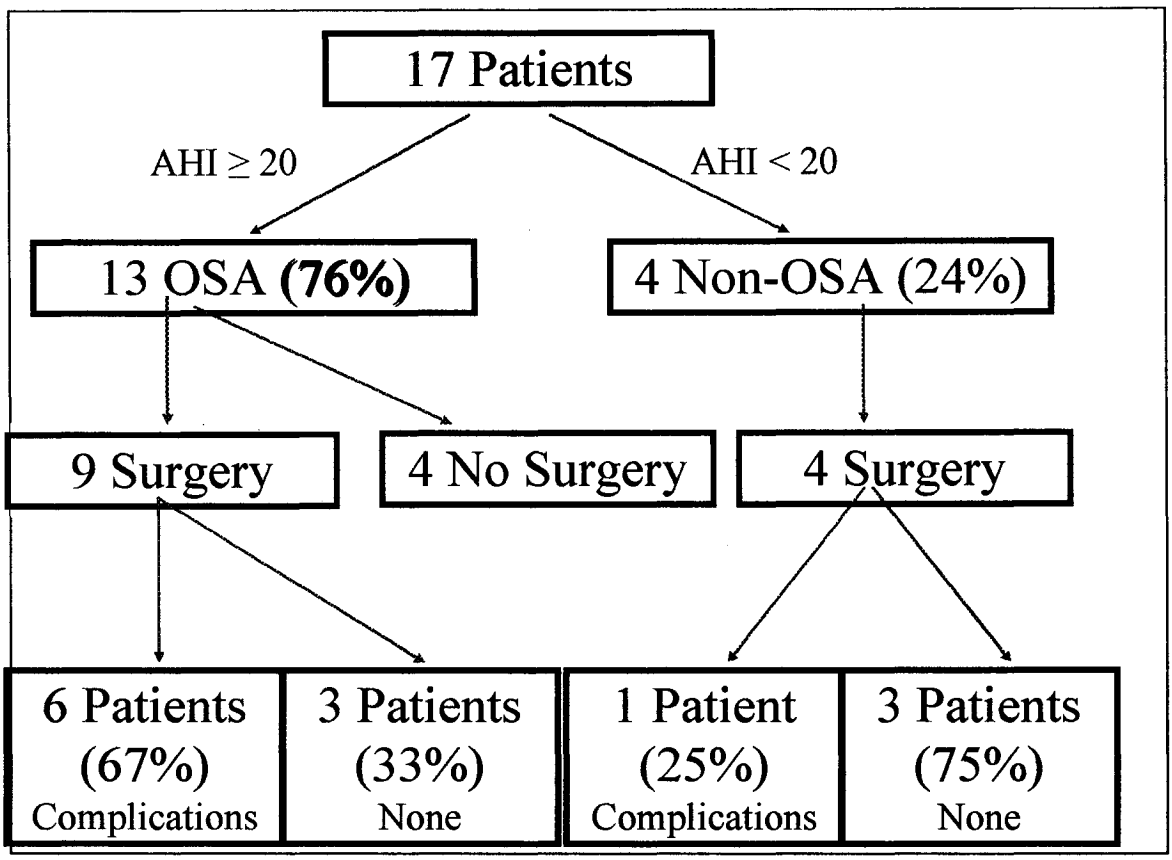
The mean size of the primary tumours was 3.47 ± 0.4 cm ranging from 1cm to 7cm. The oral cavity was the site of the primary in 9 of the cases and the oropharynx was the site in the remaining 8 patients (Table 4).

Table 4 - Size and Site of the Primary Tumour For All Subjects

AHI score	Site	Size (cm)
7.4	Oropharynx	3
13.8	Oral Cavity	2.5
14.2	Oral Cavity	2.5
14.5	Oral Cavity	5
23.5	Oral Cavity	3
24.8	Oral Cavity	4
34.8	Oropharynx	1
41.2	Oral Cavity	2
41.7	Oral Cavity	3
41.7	Oropharynx	3
42.9	Oropharynx	7
44.9	Oropharynx	4.5
46.2	Oropharynx	6
54.8	Oropharynx	3.5
60.1	Oral Cavity	6
61.6	Oral Cavity	2
62.4	Oropharynx	1

Of the 17 patients enrolled in the study, 4 underwent polysomnography but failed to undergo surgery. Two of the patients developed comorbid conditions that precluded surgical intervention, one of which was directly related to cardiopulmonary status. One patient needed a tracheotomy prior to the definitive surgery due to respiratory distress. One patient died of a myocardial infarction secondary to an arrhythmia 2 days before the scheduled operation. As a result, the data used for comparing postoperative morbidities was compiled from the remaining 13 patients (Figure 7).

Figure 7 - Patient Grouping With Respect to AHI Score



3.2.1 Prevalence of OSA

The polysomnographic recordings were of high quality, and were adequate for diagnosis in all subjects. Of the 17 subjects, 13 were found to have an AHI ≥ 20 events per hour, yielding a prevalence of OSA in this subject group of 76%. The tendency to an increase in Stage 1 sleep, and reductions in Stage 3 & 4 and REM sleep, along with the marked increase in arousal index in the OSA group are consistent with the anticipated effects of sleep-disordered breathing on sleep structure. It should be noted that for the majority of patients with OSA (77%) the AHI was > 40 events per hour, consistent with a severe degree of sleep-disordered breathing (Table 5).

Table 5 - Sleep Data For All Subjects

	OSA	Non-OSA
AHI score (events/hour)	44.7 ± 3.5	12.5 ± 1.7
Total Sleep Time (min)	293.9 ± 25.4	221.4 ± 23.1
Arousal (n/hour)	61 ± 12	20 ± 8.3
Stage 1 (%TST)	10.9 ± 2.7	6.3 ± 2.7
Stage 2 (%TST)	63.3 ± 3.6	51.9 ± 6.7
Stage 3 (%TST)	6.4 ± 1.9	15.1 ± 5
Stage 4 (%TST)	6.2 ± 2	1.9 ± 1.6
REM (%TST)	13.3 ± 2.6	24.9 ± 7.4
Minimum SaO_2 (%)	88.2 ± 1.8	89.5 ± 1.2

Values are mean ± standard error
AHI: Apnea-hypopnea index
TST: Total sleep time
REM: Rapid eye movement stage of sleep
SaO_2: Oxygen saturation

The OSA and non-OSA subject groups were similar with respect to age, 63 ± 2.4 and 67 ± 3.8 respectively (p = NS), and body mass index, 27 ± 1.5 and 25 ± 2.5 respectively (p = NS). The mean radiological size of the primary tumour was 3.5 ± 0.5 cm in patients with sleep apnea and 3.3 ± 0.6 cm in the non-OSA group (p = NS) (Table 6). There was no relationship between oropharyngeal tumour size and OSA severity.

Table 6 - Group Characteristics for OSA and Non-OSA Subjects

	OSA	Non-OSA
Subjects	13	4
Age (±SE)	63 ± 2.4	67 ± 3.8
BMI (kg/m2)	27 ± 1.5	25 ± 2.5
Tumour Size (cm)	3.5 ± 0.5	3.3 ± 0.6
Duration of Surgery (hours)	9.7 ± 1.2	6 ± 1.4

OSA = Obstructive sleep apnea
SE = Standard Error

3.2.2 Postoperative Morbidities

Preoperative cardiopulmonary complications occurred in 3 subjects. One of these patients died of an arrhythmia leading to a myocardial infarction 2 days prior to surgery. Intraoperative complications such as prolonged operative time, airway management difficulties, induction of anesthesia, and cardiopulmonary complications as previously defined did not occur in any of the subjects. The average duration of the surgery was 9.7 ± 1.2 hours in OSA and 6 ± 1.4 hours in non-OSA patients. Prolonged ICU stay occurred in 56% (5/9) of patients with OSA and 25% (1/4) of patients with an AHI<20. The mean ICU stay was 3.3 days for OSA patients and 1 day for non-OSA patients. Mechanical ventilation was necessary for 3 patients with OSA and not required for patients without sleep apnea. Cardiopulmonary complications occurred in 33% (3/9) of patients with an AHI≥20 and failed to occur in the other patient group. The cardiopulmonary morbidities which were observed in patients with OSA included arrhythmias, pulmonary edema, pleural effusion, and hypoxemia. In total, 67% of patients with an AHI≥20 and 25% of patients with an AHI<20 ($p = 0.27$, Fisher exact test) had one of the above-described postoperative complications (Tables 7 and 8). If the preoperative cardiopulmonary complications are considered together with postoperative complications, a total of 9 of 13 (69%) of OSA patients and 1 of 4 (25%) of non-OSA experienced perioperative morbidity ($p = 0.11$, Fisher exact test). Thus while these findings do not achieve statistical significance in this relatively small sample size, and it is not possible to establish a direct link between OSA and perioperative complications, there appears to be a clear tendency for a higher rate of perioperative complications among patients with OSA than those without OSA.

Table 7 - Postoperative Complications

AHI	ICU	Ventilated	Cardiopulmonary
7.4	1	0	None
13.8	1	0	None
14.2	0	0	None
14.5	2	0	None
23.5	10	144	Pulmonary Edema, Hypoxemia
24.8	3	41	None
41.7	9	0	Pleural Effusion, Arrhythmia
41.7	1	0	Arrhythmia
42.9	1	0	None
46.2	2	26	None
54.8	1	0	None
60.1	2	0	None
61.6	1	0	None

Table 8 - Postoperative Complications Separated By Grouping

AHI Score	ICU Stay (mean days)	Prolonged ICU Stay	Mechanical Ventilation	Cardiopulmonary Complications	Total Complications
< 20 (n=4)	1 ± 0.4	n = 1	n = 0	n = 0	n = 1
≥ 20 (n=9)	3.3 ± 1.2	n =5	n = 3	n = 3	n = 6

CHAPTER IV: DISCUSSION

4.1 Discussion of Results

4.1.1 Laryngopharyngeal Reflux

In this study, we used a validated endoscopic scoring algorithm to assess LPR among patients with obstructive sleep apnea and found a dramatically higher prevalence (93%) for LPR than that reported for the general population.[13,31,33,63,64] Furthermore, the severity of LPR as reflected by RFS values correlated significantly with several key measures of apnea severity, pointing to an important interaction between these two disorders. The severity of LPR correlated with laryngeal sensory dysfunction (as previously reported by Aviv and co-workers[18]), but not oropharyngeal or velopharyngeal sensory impairment (not previously evaluated). Moreover, previous observations that laryngeal, but not oropharyngeal or velopharyngeal sensory dysfunction correlates with apnea severity was validated.[14]

To our knowledge, the relationship between OSA and LPR has not previously been evaluated. A number of studies have focussed on the relationship between OSA and gastro-esophageal reflux disease, reporting a prevalence of GERD ranging from 55 – 75% in OSA patients.[65-67] The severity of GERD based on questionnaire correlates with apnea severity[65], although nocturnal physiologic recording studies have not shown a direct temporal link between apneic and GERD events.[68,69] Mechanisms postulated to account for the interaction of GERD and OSA include the large negative intrathoracic pressure swings generated during obstructive apneas, and respiratory-related microarousals which appear to be associated with LES relaxation.[67,68]

As noted above, LPR has come to be recognized as not simply the hypopharyngeal manifestation of GERD, but rather as a distinct entity within the spectrum of gastric material reflux syndromes, with characteristic double pH probe profiles and clinical symptoms.[13,31-33,64,70-72] While the clinical syndrome of GERD is primarily related to overflow of gastric contents into the esophagus due to LES dysfunction, with relative protection of the upper airway by the UES, LPR is believed to occur typically in the context of minimal esophageal reflux but UES malfunction, resulting in primarily pharyngolaryngeal symptoms.[32,70-72]

Given the pathophysiologic differences between these conditions, a high prevalence of GERD among OSA patients cannot be assumed to be equivalent to a high prevalence of LPR. However in the present study, we specifically evaluated consecutive OSA patients for LPR and found a very high prevalence of RFS values consistent with LPR in these subjects. This study did not address the mechanisms which may lead to LPR in OSA, and while these may not be dissimilar to those factors which affect LES function, the interaction between OSA, UES function and LPR will have to be specifically evaluated using manometric and pH recording studies during sleep.

The gold standard for the diagnosis of LPR is ambulatory 24-hour double-probe pH monitoring.[31,37,73] However the endoscopic reflux finding score has gained increasing acceptance as an effective predictor of LPR when compared to pH monitoring.[37,74] One potential criticism of this study, however, is that the RFS, which is based on visual scoring of inflammation and irritation, has not been validated in the context of known

OSA. There is considerable previous clinical, radiologic and histopathologic evidence for inflammation of the oropharyngeal mucosa in OSA patients.[16,17,75] This inflammation has previously been postulated to result from mechanical trauma during snoring and apneas, and possibly from irritation associated with smoking and alcohol.[5,12,15,38-40] Such mechanisms could therefore have accounted for some or all of the findings noted on laryngeal endoscopic examination in our OSA and without pH monitoring, the RFS findings cannot necessarily be assumed to be related to LPR in this context.

However the changes we observed during endoscopy in our OSA patients were entirely typical of those found in patients presenting with classical clinical findings of LPR. Furthermore, the strong relationship between LPR and OSA in this study suggests that there may well have been patients with undiagnosed OSA included in previous studies which compared pH probe and RFS results.[33,37,72,74] In addition, there was a strong correlation between RFS values and laryngeal sensory and LAR thresholds, which has previously been reported in the context of pH – documented LPR.[18] It is therefore believed that the inflammatory changes of the hypopharyngeal and laryngeal mucosa observed in our OSA patients are indeed reflective of LPR.

Recent studies from our centre provide evidence that the neural changes underlying the sensory impairment of the upper airway mucosal in OSA are mediated by inflammatory mechanisms.[14-17] Thus the correlation between RFS values and laryngeal sensory measures suggests that LPR-related inflammation leads to mucosal neural dysfunction at the laryngeal level in OSA. In contrast, the oropharyngeal and velopharyngeal sensory thresholds in our patients correlated with each other, but not with

laryngeal thresholds, and not with the severity of LPR based on RFS values. The sensory impairment at these higher levels may be more related to inflammation resulting from mechanical trauma, particularly in view of the fact that this is typically the site of upper airway vibration and forceful suction collapse during snoring and apneas.[14-16,76] The laryngeal mucosa on the other hand is below the site of obstruction and may therefore be subjected to less mechanical trauma or deformation, with injury and inflammation being more closely related to reflux of gastric material.

A major question raised by the correlations between LPR and OSA in this study is whether this interaction is due to a worsening of LPR by OSA, or whether LPR leads to worsened OSA. In fact, both may be true; there may be a reciprocal interaction between the two conditions. Thus, neural and/or mechanical factors associated with OSA likely lead to UES dysfunction and LPR.[67,68] However the resulting irritation and edema of the laryngeal mucosa then undoubtedly contribute to worsened upper airway function. Mucosal inflammation in OSA has been shown to reduce upper airway calibre due to edema and may alter tissue biomechanics which could compromise upper airway function.[75,77] As discussed above, mucosal inflammation likely also produces the sensory dysfunction we have described here,[14,15] and there is considerable evidence that inhibition of afferent upper airway neural function can increase upper airway resistance,[78,79] prolong apneic events[80] and inhibit dilator muscle reflexes (which have important laryngeal inputs) that act to defend airway patency in the context of threatened collapse.[79,81,82] Thus, laryngeal mucosal injury from LPR would be expected contribute to worsen upper airway obstruction during sleep, and this worsening of OSA would in turn exacerbate LPR.

Further studies will be required to evaluate whether this proposed interaction indeed occurs, the precise mechanisms involved, and the extent to which this contributes to the overall pathophysiology of OSA. The contribution of LPR to the development and/or progression of OSA could be evaluated by means of a randomized controlled trial of the effects of LPR therapy with proton pump inhibitor medication on apnea severity in OSA patients with LPR. Such a study is warranted based on the findings presented here, and that this may potentially represent an important innovative therapeutic adjunct in OSA.

It should be noted that while the present study evaluated patients referred for primary complaints referable to OSA without any screening for symptoms of LPR, the close relationship between OSA and LPR raises the intriguing possibility that there may be many cases of unrecognized OSA among patients presenting for evaluation of LPR. Further study is warranted to specifically assess the prevalence of OSA among patients presenting to otolaryngology clinics with primary complaints related to LPR.

4.1.2 Cancer of the Oral Cavity and Oropharynx

In the present study, we found a very high prevalence (76%) of OSA among patients awaiting surgical intervention for malignancies of the oral cavity and oropharynx. This represents the first report assessing OSA prevalence in consecutive patients with head and neck malignancies. The patients in this study were not selected with respect to symptomatology of OSA, but rather if they had malignancies of the oral cavity or oropharynx amenable to primary surgical resection. The high prevalence of OSA in this patient population is likely representative of the larger population, but should be corroborated with larger trials. Complete polysomnography was utilized to document the presence of sleep-disordered breathing in this population. However this approach is cost and labour-intensive and not readily accessible in all centers. Nonetheless there have been considerable advances in screening methodology for OSA which may improve access to appropriate testing.[53,83]

It is generally accepted that OSA develops in association with upper airway anatomical abnormalities, upper airway neuromuscular dysfunction, and truncal obesity.[3,4,15,84,85] Anatomical abnormalities including deformities of the septum, enlarged tongue base, redundant soft palate mucosa, and skeletal irregularities have all been implicated. An increase in OSA in patients with malignancy could result from mass effect of the tumour leading to either anatomic obstruction or alterations in functional neuromuscular relationships due to distortion of upper airway structures. Alternatively, common etiologic factors, such as airway effects of cigarette smoke and alcohol use could play a role. Furthermore, recent studies provide evidence of increases in both upper airway and systemic inflammation in OSA patients without malignancies, which may

contribute to upper airway neuromuscular dysfunction. Thus local and/or systemic mediator release from upper airway malignancies could potentially predispose to OSA through similar mechanisms.[11,12,22,38,39,49,86,87] In the present study the presence or absence of sleep apnea tended to be independent of size and location of the primary tumour, suggesting that the mechanism of interaction is other than simply anatomic. However, further studies will be required to determine the nature of the interaction between sleep disordered breathing and head and neck malignancies.

There are many cardiopulmonary morbidities associated with obstructive sleep apnea. These conditions include hypertension, arrhythmias, pulmonary hypertension, myocardial infarction, congestive heart failure, cerebrovascular events, and hypoxemia.[3,42-48,88,89] It would therefore be anticipated that increased cardiopulmonary morbidity would be observed in patients with untreated OSA subjected to major surgery. In the present study, a tendency for increased postoperative complication rates among OSA versus non-OSA (67% versus 25%) defined as prolonged ICU stay, need for mechanical ventilation, and cardiopulmonary morbidities was observed. These results are independent of variables such as age, body mass index, and cardiopulmonary history in this patient population. More than half (4/7) of the patients developing postoperative complications had no prior history of cardiopulmonary disease. On the other hand, 86% of patients suffering from postoperative complications had an AHI≥20 events per hour (Tables 4 and 5). This finding is significant in that it identifies sleep apnea as a potential contributing factor to postoperative morbidity in patients with cancer of the oral cavity and oropharynx. This finding is consistent with that of Gupta et al who identified OSA as

a risk factor for adverse perioperative events in individuals undergoing outpatient surgery.[90]

A difference in mean operating time exists between the 2 groups. The average duration of surgery was 9.7 ± 1.2 hours in OSA patients and 6 ± 1.4 hours in non-OSA patients. This disparity may have contributed to the increase in postoperative morbidities in the OSA group. Nonetheless, the increased complication rate can also be attributed to the presence of OSA, a combination of the effects of the longer operative time and OSA, as well as the multitude of other potential factors contributing to postoperative morbidities. While patients with OSA appear to be at higher postoperative risk of adverse cardiopulmonary and other complications, carefully conducted large-scale trials will be necessary to evaluate the independent contribution of OSA to perioperative morbidity and the mechanisms by which this may occur.[22,42-48,60,86-100]

4.2 Limitations

4.2.1 Laryngopharyngeal Reflux

Flexible fiberoptic laryngoscopy to calculate the RFS was utilized to document the presence of LPR. While ambulatory 24 hour double-probe pH monitoring is considered as the gold standard in the diagnosis of LPR, RFS has been shown to be of similar diagnostic value.[37] Nevertheless, the findings of this study should be corroborated by a trial involving both RFS scoring as well as ambulatory 24 hour double-probe pH monitoring.

The patients in this study were selected based on the suspicion of sleep apnea. As a result of the study design, the prevalence of OSA in patients with LPR is subject to bias. Moreover, in order to account for confounders, a randomized control trial is necessary to truly assess the prevalence of LPR in patients with OSA.

4.2.2 Cancer of the Oral Cavity and Oropharynx

Patients with cancer of the oral cavity and oropharynx often have multiple medical problems in addition to comorbid conditions. Many of these comorbidities are similar to those commonly seen in patients with OSA. This study determined the prevalence of OSA in this patient population with cancer to be 76%. Larger studies with more subjects are required to validate this finding. In terms of linking OSA to postoperative morbidities, none of the findings in this study had statistical significance. Larger multicenter trials are necessary to truly elucidate the relationship. An inherent limitation to this type of investigation are the multiple confounding variables that are present including: comorbidities, size and location of the tumour, and duration of the surgery. Moreover, since these patients are often quite ill and need multiple tests prior to surgery, the need to conduct polysomnography in relatively short periods of time can be difficult from a logistical point of view. The advent of portable polysomnography machines and other methods of determining the presence of OSA may resolve some of these concerns.

4.3 Clinical Implications and Future Directions

4.3.1 *Laryngopharyngeal Reflux*

This study demonstrates a direct association between laryngopharyngeal reflux and obstructive sleep apnea by comparing AHI, RFS, LAR, and aryepiglottic fold sensation. The mechanism leading to this association is unknown, TNF-α may be one of a multitude of contributors, however it is evident that the progression of one of the diseases results in a concurrent worsening of the other. A potential role in the upper airway of OSA may exist. This could lead to a cyclical interaction of LPR, leading to worsening upper airway sensory dysfunction, contributing to perpetuation and/or progression of apnea severity. Consequently treating one of the conditions may in fact lead to an improvement in both. Randomized, controlled trials are needed to corroborate the findings of this study and to further elucidate the pathophysiological relationship between OSA and LPR.

4.3.2 Cancer of the Oral Cavity and Oropharynx

As a result of the very high prevalence of sleep apnea in this patient population and it's links to cardiovascular disease and increased perioperative complications, there is a strong rationale to prioritize evaluation for OSA and initiation of definitive treatment prior to surgery.[3,51,53,58-60,90,91,95] In further support of this, definitive treatment of OSA with nasal CPAP and tracheotomy have been shown to improve or reverse many of the adverse cardiopulmonary sequelae of sleep apnea.[42-51,91,92] For example, in OSA patients with hypertension nasal CPAP reduces not only the AHI but also the mean blood pressure.[42,43,46,91,92] Kaneko et al have demonstrated that left ventricular ejection fraction improves in OSA patients with heart failure after 1 month of CPAP.[48] Kaye reported on

the value of CPAP in patients with heart failure after only 10 minutes of treatment.[50] The adverse effects of OSA include changes in coagulation profile which may predispose to an increase in cerebrovascular and cardiovascular events.[93,94] These changes can be reversed by nasal CPAP treatment.[93,94]

Studies have also demonstrated that CPAP used prior to surgery improves patients preoperative cardiopulmonary health status with as little as 24 hours of treatment.[42-51,95-98] These studies have also demonstrated fewer postoperative morbidities such as cardiac events, hypoxemia, unplanned intensive care unit stays, and reintubations. Tracheotomy is a practical alternative to CPAP in patients undergoing surgery for cancer of the head and neck since it is often performed as part of the operative procedure. In fact, the preoperative diagnosis of severe OSA may influence the surgeon to perform a tracheotomy in those patients who otherwise would not have necessarily needed one. As a result, the short term use of CPAP or preoperative tracheotomy may be warranted to improve patients cardiopulmonary status prior to the definitive surgical intervention for cancer of the oral cavity and oropharynx.[99,100]

This study was done in a prospective blinded manner. By design, the results of the polysomnographic studies were not linked to the individual patients until the outcome analysis had been completed. It is of note, however, that 54% (7/13) of the patients undergoing surgery had an AHI > 40 events per hour. Had the severity of the sleep apnea been known preoperatively, on the basis of usual clinical practice[53], patients would have been sent for evaluation by a respirologist to determine whether treatment with a short term trial of CPAP or tracheotomy was warranted.

It is evident that more studies are needed with larger sample sizes to corroborate the findings of an association between OSA and postoperative morbidities in patients with malignancies of the oral cavity and oropharynx. Moreover, investigations determining whether the above association exists for other regions of the head and neck, specifically the nasopharynx, larynx and hypopharynx, should be undertaken. The effectiveness of preoperative treatment of OSA using short term CPAP and tracheotomy must be evaluated in patients with malignancies of the head and neck. Finally the potential role of TNF-α in producing neuromuscular dysfunction in the upper airway in OSA must be further investigated.

4.4 Conclusions *(claims to originality are bold faced)*

4.4.1 Laryngopharyngeal Reflux

Laryngopharyngeal reflux is common among patients with OSA, occurring at a frequency much above that in the general population (93% in this study). Laryngeal sensation, as reflected in both the sensory detection and laryngeal adductor reflex thresholds correlates with apnea severity. The severity of laryngopharyngeal reflux, measured by the reflux finding score, correlates with laryngeal but not pharyngeal sensory measures, as well as with OSA severity. These findings are consistent with the hypothesis that LPR contributes to laryngeal sensory dysfunction in OSA, which in turn contributes to the perpetuation or progression of apnea severity.

Further studies will be required to test the validity of this proposed interaction and to investigate the extent to which this contributes to the overall pathophysiology of OSA. A

randomized controlled trial of the effects of LPR therapy with proton pump inhibitor medication on apnea severity in OSA patients with LPR may be warranted, since it may represent an important innovative therapeutic adjunct in OSA.

4.4.2 Cancer of the Oral Cavity and Oropharynx

The prevalence of OSA in patients with malignancies of the oral cavity and oropharynx amenable to primary surgical resection is significantly higher than in the general population (76% in this subject group). Further investigations are required to evaluate the prevalence of OSA in a large sample of subjects awaiting surgical intervention for head and neck malignancies, to determine the mechanisms underlying this association, and to validate methods for preoperative screening of sleep apnea. There was a tendency for postoperative complications, as measured by prolonged ICU stay, the need for mechanical ventilation, and cardiopulmonary morbidities, to be more common among patients with OSA, occurring in 67% of OSA patients and 25% of non-OSA patients. Clinical trials are warranted to evaluate the role of preoperative treatment of OSA with CPAP or tracheotomy in decreasing postoperative morbidity and mortality.

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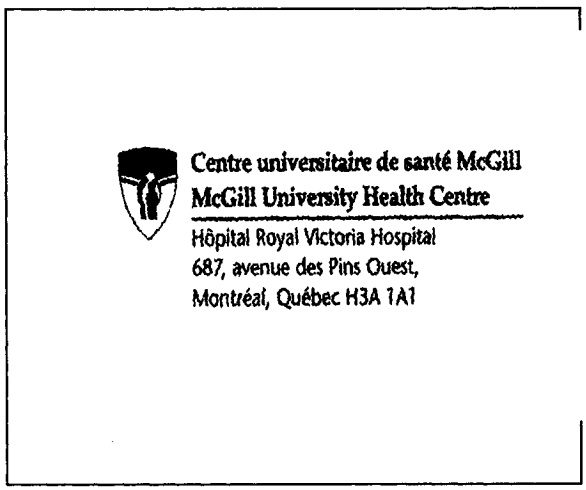
CHAPTER VI: APPENDICES

6.1 Consent Form (English)

Consent Form

Upper Airway Afferent Stimulation in Snorers (SN)and Obstructive Sleep Apnea (OSA) patients.

McGill University Health Center
Sleep Laboratory
Principal Investigator: Dr John Kimoff



Introduction:
Obstructive sleep apnea (OSA) is a common and important medical condition, of which the causes and the ways in which it progresses over time are not well understood. Previous research suggests that changes in the function of the sensory nerves in the upper airway (mouth and throat) contribute to this disease. These studies you are being asked to participate in are being conducted by Dr. John Kimoff and his colleagues in the Sleep Laboratory of the Royal Victoria Hospital pavilion of the McGill University Health Center, to see if stimulation of the nerves in the throat will have an influence on upper airway function.

Study Procedures:

Module 1: *Overnight screening study: (normal controls only):*
You will undergo a home monitoring study to be sure you do not have any significant snoring or unexpected irregularities of breathing during sleep. You will be given a device to take home which records snoring, breathing movements and oxygen level. You will be instructed at the hospital on how to use the machine, take the machine home for one night and record yourself and then return the equipment to the Hospital the next day. If this study is found to be abnormal, you will be asked to attend a more complete sleep study in the hospital (module 2). After the study is done, if it still shows significant abnormalities, you will be offered to consult a physician specialized in sleep diseases to explain the results to you and possible implications for your health. If it shows your sleep to be normal, you will be asked to continue in the study.

Risks and discomforts: The recording is not painful or dangerous in any way. There may be some minor inconvenience associated with sleeping with wires attached on the skin, as well as the minor inconvenience of transporting the small device to and from the hospital.

Module 2: *Overnight sleep study (Polysomnography) (OSA patients and Snorers)*
This study permits a complete evaluation of your sleep and is done regularly in the Royal Victoria Hospital-MUHC Sleep Laboratory. It measures your heart rate, breathing movements, electroencephalogram (your brain activity) and movements of your jaw and legs. These measurements are made with wires that are put on your skin with glue, with a pressure sensor that measures airflow under your nose and movement sensors around your waist and chest. You will be asked to sleep in the laboratory for the entire night.

Risks and discomforts: The recording is not painful or dangerous in any way. There may be some minor inconvenience associated with sleeping with wires attached. A technician will be available all night long if any problem or question occurs.

Module 3: *Upper airway sensory testing (All Subjects):*
This will involve two sessions (on two different days) of approximately 20-30 minutes of testing during the daytime. Just before beginning the measurements, a dilute solution that contains capsaicin, menthol or the liquid in which these substances are dissolved (which is water with a minimal concentration of alcohol (0.1%)) will be sprayed at the back of your throat using an aerosol device. Also, a small tube (approximately 4 mm. external diameter) will be inserted down the back of the nose and throat and will permit the application the same solution throughout the experiment. Capsaicin is the active ingredient in chili peppers. Menthol is a mint-like substance present in food and candy. One of the two sessions will be with capsaicin or menthol infused, the other session (on a different day) will be with liquid in which these two substances are dissolved. Neither you nor the technician performing the test will be aware of which of the two solutions you are receiving. After the substance is sprayed at the back of your throat and as it is infused , your sensation of touch will be tested in several places including your hand, lower lip and the inside of your mouth at the back. The testing will involve touching various objects to the skin at these points, and asking you to report the presence or absence of a gentle buzzing sensation, or to indicate whether you are being touched in one or two places.No needles or medications are involved. The objects used to test you will be sterilized prior to use.

Risks and discomforts: There is no major risk associated with these tests. There is no discomfort with the sensory testing on the hand or lip. Testing in the throat may in some instances cause gagging. If this is a problem, testing will be stopped. You might feel a slightly burning or cold sensation and you might have a little bit of coughing when the substance is sprayed at the back of your throat. Before the tube is inserted, a small amount of numbing or freezing medication will be applied to the nose and back of the throat, in order to minimize any discomfort associated with the placement of the tube. If you have any history of allergy or adverse reaction to freezing or local anesthetic medications, you should not participate in this part of the study. There is a very small risk of provoking bleeding in the nose during placement of the catheter. If bleeding occurs, the catheter will be withdrawn. There could be minor discomfort with the catheter in the nose and throat

during the testing procedures. Also, because the study substance will be infused throughout the experiment with the catheter, you may feel a little discomfort by having liquid at the back of your throat that will make you swallow more than usual. If this is excessive, the tube will be removed. The capsaicin solution may cause a little burning sensation as if eating spicy food. Menthol solution may cause a cold sensation.

Module 4: *Daytime testing of upper airway dilator reflexes:*
This will involve 1 to 2 hours of testing during daytime sessions (It will be done after testing described in module 3 on the same day.) The testing will be done on separate days with and without one of the study substance sprayed and infused on to the back of the throat as described in module 3. The aim of the testing is to measure the responses of two upper airway muscles to brief (one-half second) pulses of suction pressure applied to the mouth and throat. Two sets of electrodes will be used to measure the activity of each of the 2 upper airway muscles. These will consist of 4 fine wires inserted through needles into a fold of skin on the side of the mouth at the back and under the tongue. A soft tube will be placed through the nose and advanced to the back of the throat for measurement of pressure. You will then breathe on a mouthpiece through some tubing with a noseclip in place. Intermittently you will feel the brief pulses of suction of varying strength applied to the mouthpiece, and we will record the muscle responses to those suction pulses.

Risks and discomforts: There is a minor risk of bleeding associated with placement of the pressure catheter through the nose, and with placement of needle electrodes. If bleeding occurs, it will be treated with withdrawal of the catheter or pressure on the electrodes, respectively. There may be minor discomfort associated with the catheter in the nose and throat, which will be minimized during insertion by application of some freezing medication. If you have any history of allergy or adverse reaction to freezing or local anesthetic medications, you should not participate in this part of the study. The back of the mouth will also be frozen or anesthetized for insertion of the needle electrodes. The needle is inserted gently into the area which has been frozen and then is withdrawn leaving the very fine (hair-like) wire electrode in place. The application of negative pressure pulses will be extremely brief and associated with minimal discomfort. The pressure pulses will not interfere with breathing. There could be mild discomfort associated with the administration of capsaicin or menthol as noted in module 3.

Potential Benefits:

Participation in this study will likely not be of immediate benefit to you. However, the results will provide important insights into the nature and causes of a serious medical disorder, and thus could help others in the longer term.

Subject Rights:

Your participation in this study is voluntary. You may decline participation or withdraw from this study at any time and for any reason, and your decision to withdraw will not affect your treatment or medical management in any way. If you have any questions about your rights as a research subject, you may contact the Patient Representative at 842-1231, local 5655.

Confidentiality:

All information derived from these studies will be kept strictly confidential and will not be released to anyone other than the study investigators and research personnel. You will remain anonymous in any scientific presentations or publications reporting the results of this study

Statement of Consent

Upper Airway Afferent Stimulation in Snorers (SN)and Obstructive Sleep Apnea (OSA) patients

Dr. John R. Kimoff

I, _____, have read the information in this consent form. I understand that this is a research study and the procedures to be followed and the possible risks and benefits of the study and am aware of the other treatments available for my illness.

I have had the opportunity to ask Dr._____ questions and have received satisfactory answers to all of them.

I understand I am free to withdraw from this study anytime for any reason and the decision to stop taking part will not affect my future medical care. By signing this document, I am not giving up any of my legal rights. I will be given a signed copy of this consent form.

Having read all the pages of this consent form and understood the requirements of the study, my signature below indicates that I voluntarily consent to participate in the study.

_____	_____	_____
Subject's Name (please print)	Subject's Signature	Date
_____	_____	_____
Investigator's Signature (please print)	Investigator's Signature	Date

For Further Information: Dr John Kimoff 514-842-1231-1568

Centre universitaire de santé McGill
McGill University Health Centre
Hôpital Royal Victoria Hospital
687, avenue des Pins Ouest,
Montréal, Québec H3A 1A1

Consent Form

(Prospective Study: Control Subjects)

"Upper Airway Sensation and Tissue Changes in Snorers and Obstructive Sleep Apnea Patients"

McGill University Health Center Sleep Laboratory
Principal Investigator: Dr John Kimoff

Introduction:

Obstructive sleep apnea (OSA) is a common and important medical condition, of which the causes and the ways in which it progresses over time are not well understood. Previous research suggests that changes in the function of the sensory nerves in the upper airway (mouth and throat) contribute to this disease. These studies you are being asked to participate in are being conducted by Dr. John Kimoff and his colleagues in the Sleep Laboratory of the McGill University Health Center, to see if snoring and/or sleep apnea are associated with changes in the muscles and nerves in the upper airway tissues. You are being asked to participate in this study because you have decided with your doctor to undergo surgery on the upper airway. The object of this research study is to perform some specialized analyses on the tissues which are removed during your routine surgical procedure.

Study Procedures:

1. Overnight screening study:

You will undergo a home monitoring study to be sure you do not have any significant snoring or unexpected irregularities of breathing during sleep. You will be given a device to take home which records snoring, breathing movements and oxygen level. You will be instructed at the hospital on how to use the machine, take the machine home for one night and record yourself and then return the equipment to the Hospital the next day. If this study is found to be abnormal, you will be asked to attend a more complete sleep study in the hospital. After the study is done, if it still shows significant abnormalities, you will be offered to consult a physician specialized in sleep diseases to explain the results to you and possible implications for your health. If it shows your sleep to be normal, you will be asked to continue in the study.

Risks and discomforts: The recording is not painful or dangerous in any way. There may be some minor inconvenience associated with sleeping with wires attached on the skin, as well as the minor inconvenience of transporting the small device to and from the hospital.

2. Overnight sleep study (Polysomnography)
If you are required to undergo an overnight sleep study, this will be done in the Royal Victoria Hospital-MUHC Sleep Laboratory. This test provides a detailed evaluation of your sleep and will be done in exactly the same way as for routine evaluation of patients from the Sleep Clinic. The test measures your heart rate, breathing movements, electroencephalogram (your brain activity) and movements of your jaw and legs. These measurements are made with wires that are attached to your skin with a special cream and tape, as well as with a pressure sensor that measures airflow under your nose and movement sensors around your waist and chest. You will be asked to sleep in the laboratory for the entire night.

Risks and discomforts: The recording is not painful or dangerous in any way. There may be some minor inconvenience associated with sleeping with wires attached. A technician is present all night long if any problem or question occurs.

3. Upper airway sensory testing:
This testing will be done in the research area of the Royal Victoria Hospital-MUHC Sleep Laboratory. The testing session lasts approximately 60 minutes in total. The testing will involve touching various objects to the skin on the hand, the lip and in the inside of your mouth and asking you to report the presence or absence of a gentle buzzing sensation, or to indicate whether you are being touched in one or two places. No needles or medications are involved. The objects used to test you will be sterilized prior to use. There will also be testing using gentle puffs of air delivered through a flexible tube called a laryngoscope. The pressure of the air puffs will varied slightly and you will be asked to report the presence or absence of a tapping sensation. Testing will be done on the lip and in the mouth, and then the tube will be passed gently into the nose and testing will be done at several levels in the throat.

Risks and discomforts: These testing procedures have been conducted on many subjects in our laboratory. There have been no serious complications, and the procedures have been associated with minimal discomfort. Testing in the mouth may in some instances cause gagging. If this is a problem, testing will be stopped. If at any time you find the procedure too uncomfortable, the tube will be withdrawn and the testing stopped. There is also a very small risk of the tube causing a nose bleed. In one recent study using the same apparatus, nosebleeding occurred only 3 times in 500 testing sessions. In all 3 cases the bleeding stopped on its own after removal of the tube.

4. Authorization for use of tissue obtained at the time of surgery (all patients). The object of this study is to perform specialized testing on tissue that is removed during the standard operation that you have planned to undergo in consultation with your surgeon. No modification of the surgical technique is required for this study and no additional tissue will be removed other than what is normally removed during the standard operation.

Risks and discomforts: There are no additional risks or discomfort associated with using your tissues for this research study, beyond those which are normally associated with your surgical procedure, which have been explained to you by your surgeon.

5. Blood test (all patients). This test will be performed before sensory testing in the same manner as when one has blood taken at a clinical laboratory, using a sterile needle. 14 ml of blood will be taken, with this procedure taking approximately five minutes. The blood will be processed to obtain its plasma, and this portion will be frozen and subsequently analyzed for stress hormones we believe to be increased by OSA.

Risks and discomforts: There is minor discomfort with the insertion of a needle to draw blood, and a small risk of local bruising. All instruments will be sterile, so there is no risk of disease transmission.

Potential Benefits:

Participation in this study will likely not be of immediate benefit to you. However, the results will provide important new knowledge concerning the causes of an important medical condition, and thus could help others in the longer term.

Subject Rights:

Your participation in this study is voluntary. You may decline participation or withdraw from this study at any time and for any reason, and your decision to withdraw will not affect your treatment or medical management in any way. If you have any questions about your rights as a research subject, you may contact the Patient Representative at 842-1231, local 35655.

Confidentiality:

All information derived from these studies will be kept strictly confidential and will not be released to anyone other than the study investigators and research personnel. Your tissues will be identified with a confidential code. Your name will not be linked to any samples or data obtained. Your tissue specimens will be kept in a secure storage area and all unused samples will be destroyed. If you choose to withdraw from the study your tissue samples will be destroyed. You will remain anonymous in any scientific presentations or publications reporting the results of this study.

Statement of Consent:

"Neuromuscular Factors in the Pathophysiology of Obstructive Sleep Apnea"

I, _____, have read the information in this consent form. I understand that this is a research study and the procedures to be followed and the possible risks and benefits of the study and am aware of the other treatments available for my illness.

I have had the opportunity to ask Dr._____ questions and have received satisfactory answers to all of them.

I understand I am free to withdraw from this study anytime for any reason and the decision to stop taking part will not affect my future medical care. By signing this document, I am not giving up any of my legal rights. I will be given a signed copy of this consent form.

Having read all the pages of this consent form and understood the requirements of the study, my signature below indicates that I voluntarily consent to participate in the study.

_____	_____	_____
Subject's Name (please print)	Subject's Signature	Date
_____	_____	_____
Investigator's Signature (please print)	Investigator's Signature	Date

For Further Information: Dr John Kimoff 514-843-1568

Consent Form (French)

Centre universitaire de santé McGill
McGill University Health Centre
Hôpital Royal Victoria Hospital
687, avenue des Pins Ouest,
Montréal, Québec H3A 1A1

Formule de consentement:

"Stimulation des afférences sensitives des voies aériennes supérieures chez les patients souffrant d'apnée obstructive du sommeil (AOS) et chez les patients ronfleurs"

Investigateur principal : Dr John Kimoff

Centre universitaire de santé McGill
Laboratoire de sommeil

Introduction

l'Apnée obtructive sommeil (AOS) est une condition médicale fréquente et importante dont les causes et la progression dans le temps ne sont pas bien comprises. Des recherches précédentes suggèrent que les changements de la fonction sensitive dans les voies aériennes supérieures (la bouche et la gorge) contribuent à cette maladie. L' étude à laquelle on vous demande de participer est dirigée par Dr. John Kimoff et ses collègues au Laboratoire de sommeil de l'hôpital de Royal Victoria du Centre Universitaire de Santé Mcgill (CUSM) et permettra de vérifier si la stimulation des nerfs dans la gorge aura une influence sur la fonction des voies aériennes supérieures.

Procédures

Module 1: *Évaluation nocturne du sommeil: (sujets témoins seulement):*
On vous fera passer un test à domicile pour s'assurer que vous ne souffrez pas d'un problème de ronflement sérieux ou d'irrégularités respiratoires pendant le sommeil. On vous fournira un appareil permettant d'enregistrer le ronflement, les mouvements de la respiration et le niveau d'oxygène. De plus, on vous expliquera le fonctionnement de l'appareil. Vous l'apporterez à la maison pour une nuit, procéderez vous même à l'enregistrement et le rapporterez à l'hôpital de lendemain. Si cette étude s'avère être anormale, on vous demandera de passer un autre examen de votre sommeil plus complet tel que décrit au module 2. Après que ce nouvel examen, si on note toujours des anomalies significatives, on vous offrira la possibilité de consulter un médecin spécialisé dans les troubles du sommeil pour vous expliquer les résultats ainsi que les implications sur votre santé. Si l'examen est

normal, on vous demandera de continuer l'étude.

Risques et Désagréments: L'enregistrement n'est pas douloureux et ne présente aucun danger. Vous pourrez ressentir un léger inconfort à dormir en présence de fils d'enregistrement sur votre peau. Le transport de l'appareil entre l'hôpital et la maison peut également présenter un certain inconvénient même si l'appareil est petit.

Module 2: *L'étude nocturne du sommeil (Polysomnographie)*
Cette étude permet une évaluation complète de votre sommeil et se fait de façon régulière dans le laboratoire de sommeil de l'hôpital Royal-Victoria (CUSM). On mesurera la fréquence cardiaque, les mouvements respiratoires, l'électroencéphalogramme (l'activité du cerveau) ainsi que les mouvements de la mâchoire et des jambes. Toutes ces mesures sont faites à l'aide de fils (électrodes) qui sont fixés sur votre peau avec de la colle, avec un capteur de pression qui mesure le flux d'air sous le nez ainsi qu'un capteur de mouvement autour de votre taille et de votre poitrine. Vous serez invité(e) à dormir dans le laboratoire pour la nuit entière.

Risques et désagréments: L'enregistrement n'est pas douloureux. Il peut y avoir un certain dérangement causé par les fils et capteurs sur votre peau. Un technicien sera disponible toute la nuit au besoin.

Module 3: *Évaluation Sensorielle des voies aériennes supérieures (tous les sujets)*
Cette évaluation, d'une durée de 20 à 30 minutes, sera effectuée le jour (deux journées différentes). Avant de débuter les mesures, une solution diluée soit de capsaïcine ou de mentol ou uniquement le liquide contenant la capsaicine ou le menthol (i.e.:le véhicule consistant en de l'eau avec une concentration très faible en alcool (0,1%)) sera vaporisée à l"arrière de votre gorge. De plus, un petit tube (diamètre externe d'approximativement 4 millimètres) sera inséré dans votre narine jusqu'à votre gorge et permettra l'application de la solution pendant l'expérience. La capsaïcine est le constituant actif du piment de cayenne. Le menthol est une substance utilisée dans beaucoup de produits comestibles disponibles sur le marché. Une des deux journées, l'expérimentation se fera avec l'une des deux substance dans la solution et l'autre journée se fera avec la solution (véhicule) seulement sans capsaïcine ou mentol. On déterminera le niveau de sensibilité tactile de diverses parties de votre corps (main, lèvre inférieure, fond de la gorge). À l'aide de différents objets, on touchera votre peau et on vous demandera de signaler la présence ou l'absence d'une légère sensation de vibration et d'indiquer si on vous touche à un ou deux endroits à la fois. Aucune aiguille ne sera utilisée. Les objets servant à faire les tests auront été stérilisés au préalable.

Risques et Désagréments: Ces tests ne comportent aucun risque important. L'évaluation sensorielle de la main et de la lèvre ne cause pas d'inconfort. L'évaluation de la gorge peut provoquer des nausées. Si cela devient trop gênant, on mettra fin à l'évaluation. Vous pourriez ressentir une sensation de brûlure ou de froid ou bien tousser un peu lorsque la solution sera vaporisée au fond de la gorge. Avant que le cathéter soit inséré, un médicament sera appliqué dans le nez et dans la gorge, afin de réduire au maximum tout inconfort lié à la mise en place du cathéter. Si vous avez une histoire

d'allergie ou d'intolérance aux anesthésiques locaux, vous ne devriez pas participer à cette partie de l'étude. Il y a un très petit risque de provoquer un saignement dans le nez pendant la mise en place du cathéter. Si un saignement se produit, le cathéter sera retiré. De plus, il pourrait y avoir un léger inconfort du fait d'avoir le cathéter en place dans le nez et la gorge pendant la procédure. De plus, puisque la solution sera infusée tout au long de l'expérience avec il se peut que vous sentiez le besoin d'avaler plus souvent qu'à l'habitude. La solution de menthol pourrait causer une sensation de froid et la capsaïcine pourrait causer une sensation de chaleur.

Module 4: *Étude de jour des réflexes dilateurs des voies aériennes supérieures.*(tous les patients)
Ceci demandera 1 à 2 heures de votre temps pendant le jour (à la suite des tests décrits au module 3). L'étude sera faite pendant des jours différents avec et sans une des substances à l'étude (capsaicine ou menthol) qui sera vaporisée et infusée au fond de la gorge tel que décrit au module 3. Le but de l'étude est de mesurer la réponse de deux muscles dilatateurs des voies aériennes supérieures à de brèves impulsions (une demi-seconde) de pression appliquées à la bouche et à la gorge. Deux ensembles d'électrodes seront utilisés pour mesurer l'activité de chacun des 2 muscles des voies aériennes supérieures. Cela consistera en 4 petits fils insérés à travers une aiguille dans un pli de la peau à l'arrière de la gorge et sous la langue. Un tube mou sera placé dans le nez et inséré au fond de la gorge pour mesurer la pression. Vous respirerez alors par un embout de caoutchouc connecté à des tuyaux. Par intermittence vous sentirez de brèves impulsions de pression d'intensité variable appliquées à l'embout, et nous enregistrerons les réponses des muscles dilatateurs à ces impulsions de pression.

Risques et désagréments: Il y a un risque mineur de saignement lié à la mise en place du cathéter par le nez et à la mise en place des électrodes. Si un saignement se produit, il sera traité respectivement par retrait du cathéter ou par une pression locale sur les électrodes. Il peut y avoir un inconfort mineur lié au cathéter dans le nez et la gorge qui sera réduit au minimum pendant l'insertion par l'application d'une petite quantité d'un médicament anesthétique. Si vous avez une histoire d'allergie ou d'intolérance aux anesthésiques locaux, vous ne devriez pas participer à cette partie de l'étude. Également, l'intérieur de la bouche sera anesthésié pour faciliter l'insertion des électrodes. L'électrode est montée dans une aiguille qui est insérée doucement dans l'endroit gelé et l'aiguille est alors retirée laissant ainsi l'électrode (grosseur d'un cheveux) en place. L'application des impulsions de pression sera extrêmement brève et ne devrait pas provoquer d'inconfort. De plus elles ne gêneront pas la respiration. Il pourrait y un léger inconfort lié à l'administration de la substance à l'étude tel que mentionné dans le module 3.

Avantages possibles:

Vous ne retirez aucun avantage immédiat de votre participation à cette étude. Cependant, les resultats obtenus permettront aux investigateurs de mieux comprendre la nature et les causes de ce trouble médical grave et ainsi d'aider d'autres patients à plus long terme.

Droits des sujets:

Votre participation à cette étude est volontaire. Vous pouvez refuser d'y participer ou vous en retirer en tout temps, pour quelques raisons que ce soit, sans préjudice quant à votre traitement ou à la qualité des soins qui vous seront prodigués. Si vous avez des questions au sujet de vos droits en tant que sujet de recherche, vous pouvez communiquer avec le représentant des patients, au 514-842-1231, local 5655.

Confidentialité:

Tous les renseignements recueillis dans le cadre de cette étude seront gardés strictement confidentiels et seuls les investigateurs de l'étude et le personnel de recherche y auront accès. Votre identité ne sera divulguée dans aucune présentation ou publication scientifique portant sur les résultats de l'étude.

Consentement

"Stimulation des afférences sensitives des voies aériennes supérieures chez les patients souffrant d'apnée obstructive du sommeil (AOS) et chez les patients ronfleurs"

Dr. John R. Kimoff

J'ai, _____, lu l'information de ce formulaire de consentement. Je comprends que c'est une étude de recherche et les procédures à suivre. Je comprends aussi les risques et les avantages possibles de l'étude. Je suis averti des autres traitements disponibles pour ma maladie.

J'ai eu l'occasion de poser des questions au Dr. _____ et j'ai reçu des réponses satisfaisantes à toutes mes questions.

Je comprends que je suis libre de me retirer de cette étude n'importe quand pour n'importe quelle raison. et La décision de cesser de participer n'affectera pas mes soins médicaux futurs. En signant ce document, je ne renie aucun de mes droits légaux. J'ai reçu une copie signée de ce formulaire de consentement.

Après avoir lu toutes les pages de ce formulaire de consentement et ayant compris les conditions de l'étude, ma signature ci-dessous indique que je consens volontairement à participer à l'étude.

_____	_____	_____
nom du sujet	signature	date
_____	_____	_____
nom de l'investigateur	signature	date

pour plus d'information : Dr John Kimoff 514-842-1231 poste 1568

Formulaire de Consentement :

Centre universitaire de santé McGill
McGill University Health Centre
Hôpital Royal Victoria Hospital
687, avenue des Pins Ouest,
Montréal, Québec H3A 1A1

(Étude prospective : sujets témoins)Sensation des voies aériennes supérieures et changement dans les tissus chez les patients ronfleurs et chez les patients souffrant d'apnée obstructive du sommeil (AOS)

Laboratoire de Sommeil du Centre universitaire de santé McGill
Investigateur principal : Dr John Kimoff

Introduction

L'apnée obstructive du sommeil (AOS) est une condition médicale fréquente et importante dont les causes et la façon de progresser ne sont pas bien comprises. Des recherches précédentes suggèrent que les changements des nerfs sensoriels dans les voies aériennes supérieures (la bouche et la gorge) contribuent à cette maladie. L'étude à laquelle on vous demande de participer est dirigée par Dr John Kimoff et ses collègues au Laboratoire de sommeil de l'hôpital Royal Victoria du Centre universitaire de santé Mcgill (CUSM) et permettra de vérifier si le ronflement et/ou l'AOS sont associé à des changements dans les muscles et les nerfs dans les tissus des voies aériennes supérieures. On vous demande de participer à cette étude parce que vous avez décidé avec votre médecin de subir une intervention chirurgicale sur vos voies aériennes supérieures dans le but de traiter votre problème de ronflement ou d'AOS. Le but de cette étude est de réaliser des analyses spécialisées sur les tissus qui seront enlevés durant votre chirurgie.

Procédures

1. Évaluation nocturne du sommeil :

On vous fera passer un test à domicile pour s'assurer que vous ne souffrez pas d'un problème de ronflement sérieux ou d'irrégularités respiratoires pendant le sommeil. On vous fournira un appareil permettant d'enregistrer le ronflement, les mouvements de la respiration et le niveau d'oxygène. De plus, on vous expliquera à l'hôpital le fonctionnement de l'appareil. Vous l'apporterez à la maison pendant une nuit, procéderez vous même à l'enregistrement et le rapporterez à l'hôpital de lendemain. Si cette étude s'avère anormale, on vous demandera de passer un autre examen de votre sommeil plus complet. Après ce nouvel examen, si on note toujours des anomalies significatives, on vous offrira la possibilité de consulter un médecin spécialisé dans les troubles du sommeil pour vous expliquer les résultats ainsi que les conséquences sur votre santé. Si l'examen est normal, on vous demandera de continuer l'étude.

Risques et Désagréments : L'enregistrement n'est pas douloureux et ne présente aucun danger d'aucune manière. Vous pourrez ressentir un léger inconfort à dormir en présence de fils d'enregistrement sur votre peau. Le transport de l'appareil entre l'hôpital et la maison peut également présenter un certain inconvénient même si l'appareil est petit.

2: L'étude nocturne du sommeil (Polysomnographie)
On vous demande de faire cette étude de nuit sur le sommeil qui sera réalisée au laboratoire de sommeil de l'hôpital Royal Victoria (CUSM). Cette étude permet une évaluation complète de votre sommeil et se fera exactement de la même façon que nos tests habituels chez les patients de la Clinique de sommeil. On mesurera la fréquence cardiaque, les mouvements respiratoires, l'électroencéphalogramme (l'activité du cerveau) ainsi que les mouvements de la mâchoire et des jambes. Toutes ces mesures sont faites à l'aide de fils (électrodes) qui sont fixés sur votre peau avec une crème spéciale et du ruban et avec un capteur de pression qui mesure le flux d'air sous votre nez ainsi qu'un capteur de mouvement autour de votre taille et de votre poitrine. Vous serez invité(e) à dormir dans le laboratoire pendant une nuit entière.

Risques et désagréments : L'enregistrement n'est pas douloureux ni dangereux d'aucune façon. Il peut y avoir un certain dérangement causé par les fils et capteurs sur votre peau. Un technicien sera disponible toute la nuit en cas de problèmes ou de questions.

3: Évaluation sensorielle des voies aériennes supérieures :
Cette évaluation sera réalise dans le centre de recherche du laboratoire de sommeil de l'hôpital Royal Victoria (CUSM). La séance sera d'une durée totale d'environ 60 minutes. À l'aide de différents objets, on touchera votre peau sur la main, la lèvre et l'intérieur de la bouche et on vous demandera de signaler la présence ou l'absence d'une légère sensation de vibration et d'indiquer si on vous touche à un ou deux endroits à la fois. Aucune aiguille ne sera utilisée. Les objets servant à faire les tests auront été stérilisés au préalable. Il y aura aussi une évaluation de la sensibilité avec un stimulateur produisant des bouffées d'air sous pression délivrées par un tube flexible appelé laryngoscope. Ces bouffées d'air produisent une sensation semblable à un toucher très léger. La pression des bouffées d'air sera variée et on vous demandera d'indiquer si vous sentez la présence ou non de ces stimulus. La sensation sera testée sur la lèvre et à l'intérieur de la bouche, et ensuite le laryngoscope sera passé doucement par le nez dans le but d'examiner différents niveaux dans la gorge.

Risques et désagréments : Ces tests ont été réalisés chez nombreux sujets dans notre laboratoire. Il n'y a pas eu de complication grave, et les tests ont été associés à un inconfort minime. L'évaluation sensorielle de la gorge peut provoquer des nausées. Si cela devient trop gênant, on mettra fin à l'évaluation. Vous pourriez ressentir un léger inconfort ou des nausées lors du passage du tube dans le nez et la gorge pendant la procédure. L'inconfort est minimisé par le petit calibre du laryngoscope (diamètre de 7 mm), et par l'utilisation d'un lubrifiant sur le tube. Si à tout moment vous trouvez le test trop inconfortable, le tube sera retiré et l'évaluation sera terminée. Il y a un très petit risque de provoquer un saignement dans le nez pendant le passage du tube. Dans une étude récente utilisant le même équipement, un saignement du nez ne s'est produit que 3 fois sur 500 procédures. Dans les 3 cas, le saignement s'est arrêté tout seul après que le tube soit retiré.

4. Autorisation à utiliser des tissus enlevés lors de votre chirurgie :

Le but de cette étude est de réaliser des analyses spécialisées sur le tissu qui sera enlevé pendant votre chirurgie, ce que vous avez décidé d'entreprendre avec votre chirurgien. Il n'y aura aucune modification de la technique chirurgicale dans le but de cette étude et aucun tissu additionnel ne sera enlevé autre que celui qui est normalement enlevé durant l'opération courante.

Risques et désagréments : Il n'y aura aucun risque ou inconfort associé à l'utilisation de vos tissus pour ce projet de recherche, autre que ceux qui sont normalement associés à l'intervention habituelle, ce qui vous a été expliqué par votre chirurgien.

Avantages possibles : Vous ne retirez aucun avantage immédiat de votre participation dans cette étude. Cependant, les résultats obtenus permettront aux investigateurs de mieux comprendre la nature et les causes de cette condition médicale grave et ainsi à aider d'autres patients à plus long terme.

Droits des sujets :

Votre participation dans cette étude est volontaire. Vous pouvez refuser d'y participer ou vous en retirer en tout temps, pour quelque raison que ce soit, sans influencer négativement votre traitement actuel ou la qualité des soins qui vous seront prodigués. Si vous avez des questions au sujet de vos droits en tant que sujet de recherche, vous pouvez communiquer avec l'ombudsman, au 514-842-1231, local 35655.

Confidentialité :

Tous les renseignements recueillis dans le cadre de cette étude seront gardés strictement confidentiels et seuls les investigateurs de l'étude et le personnel de recherche y auront accès. Vos tissus seront identifiés avec un code confidentiel. Votre nom ne sera pas associé à des tissus ou des données obtenus. Les spécimens de vos tissus seront gardés dans un endroit sécurisé, et les tissus qui ne sont pas utilisés pour l'étude seront détruits. Si vous optez de vous retirer de cette étude, les échantillons de vos tissus seront détruits. Votre identité ne sera pas divulguée dans aucune présentation ou publication scientifique portant sur les résultats de l'étude.

Consentement

Facteurs neuromusculaires dans la pathophysiologie de l'apnée obstructive du sommeil

J'ai,lu l'information dans ce formulaire de consentement. Je comprends que c'est une étude de recherche et qu'il y a des procédures à suivre. Je comprends aussi les risques et les avantages possibles de l'étude. Je suis au courant des autres traitements disponibles contre ma maladie.

J'ai eu l'occasion de poser des questions au D^{r} _____ et j'ai reçu des réponses satisfaisantes à toutes mes questions.

Je comprends que je suis libre de me retirer de cette étude n'importe quand pour n'importe quelle raison. La décision de cesser de participer n'affectera pas mes soins médicaux futurs. En signant ce document, je ne renie aucun de mes droits. Je recevrai une copie signée de ce formulaire de consentement.

Après avoir lu toutes les pages de ce formulaire de consentement et ayant compris les conditions de l'étude, ma signature ci-dessous indique que je consens volontairement à participer à l'étude.

_____ _____ _____
nom du sujet signature date

_____ _____ _____
nom de l'investigateur signature date

pour plus d'information : D^{r} John Kimoff 514-843-1568

6.2 Ethics Certificate

Centre hospitalier de St. Mary

St. Mary's Hospital Center

3830, avenue Lacombe, Montréal (Québec) H3T 1M5

RESEARCH REVIEW OFFICE
DEPARTMENT OF CLINICAL EPIDEMIOLOGY AND COMMUNITY STUDIES
ROOM 2506 ❖ TEL.: (514) 345-3511 EXT. 3698 ❖ FAX: (514) 734-2652

Date: January 20, 2004

To: Dr. J. Kimoff
Royal Victoria Hospital
Respiratory Div. Rm. L408
687 Pins Ave. W.
Montreal, QC
H3A 1A1

Re: Status of Protocol #03-29 entitled "Upper airway sensation and tissue changes in snorers (SN) and Obstructive sleep apnea (OSA) patients"

We are pleased to inform you that the above-mentioned protocol has received full institutional approval at St. Mary's Hospital Center. This approval is valid for a period of one year from January 20, 2004 to January 19, 2005.

The following documents were approved:

Protocol dated: December 8, 2003
English Consent forms dated January 19, 2004

Consent Form: The English consent forms have been stamped to indicate the Chair of the Research Ethics Committee approval. Please make copies of this stamped consent form for use in your study.
Please forward the French Consent form for approval as soon as possible.

A copy of the consent form is to be filed in the patient's chart with a cover sheet. Enclosed is a cover sheet that must be completed for each patient enrolled on the protocol. Please complete and return a cover master sheet of all standard information for approval (this should include all required information except for the date of study entry).

For each patient enrolled in the study, the following should be given to the ward clerk for filing in the outpatient section of the patient chart:

1) The cover sheet completed with the date of study enrolment and the signature of the investigator or delegated research assistant
2) A copy of the signed consent form. The investigator (or delegated research assistant) should write on the copy of the consent form **"copie conforme à l'original"** and sign this.

Research Subject Log: Enclosed you will also find a log sheet requesting the chart number and date for each patient enrolled on the study. Copies of the form can be made as required. This information should be forwarded to the Research Review Office of the Department of Clinical Epidemiology and Community Studies on a **monthly** basis.

Monitoring: The REC has recommended patient consent form monitoring for your protocol. Please be advised that our Research Monitor, Ms. Tina Emond, will contact you shortly to schedule a meeting to discuss the monitoring in greater detail.

Additional Information: In addition, you will find enclosed an information sheet for fully approved protocols detailing specific guidelines to follow to maintain this full institutional approval status. You are responsible for informing this office of any changes to the protocol or of serious adverse events. It is strongly advised that you keep this information sheet throughout the course of your research for reference purposes.

Please forward all future correspondence to Ms. Claudette Garrison, Research Administrative Secretary, Department of Clinical Epidemiology and Community Studies, St. Mary's Hospital, (514) 345-3511 ext. 3698

Dr. Martin Cole
Chair, Research Ethics Committee

Dr. Jane McCusker
Chair, Scientific Research Committee

cc:
Dr. Richard Payne
Dr. J. R. Sutton
Dr. George Sejean
Ms. Tina Emond

Encl.
Approved consent form(s)
Consent form cover sheet
Research subject log
Information sheet