Acoustical Analysis of Respiratory Sounds for Detection of Obstructive Sleep Apnea

by

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A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfillment of the requirements for the degree of

Master of Science

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Winnipeg, MB, Canada

To

Nasrin & Ali,

&

To

People with Sleep Apnea Syndrome

Abstract

Obstructive Sleep Apnea (OSA) is a common respiratory disorder during sleep. Apnea is cessation of airflow to the lungs, which lasts for at least 10 seconds accompanied by more than 4% drop of the blood's Oxygen saturation. Polysomnography during the entire night is the Gold Standard diagnostic method of OSA. It's high cost and inconvenience for patients persuaded researchers to seek alternative OSA detection methods.

This thesis proposes a technique for assessment of OSA during wakefulness. We recorded tracheal breath sounds of 17 non-apneic individuals and 35 people with various degrees of OSA severity in supine and upright positions during nose and mouth breathing at medium flow rate. We calculated the power spectrum, Kurtosis, and Katz fractal dimensions of the recorded signals. Then, we reduced the number of characteristic features to two.

We classified the participant into severe OSA and non-OSA groups as well as non-OSA or mild vs. moderate and severe OSA groups. The results showed more than 91 and 83% accuracy; for the two types of classification. Once verified on a larger population, the proposed method may be used as a simple and non-invasive screening tool for assessment of OSA during wakefulness.

Acknowledgments

I would like to express my gratitude to all those who gave me the possibility to complete this thesis.

Firs, my outmost gratitude goes to my supervisor, Prof. Zahra Moussavi, for encouragement, supervision, patience and support throughout my research.

My thanks and appreciation goes to my thesis committee members, Dr. Sherif Sherif and Jitendra Paliwal. I am grateful to Dr. Ellini Gianouli for her valuable inputs and comments.

This study was supported by Telecommunication Research Labs (TRLabs), Winnipeg, Canada. I thank the administration of TRLabs, especially Dr. Sergio Camorlinga.

I wish to acknowledge and thank Wayne Thompson and Misericordia Sleep Center staff for their assistance in clinical data recording. I would like to show my gratitude to my colleagues Ali Azarbarzin, Azade Yadollahi and Saiful Huq for their help in recording data from volunteers and also Shekoofeh Saboktakin and Samaneh Sarraf for their support. I am also grateful to Amy Dario for her help.

Last but certainly not least, I would like to thank my wonderful parents, Nasrin and Ali, brothers, Ehsan and Amin and friends for their priceless help and support.

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Chapter 1

Introduction

1.1 Motivation & Thesis Objectives

Obstructive Sleep apnea (OSA) is a common respiratory disorder that can become a serious condition. By definition, sleep apnea (or hypopnea) is the cessation (or more than 50% reduction) of airflow to the lungs during sleep that lasts for at least 10 seconds, and is usually associated with more than 4% drop of the blood's Oxygen saturation (SaO2) level (SaO2) [1]. It is most common in obese people, people with high blood pressure, and people with narrowed airway due to tonsils or adenoids, people with stroke or brain injuries, and smokers. Sleep apnea occurs two to three times more often in the elderly and also more in males than in females. It is associated with cardiovascular problems, daytime fatigue, irritability, lack of concentration and sleepiness, causing accidents.

The current gold standard for sleep apnea diagnosis is full night Polysomnography (PSG). PSG is a costly assessment, uncomfortable for the patient due to the connection of many

sensors, not portable and in need of technical supervision for the entire night. PSG assessment has a long waiting list in Manitoba (1-3 years). The aim of this thesis is to provide a simple and quick screening test during wake time that would be possible to be used in physicians' office.

We hypothesize that the breathing sound signals of patients with apnea are significantly different from those of healthy individuals at different body positions and different breathing manoeuvres, i.e. mouth breathing versus nose breathing. In order to investigate this hypothesis, we recorded and compared respiratory sounds from two groups of people with and without OSA in different body positions. We extracted the characteristic features from the respiratory sounds, and classified participants with different OSA severity.

1.2 Outline of Chapters

The chapter 2 present background information pertaining the details about:

- Respiratory Sounds & Systems
  - Upper Airway Tract Models
  - Breathing Sounds Specifications
  - Factors Influencing Upper Airway
  - Specifications of Inspiratory Breathing Cycles
  - Specifications of Expiratory Breathing Cycles

- Sleep Apnea
  - Definition
  - Diagnosis Methods

Chapter 3 contains the details of methods which used for:

- Data Recording
- Signal Processing

Chapter 4 presents the results of feature selection and classification methods discussed in the chapter 3 and also discussion of the achieved results. The chapter 5 presents conclusion and possible future works. Appendix A contains details of ANOVA algorithm and Appendix B contains a list of publications.

The author of this thesis was an active member of the team involved in data acquisition. His roles included setting up hardware and preparing software for data acquisition, placing sensors on subjects, explaining consent forms to subjects (and their guardians as necessary), guiding subjects through each protocol, ensuring data storage and analyzing the recorded data.

Chapter 2

Background

2.1 Respiratory Sound & System

2.1.1 Structure of The Respiratory System

The main objective of the respiratory system is inhaling O_2 and exhaling waste gases. The main organs involved in respiratory acts are respiratory tract, and lungs [2]. The respiratory tract is a ventilation system which consists of nasal cavity, oral cavity, pharynx, larynx, and trachea [2]It extracts oxygen from atmospheric air and transfers it to the lungs, while extracting CO2 from the lungs to be transferred out of body [2].

During inhalation, air enters nasal or oral cavities from nose or mouth. These two cavities join each other posteriorly and form the pharynx. Air draws into the larynx through the pharynx and then enters the trachea. The trachea branches to form right and left main bronchi, one bronchus to each lung. Air passes from main bronchus to bronchial

tree, ultimately enters alveolar sacs. Blood diffuses the carbon dioxide and other wastes through the alveoli walls, and in turn receives oxygen.

2.1.2 Upper Airway Model

Many researchers employed physical and/or mathematical models to describe how a biological system works. The most basic one is to model the airway canal as a rigid tube assuming a linear relationship between flow and driving pressure (fixed resistance) [3]. However, the negative intrathoracic pressure, transmitted to the passive upper airway during inspiration causes a reduction in the pharyngeal cross sectional area. Therefore, a more realistic approach is to assume a varying resistance during inspiratory cycles. Starling resistors are a specific model of collapsible tube behaviour which model a dynamic interaction between flow and pressure [4].

In the Starling resistors model, the relationship between flow and driving pressure is approximately linear under a critical driving pressure. Above that point, flow progressively plateaus despite the increase in driving pressure [5, 6]. This model can be demonstrated physically by a thin elastic (collapsible) tube enclosed in a chamber. The transmural pressure inside chamber, which is surrounding the collapsible tube is called P_{crit}. It corresponds to the tissue pressure in the collapsible parts of the upper airway. The maximum flow inside the tube can be determined by the resistance at the upstream segment and the transmural pressure surrounding the collapsible segment (P_{crit}) [3].

When $P_{crit} << 0$, the airway remains open. There is a strong evidence that the hypotonic pharyngeal airway behaves like a Starling resistor [3]. This implies below when the pressure is below P_{crit}, the airways remains closed despite the increase in driving pressure. The studies have shown that, the measured P_{crit} is positive, in patients with OSA while, it is negative in non-OSA people [4]. On the other hand, the negative intraluminal airway pressure is higher for patients with OSA during wakefulness; this is the most important local stimulus to pharyngeal dilator muscle activity [7].

2.1.3 Factors Influencing Upper Airway's Behavior

The collapsibility/resistance of the upper airway in humans depends also on additional factors such as the following [3]:

- Upstream airway (e.g. nasal and nasopharyngeal) resistance within the nasal airway: The nose has a relatively high resistance, which is increased by mucosal congestion
- Gender: There might be gender specific differences in the airway mechanics
- Hormonal status
- Age: Age increases pharyngeal resistance during sleep and wakefulness, and decreases the muscles' activity.
- Sleep: Sleep affects multiple aspects of upper airway's behavior including muscle tone, load response, and CO_2 level (affecting muscle activity during sleep)

- Extrinsic anatomic and static factors including neck and jaw posture, surface adhesive forces, obesity, and tracheal tug.

2.2 Sleep Apnea

Sleep apnea is a common respiratory disorder that can have serious impacts; it leads to daytime sleepiness, poor job performance, increased risk of accidents and cardiovascular problems. By definition, sleep apnea (or hypopnea) is the cessation (or more than 50% reduction) of airflow to the lungs during sleep that lasts for at least 10 seconds, and is usually associated with more than 4% drop of the blood's Oxygen saturation (SaO2) level (SaO2) [1]. There are three forms of sleep apnea: obstructive, central and mixed; they account for approximately 84.6%, 0.4% and 15% of the reported cases, respectively. Central apnea occurs due to neurological impairment, while obstructive sleep apnea (OSA) occurs due to airway impairment. Mixed apnea is a combination of the other two [1].

OSA is common in smokers [8], in people with high blood pressure and those with narrowed airway due to tonsils or adenoids [9]. Sleep apnea occurs two to three times more often among men and elderly [9]. It is also associated with cardiovascular problems, daytime fatigue, irritability, and lack of concentration [10-13]. Sleep apnea is highly prevalent in the general population, 4% of women and 9% of men develop more than 15 discrete obstructive events per hour [14], but most of the cases are thought to go undiagnosed.

2.2.1 Pathophysiology of Obstructive Sleep Apnoea Syndrome

OSA occurs when collapse of pharynx presents a significant mechanical constraint to ventilation. The pharynx of people with OSA is, on average, smaller and more collapsible than those of healthy individuals [15]. Individuals with OSA have no breathing difficulty during wakefulness, because pharynx narrowing is usually compensated with an increase in dilator muscle activities [16, 17]. This increased activity of the dilator muscles, observed during wakefulness, no longer exists during sleep; therefore, their pharynx collapses and obstructs the airflow [18, 19]. On the other hand, dilator muscles' activities decrease also in the healthy individuals during sleep, but their airway size dose not decrease to the extent to obstruct airflow [20, 18].

Mechanical Characteristics of the Passive Pharynx

The upper airway in normal people generally (not always) remains patent in the absence of all muscle tone when intraluminal pressure is zero [7]. Application of intraluminal negative pressure (during inspiration) may result in collapse of airways. The luminal pressure at which the upper airways collapse, has been referred to as P_{close} [21].

When a negative luminal pressure is applied, the mechanical properties of the passive human pharynx determine how much the pharyngeal dilator muscles must be activated to maintain an adequate air flow. In addition, the pharynx cross-sectional area varies with the luminal pressure [21], as it is anchored to bone and cartilage (larynx) at its upper

and lower ends, respectively. The cross-sectional area of pharynx increases as the luminal pressure increases; the relationship between them is not linear.

The maximum flow passing through pharynx called V_{MAX}; this is obtained by applying a certain amount of negative pressure called P_{MAX} [22]. Further increase in the negative pressure does not increase the maximum passing flow; under some circumstances, it even reduces the passing flow [22]. In theory, V_{Max} can increase by different mechanisms:

- Increase in lung volume due to an increase in pump muscles activity (e.g., diaphragm) [23].
- Reduction of respiratory effort, when negative effort dependency exists [22].
- Increase in pharyngeal muscle activities.

When an obstructive event occurs, lung volume cannot increase, while inspiratory effort will increase. Therefore, once an obstructive event is initiated, V_{MAX} can increase only by an increase in pharyngeal muscle activities [7]. The maximum flow in the collapsible tube can be obtained as follow [7]:

$$\dot{V}_{MAX} = A \times \{A/[\rho(\Delta A/\Delta P)]\}^{0.5}, \tag{2.1}$$

where A is the prospection area, $\Delta A/\Delta P$ is tube compliance, and ρ is the gas density. Thus, $\dot{V}_{MAX}$ is related directly to the tube's area and inversely to it's compliance.The

relation between luminal pressure and V_{MAX} is almost close to linear. Hence, the mechanical properties of an individual pharynx can be described by a slope and an intercept (P_{Close}) [24] like a Starling resistor. The range of slope and intercept varies among different subjects. Intercept ranges from -10 to 10 cmH_2O, while the slope ranges from 16 to 103 $l.s^{-1}.cmH_2O^{-1}$ [25].

2.2.2 Diagnostic Methods

General Information

Respiratory sounds are useful tools in the assessment of respiratory diseases [26]. For listening to the respiratory sounds, stethoscopes have been widely used [26]. There were two general types of stethoscope: analog and digital. Both of them have some limitations. It has been shown tracheal respiratory sounds' major components are below 1000 Hz, but in deep breathing it can have components up to 2 kHz [2]. The common analog stethoscopes attenuate frequency components higher than 112 HZ [27], while electronic stethoscopes typically attenuate the frequencies above 500 Hz [27]. Therefore, they cannot transmit the entire bandwidth of respiratory sounds. Moreover, stethoscopes provide subjective point of care and they cannot monitor the breathing flow. In addition, analog stethoscopes alter frequency components of the respiratory sounds [26]. As a result, many researches record and analyze lung and tracheal sounds via computer [28].

Polysomnography

Polysomnography (PSG) during the entire night is currently the accepted Gold Standard diagnostic method for assessment of sleep apnea. The standard PSG consists of recording various biological signals including EEG, ECG, EMG of chins and legs, nasal airflow, electro-oculogram (EOG), and abdominal and thoracic movements [29]. PSG is an expensive test for the health care system as it needs full night supervision, is not portable, and is also inconvenient for patients. Therefore, many researchers have attempted to develop an alternative, non-invasive and portable OSA monitoring tools.

Current Research on Sleep Apnea Detection

There are many different technologies that record a reduced number of signals, and claim detecting apnea events during sleep. Most of these technologies record 4 signals including airflow, SaO2, respiratory effort and snoring sound by an ambient microphone [30-32]. In these technologies, airflow is measured by either face mask or nasal cannulae connected to a pressure transducer, whose output reduction or cessation associated with a drop of more than 4% of SaO2 is detected as the main diagnostic sign of OSA. In case of mouth breathing, which may happen often during the night, the nasal cannulae will not register airflow; hence, it is not reliable. On the other hand, face mask, which is considered reliable for airflow measurement, may change the breathing pattern; it is also difficult for some patients to fall asleep with mask.

While there have been many studies and developed technologies to diagnose OSA during sleep [33], few studies attempted to diagnose OSA during wakefulness [34-39]. In [34], it was claimed that OSA can be diagnosed from a short-time, daytime recording of the nasal airway pressure. However, that study [34] suffers from several limitations including the number of studied subjects. They applied their proposed method to two different groups: Group 1 including 15 non-OSA and 3 OSA, and Group 2 including 14 OSA and 2 non-OSA individuals. Although the reported accuracy of classification is very high, the numbers of class members (OSA vs. non-OSA) in each of their classifications were unbalanced. Therefore, the classification results were not reliable.

In one study [35], an OSA detection method was proposed using Ultrafast Magnetic Resonance Imaging from pharyngeal airway. Data were recorded during both wakefulness and sleep. The results ith central apnea and 10 non-OSA individuals were compared using the coefficient of variation (CV) and sample entropy of the inspiratory, expiratory cycles and complete breath sounds. The results showed that the breathing irregularity (defined by higher CV and sample entropy values) during wakefulness was greater in patients with mixed apnea compared to that of OSA and control subjects; though, they did not provide classification results.

By combining the Gaussian mixture model (GMM)-based classifier and feature selection methods, a technique for detection of OSA using oronasal airway pressure signal was proposed [37]. They achieved good results (>85% accuracy between OSA and non-OSA) for

41 subjects but the feature space dimension was too high for their database size (overfitting). This implies the results may not be as promising as reported if the population size changes. Furthermore, no physiological reasons for the calculated features were provided.

Recently, a group of researchers investigated the correlation between speech disorder and OSA [38]. The acoustic features of 10 non-OSA and 18 OSA individuals during speaking were compared, and substantial differences were found, though no classification was performed [38].

In addition, previous studies have shown that patients with OSA have a defective ability to dilate the pharynx during inspiration [39, 40]. In [39], to show the pharynx dilator muscles abnormality during wake time, the tracheal breath sound intensity of 7 patients with OSA were compared to that of 8 individuals in control group. The results showed significant increase in breath sound intensity of people with OSA with respect to healthy individuals.

2.3 Current Study

Given that people with some degrees of upper airway congestion are more prone to develop OSA, we hypothesized that there must be some noticeable differences between the nose and mouth breathing intensity, complexity and smoothness of the breath sounds of people with OSA in the supine and upright sitting positions as compared to those of

non-OSA people.

To investigate this hypothesis, the breathing tracheal sounds of 52 participants (healthy individuals and people with different severity degree of OSA) were recorded. Then, participants were classified based on the analysis of recorded sound signals.

Chapter 3

Method

3.1 Data Recording

Fifty two participants (37 males) suspected of having OSA, filled written consent to be enrolled in this study. The study was approved by the Biomedical Research Ethics Board of the University of Manitoba. Forty one of the study participants were referred for full-night PSG assessment at the Sleep Disorder Center at Misericordia Health Center, Winnipeg MB. The other 11 participants were tested with the Acoustic Sleep Apnea Detection (ASAD) box [41]. Based on the subjects' apnea/hypopnea (AHI) scores (determined by the PSG and/or ASAD), we grouped them into non-OSA (AHI $<$ 5), mild (5$<$ AHI $<$ 15), moderate (15$<$ AHI $<$ 30) and severe OSA (30$<$ AHI). The average age, body mass index (BMI) and AHI values of the participants are summarized in Table 3.1.

Tracheal breath sound signals were collected by a Sony microphone (ECM-77B) embedded in a chamber (diameter of 6 mm, with a the 2 mm cone space in its middle)

Table 3.1: *AVERAGE AGE, BODY MASS INDEX (BMI), AHI VALUES OF THE PARTICIPANTS.*

Groups	Number of Subjects	Age	BMI	AHI
AHI<5	17	40.3± 8.0	26.5 ± 5.7	1.3 ± 1.7
5<AHI & AHI<15	13	47.8 ± 9.6	30.8 ± 6.3	11.4 ± 2.8
15<AHI & AHI<30	7	50.6 ± 6.8	29.2 ± 3.1	23.8 ± 4.4
AHI>30	15	49.9 ± 10.4	38.4 ± 5.5	76.7 ± 40.3

placed over the suprasternal notch of trachea using double-sided adhesive tapes. The sound signals were amplified, filtered using a band pass filter (BPF) (0.05-5000 Hz), and digitized at 10240 Hz sampling rate. The recordings were done in two different body positions: upright and supine. In each body position breath sounds were recorded during two breathing maneuvers for at least five full breaths in each trial. The two breathing maneuvers were breathing through the nose and then through the mouth with a nose clip in place at medium flow rate (the subject's comfortable normal medium flow rate). Therefore, for every participant, we recorded a total of 4 breathing signals (2 breathing maneuvers at 2 different body positions). Figure 3.1 shows a sample recorded breathing sound signal.

Out of 52 participants, we excluded the recorded data from 10 subjects that contained vocal noise in the environment.

3.1.1 Signal Analysis

We performed Signal analysis in three steps:

1. onset detection using the method proposed in [42]

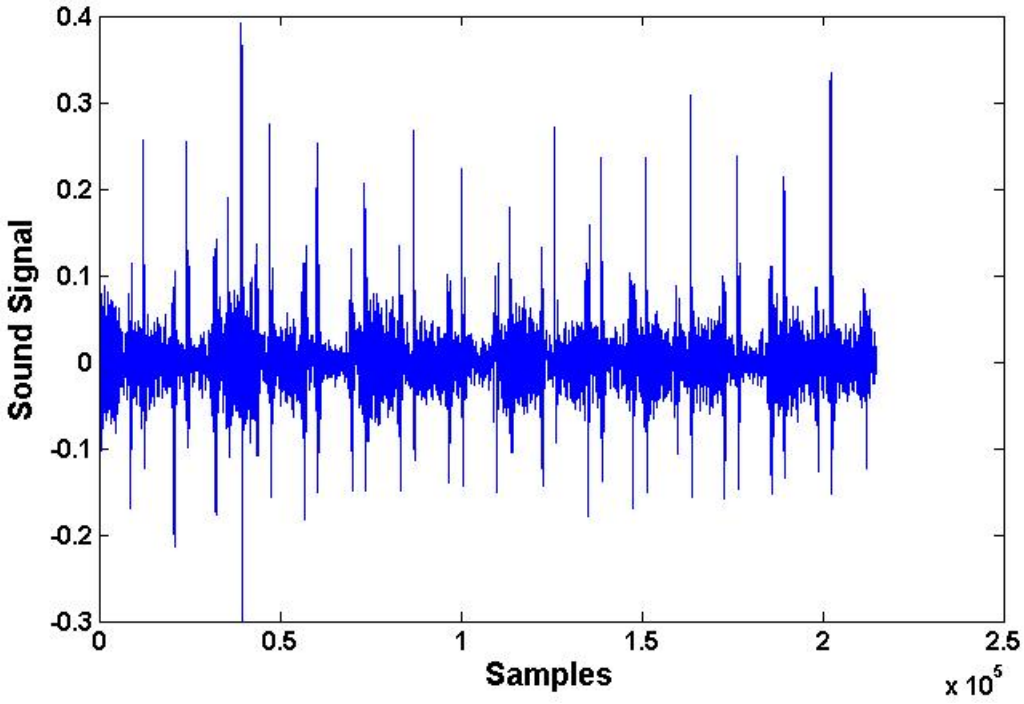


Figure 3.1: *Sample recorded breathing sound signal. (Fs = 10240).*

2. feature extraction using One-Way Analysis of Variance (ANOVA) [43] and Maximum Relevancy Minimum Redundancy (mRMR) [44]

3. classification using Linear and Quadratic Discriminant Analysis [45]

Onset Detection

Inspiration is an active process, while expiration is a passive process. Therefore, we analyzed the inspiration and expiration phases separately. The signals were band pass filtered over 150-800 Hz to reduce the effects of heart sound and background noise. Among several features derived from tracheal breathing sounds, the log of variance of recorded sound signals has been shown to be the best feature for onset detection [42]. Therefore,

we calculated the log of variance of the sound signals in every 50 ms time windows with 50% overlap between successive windows. Then the valleys of the resultant signal were extracted as the potential breath onsets followed by a routine to remove the false onsets, using the method described in [42]. However, in this study, all the detected breath onsets were verified manually as well. Using the detected breath onsets, the inspiratory and expiratory sound signals were extracted from the original data to be analyzed separately. Figure 3.2 shows the flow samples of the recorded flow signal (we used the flow signal which was recorded in [42]) along with the calculated log of variance of tracheal sound over [150-850] Hz. The positive and negative values of the recorded flow signal are related to inspiratory and expiratory phases, respectively. The exact and calculated values of the breathing onsets are depicted on the flow signal and log of variance of the tracheal sounds by the circle marks. It can be seen that the calculated log of variance follows the changes in absolute value of recorded flow signal.

Feature Extraction (Statistical Features)

The feature extraction was performed in three steps. First, we created a large feature space from three main classes of features. Second, we ran One-Way ANOVA test on the features. Third, we used mRMR algorithm to find the best two or three features. We tested the overall statistical significance of the selected features using One-Way MANOVA.

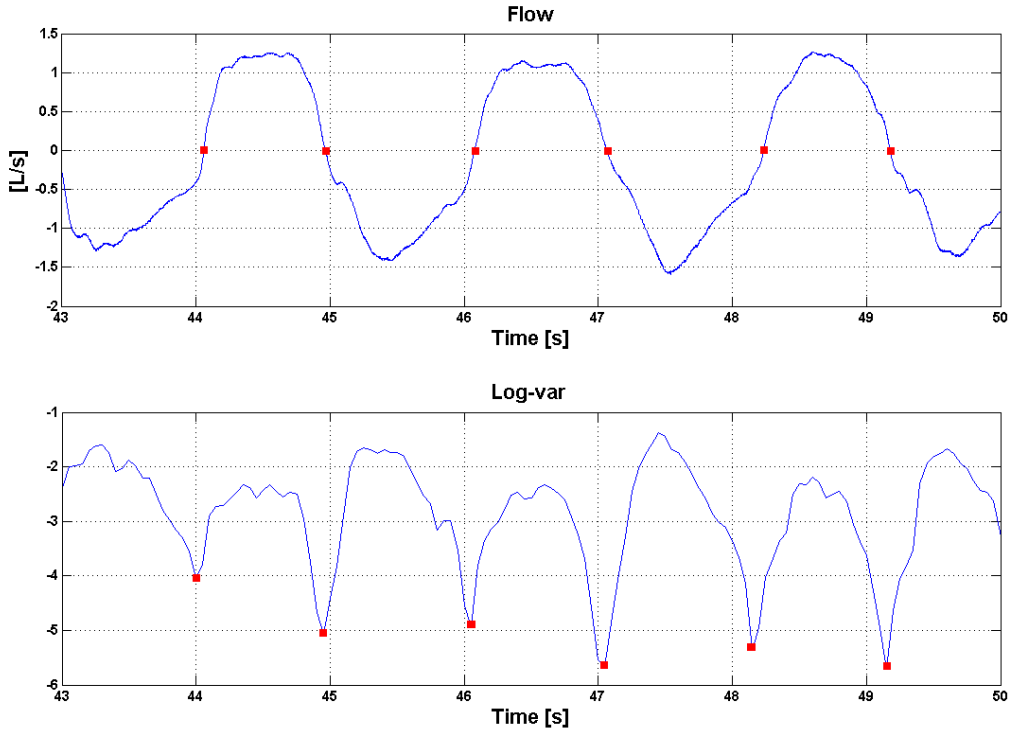


Figure 3.2: *From top to bottom, high flow samples of the recorded signal and the calculated log of variance of the breathing sound (in 50 ms windows with 50% overlap). The red points show the breathing onsets*

Feature Space

For each respiratory phase in each breath, we calculated the power spectrum density (PSD), Katz Fractal Dimension FD and Kurtosis in every 50 ms window with 50% overlap with the adjacent windows, and averaged over the segments within the breath phase, denoted as $P^{(b_i)}$, $FD^{(b_i)}$ and $Kurt^{(b_i)}$ respectively; where b_i represent the breath number 1 to 5. Next, we calculated the average curves of the $P^{(b_i)}$, $FD^{(b_i)}$ and $Kurt^{(b_i)}$ over five breath cycles for each inspiration and expiration separately. They are denoted as Ave^{Pow}, Ave^{FD} and Ave^{Kurt}. Then, the variance and median values of these average curves were

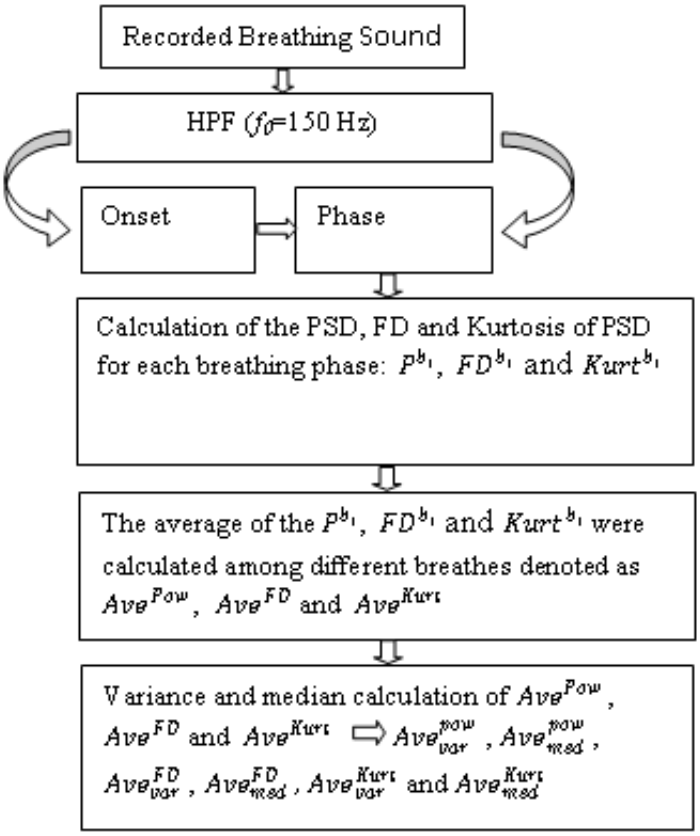


Figure 3.3: *The flowchart of signal processing stages*

calculated, denoted as Var^{ave}_{pow}, Med^{ave}_{pow}, Var^{ave}_{FD}, Med^{ave}_{FD}, Var^{ave}_{Kurt} and Med^{ave}_{Kurt}.

These six features were chosen for further analysis. Figure 3.3 shows the algorithm of the proposed signal processing method up to this stage schematically.

Having recorded in two breathing maneuvers and in two different positions, for each participant we had 4 recorded sound signals. Then, separation of inspiratory and expiratory phases would result in 8 signals per participant. In addition, we investigated the difference between nose and mouth breathing in each position as well as the differences between the positions in each nose and mouth breathing signals, resulting 4 extra signals for each inspiration and expiration phases. Therefore, extracting the 6 features from each signal (16 in total) would result in 96 features in total per participant. Figure 3.4 shows the different conditions for one feature schematically.

ANOVA Test

To select features with statistically significant difference between the subjects, we ran One-Way Anova test on the features. Since the goal was to classify healthy participants (AHI<5) from the participants with severe OSA (AHI>30), and also to estimate the level of severity of each participant; thus, the chosen features must be statistically significant not only between non-OSA and severe OSA but also between OSA individuals with different level of apnea severity. Therefore, first we divided the study participants into two groups: participants with AHI>30 and those with AHI<5. Then, we ran One-Way

ANOVA test on each of the 96 features separately.

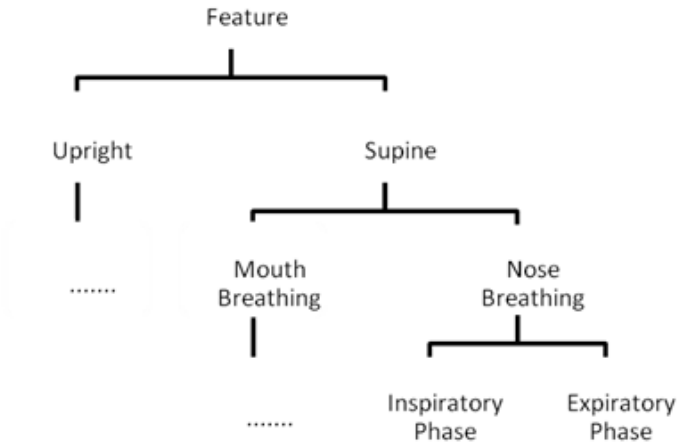


Figure 3.4: *The different conditions for one feature. In addition, to these conditions, we also looked at the difference between mouth breathing and nose breathing and also difference between upright and supine positions.*

Twenty one features were statistically significant between the non-OSA and severe OSA groups ($p_value < 0.05$); these features formed the first selected set. Second, we divided the study participants into participants with AHI>15 and those with AHI<15. We ran the One-Way ANOVA test on the feature set. This time, 17 features were found to be statistically significant between the mentioned groups ($p_value < 0.05$); they formed the second set. Then, out of the first and second set of features, we selected the common features (12) for further analysis.

Maximum Relevancy Minimum Redundancy

To find the best subspace for classification, a search algorithm was needed. We used the Maximum Relevancy Minimum Redundancy (mRMR) method [44]. The mutual

information of two random variables x and y with $p(x)$, $p(y)$ as their probability density function is defined as follow:

$$I(x;y) = \int\int p(x,y) log \frac{p(x,y)}{p(x)p(y)} dxdy. \tag{3.1}$$

The purpose of this feature selection method is to find a feature set S with m features, x_i (in our study $m = 2$). The selected features jointly have the largest dependency on the target classes. This procedure, called Max-Dependency.

$$maxD(S,c), D = I(\{x_i, i = 1, ..., m\}; c)), \tag{3.2}$$

when $m = 1$, the solution is the feature which has individually the highest mutual informal $I(x_i; c)$ with the target class c. Where $m > 1$, an incremental search method is to add one feature at one time. In the other words, by having a set of $m-1$ feature space, S_{m-1}, the mth feature was chosen by maximizing $I(S; c)$. Therefore, we have the following equations:

$$\begin{aligned} I(S_m; c) &= \int\int p(S_m, c) log \frac{p(S_m, c)}{p(S_m)p(c)} dS_m dc \\ &= \int\int p(S_{m-1}, x_m, c) log \frac{p(S_{m-1}, x_m, c)}{p(S_{m-1}, x_m)p(c)} dS_{m-1} dx_m dc \\ &= \int ... \int p(x_1, ..., x_m, c) log \frac{p(x_1, ..., x_m, c)}{p(x_1, ..., x_m)p(c)} dx_1 ... dx_m dc. \end{aligned} \tag{3.3}$$

It is often hard to estimate $p(x_1, ..., x_m)$ and $p(x_1, ..., x_m, c)$ accurately. Hence, an

alternative is to select features which maximize Max-Relevance criteria (3.4). In (3.4), $D(S, c)$ approximated with the mean value of all mutual information values between individual feature x_i and class c:

$$maxD(S, c), D = \frac{1}{|S|}\Sigma_{x \in S} I(x_i; c). \tag{3.4}$$

On the other hand, it has been shown that the m best features are not the best m features for classification [46]. Therefore, some studies tried to reduce redundancy among the features and select the features with minimum redundancy (Min-Redundancy) [46, 47]. In the other words, by removing one of two dependent features, the class-discriminative power would not change. The Min-Redundancy criteria is as follow (3.5):

$$maxR(S, c), R = \frac{1}{|S|^2}\Sigma_{x_i, x_j \in S} I(x_i; x_j). \tag{3.5}$$

By combining (3.5) and (3.4), we can optimize D and R simultaneously:

$$max\Phi(S, c), \Phi = D - R. \tag{3.6}$$

This criterion is called mRMR (3.7). Suppose we selected the feature set with $m - 1$ features, S_{m-1}. We want to find the mth feature by maximizing (3.7) from the set $X - S_{m-1}$. The respective algorithm optimizes the following condition:

$$max_{x_j \in X - S_{m-1}}[I(x_j; c) - \frac{1}{m-1}\Sigma_{x_j \in S_{m-1}} I(x_j; x_i)]. \quad (3.7)$$

MANOVA

After selecting the features, one-way Multivariate Analysis of Variance was run (MANOVA) [43] to verify that the combination of selected features was also statistically significant between the study participants. Figure 3.5 shows the stages of feature selection procedure.

Classification

We used linear discriminant analysis (LDA) and quadratic discriminant analysis (QDA) classifiers as classification methods [45]. Basically, for two class classification, LDA approaches the problem by assuming that the conditional probability density functions are both normally distributed with mean calculated from training set and pooled estimation of covariance matrix. Under this assumption, the Bayes' optimal solution is to predict points as being from the second class if the ratio of the log-likelihoods is below some threshold. On the other hand, QDA approach is the same as the LDA, except for estimation of the covariance matrix which is stratified by group [45].

Using both of these methods, the following measures of accuracy were calcualted: the number of true positives (TP; correctly classified subjects with higher AHI), true negative (TN; correctly classified subjects with lower AHI), false positive (FP; misclassified subjects with lower AHI) and false negative (FN; misclassified subjects with higher AHI)

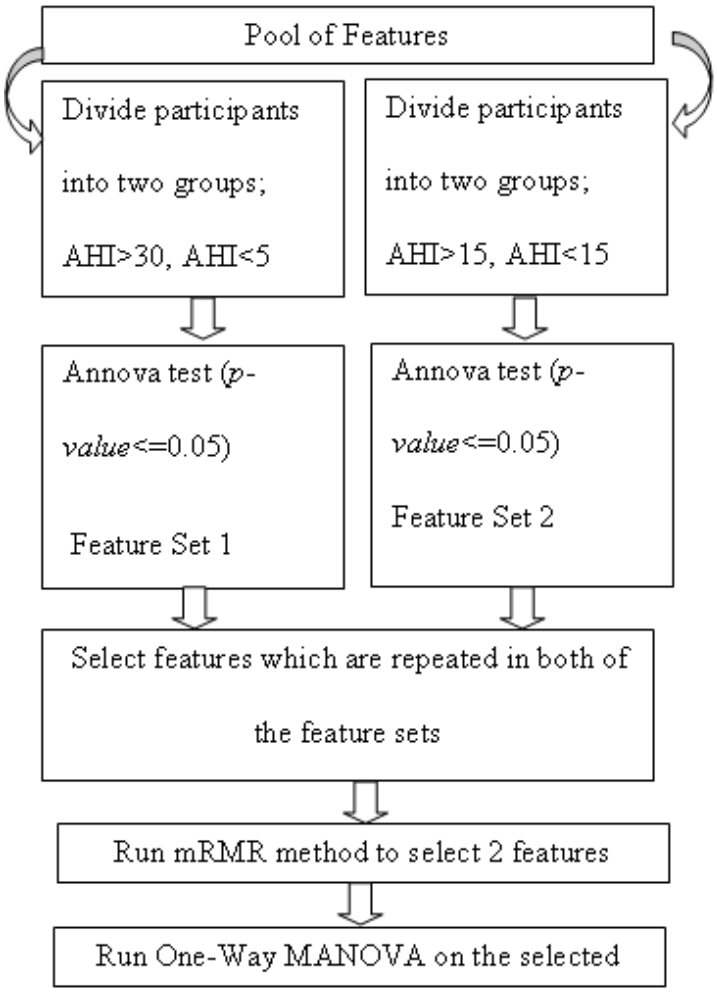


Figure 3.5: *The flowchart of signal processing stages (Feature Extraction)*

and using the Leave One Out method, the sensitivity, specificity and classification accuracy were determined as the followings:

- Sensitivity: $\frac{TP}{TP+FN}.100$
- Specificity: $\frac{TN}{TN+FP}.100$
- Classification Accuracy: $\frac{\text{Number of Correctly Classified Subjects}}{\text{Number of Total Subjects}}.100$

Chapter 4

Results and Discussions

4.1 Results

4.1.1 Selected Features

The feature extraction routine mentioned in Chapter 3 resulted in the following three features:

- MPUNI: Med_{pow}^{ave} of the Upright position, Nose breathing, Inspiratory phase
- MKSNI: Med_{Kurt}^{ave} of the Supine position, Nose Breathing, Inspiratory phase
- VKUNI: Var_{Kurt}^{ave} of the Upright position, Nose breathing, Inspiratory phase

Figure 4.1(a), 4.1(b) and 4.1(c) show the mean and standard deviation of the MPUNI, MKSNI and VKUNI calculated for participants with AHI<15 and AHI>15, respectively. Figures 4.2(a) and 4.2(b) show the 3-D scatter plot of the three selected best features

Table 4.1: *ONE-WAY MANOVA RESULTS OF SELECTED FEATURE SPACES (3D & 2D) BETWEEN PARTICIPANTS WITH AHI<5 & AHI>30 AND AHI<15 & AHI>15*

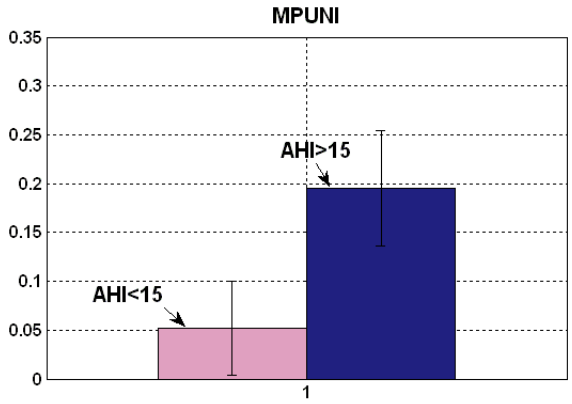
	AHI<5 &30<AHI	15<AHI & AHI<15
2D	1.810^{-4}	1.410^{-4}
3D	0.005	0.001

for participants with AHI<15 and AHI>15 and for those with AHI<5 and AHI>30, respectively.

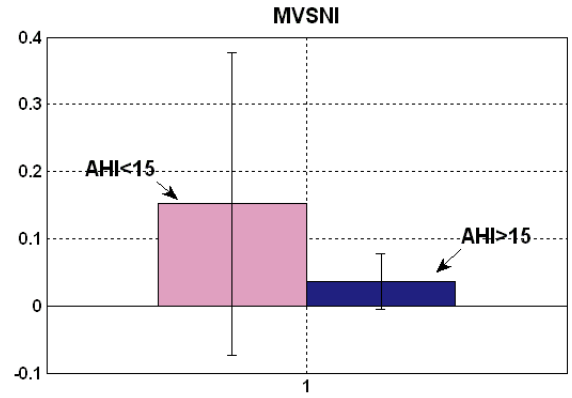
When we limited the best features to 2, MPUNI and VKUNI were selected again. The 2D scatter plot are shown as in Fig. 4.3 and 4.4(a) for the participants with AHI<5 and AHI>30 and those with AHI<15 and AHI>15 using the two best features: MPUNI and VKUNI. Figures 4.4(b) and 4.4(c) show the mean and standard deviation of the calculated MPUNI and VKUNI, respectively for the mentioned groups.

4.1.2 MANOVA

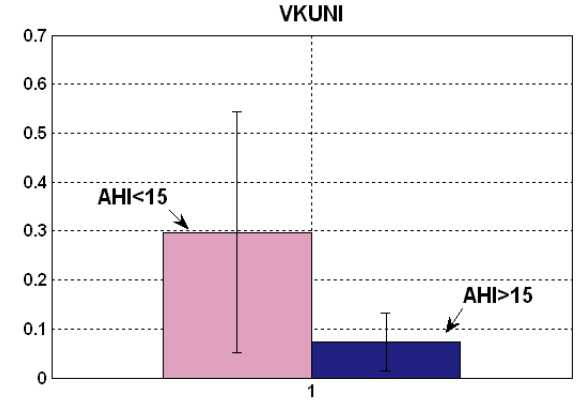
To ensure whether the three or two selected best features were also statistically significant between the groups, we ran MANOVA statistical test. The test showed p_values less than 0.001 among the groups of AHI>15 and AHI<15 and also among the groups of AHI<5 and AHI>30. Therefore, these features were selected to classify participants with different OSA severity. The results are shown in Table 4.1.



(a)

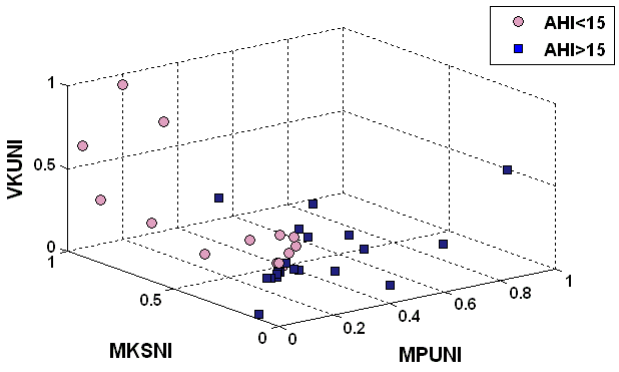


(b)

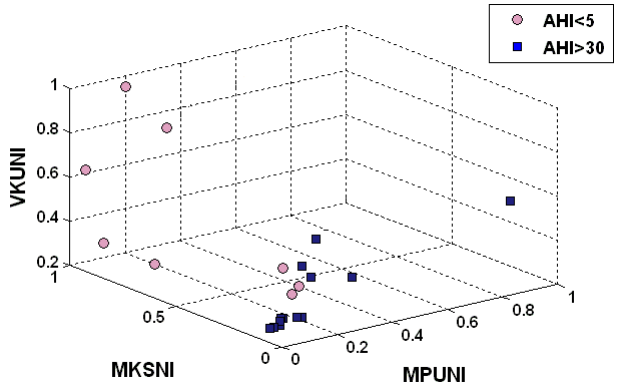


(c)

Figure 4.1: *(a)The mean and standard deviation of the MPUNI for participants with AHI<15 and AHI>15; (b) the mean and standard deviation of the MVSNI for the mentioned groups; (c) the mean and standard deviation of the VKUNI for the mentioned groups.*



(a)



(b)

Figure 4.2: *(a) The 3-D scatter plot (MPUNI, MKSNI, VKUNI) for subjects with AHI<15 and AHI>15. Circles represent subjects with AHI<15; squares represent subjects with AHI>15. (b) The 3-D scatter plot (MPUNI, MKSNI, VKUNI) for subjects with AHI<5 and AHI>30.*

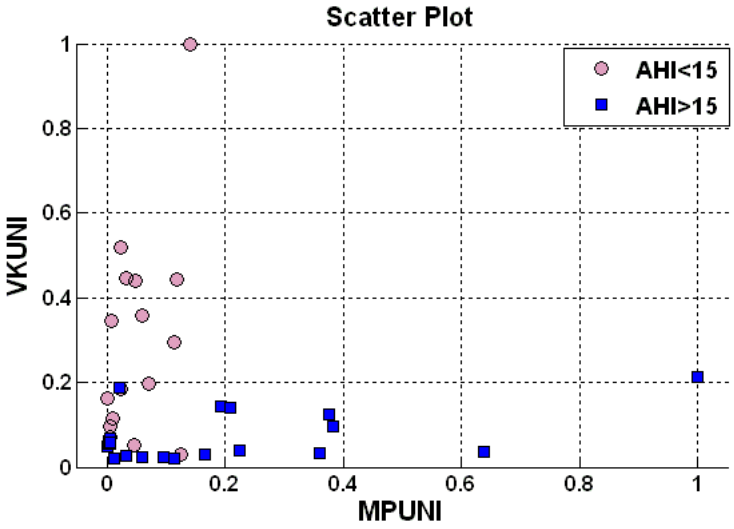
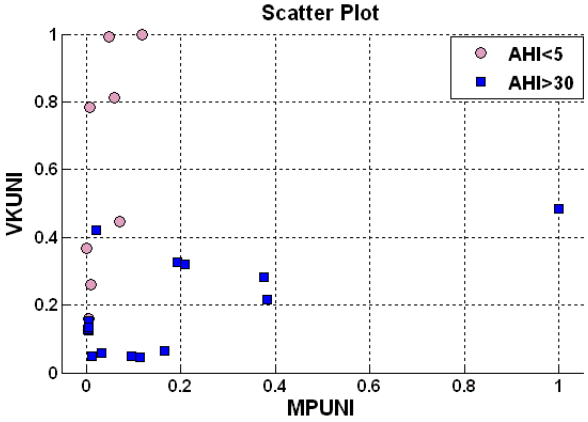
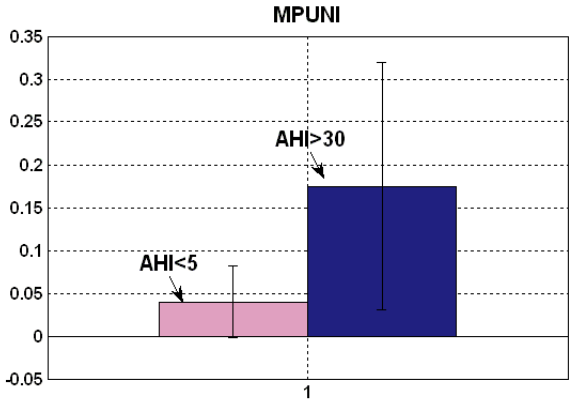


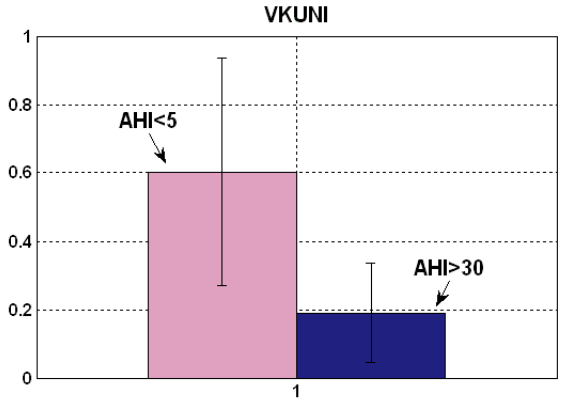
Figure 4.3: *The 2-D scatter plot (MPUNI, VKUNI) for subjects with AHI<5 and AHI>30.*



(a)



(b)



(c)

Figure 4.4: *(a)The 2-D scatter plot (MPUNI, VKUNI) for subjects with AHI<5 and AHI>30; (b) the mean and standard deviation of the MPUNI for the mentioned groups; (c) the mean and standard deviation of the MPUNI for the mentioned groups.*

4.1.3 Classification

Tables 4.2 and 4.3 show the specificity, sensitivity and classification accuracy achieved using LDA classifier for 2D and 3D feature spaces, respectively. We calculated these values using the Leave-One-Out method [45]. Tables 4.4 and 4.5 show the same results of the same test as in Tables 4.2 and 4.3 but using the QDA classifier.

Table 4.2: *SENSITIVITY, SPECIFICITY AND CLASSIFICATION ACCURACY FOR THE LDA CLASSIFIER USING MPUNI, VKUNI AND MKSNI AS THE CLASSIFICATION FEATURES*

LDA Classifier	Sensitivity	Specificity	Classification Accuracy
AHI<5 & AHI>30	92.3%	50.0%	78.9%
AHI<15 & AHI>15	94.6%	57.1%	77.4%

Table 4.3: *SENSITIVITY, SPECIFICITY AND CLASSIFICATION ACCURACY FOR THE LDA CLASSIFIER USING MPUNI AND VKUNI AS THE CLASSIFICATION FEATURES*

LDA Classifier	Sensitivity	Specificity	Classification Accuracy
AHI<5 & AHI>30	92.9%	75.0%	86.4%
AHI<15 & AHI>15	95.0%	68.8%	83.3%

Table 4.4: *SENSITIVITY, SPECIFICITY AND CLASSIFICATION ACCURACY FOR THE QDA CLASSIFIER USING MPUNI, VKUNI AND MKSNI AS THE CLASSIFICATION FEATURES*

QDA Classifier	Sensitivity	Specificity	Classification Accuracy
AHI<5 & AHI>30	100.0%	83.3%	94.7%
AHI<15 & AHI>15	88.9%	69.2%	81.7%

Table 4.5: *SENSITIVITY, SPECIFICITY AND CLASSIFICATION ACCURACY FOR THE QDA CLASSIFIER USING MPUNI AND VKUNI AS THE CLASSIFICATION FEATURES*

QDA Classifier	Sensitivity	Specificity	Classification Accuracy
AHI<5 & AHI>30	92.9%	75.0%	86.4%
AHI<15 & AHI>15	95.0%	68.8%	83.3%

4.1.4 2D Classification

Overall, QDA classifier outperformed the LDA. Using the QDA classifier, the overall accuracy for classifying the groups of non-OSA and severe OSA with 2D classifier as well as those above and below AHI=15 were 91.7% and 83.3%, respectively; using the LDA classifier, they were 86.4% and 83.3%, respectively. Except for the sensitivity for classifying participants with AHI<15 from AHI>15, the QDA classifier out performed the LDA classifier.

For further investigation, we extracted the AHI of the misclassified participants in both classification approaches using either LDA or QDA. When classifying the severe OSA from non-OSA individuals, three subjects with AHI of 3.6, 3.9 and 30.7 with either LDA or QDA were misclassified. On the other hand, when using AHI=15 as the threshold to divide people into two groups, the AHI of misclassified subjects were 3.6, 3.9, 10.3,13.7, 14 and 30.7 using LDA and 3.6, 13.7, 14, 30.7, 35.6 and 115.6 using QDA.

Figure 4.5 shows the 2D scatter plot of the two selected features of all the participants in different AHI groups. TN, FP, TP and FN represent:

- The misclassified participants with AHI<15 (FP)

- The participants with AHI>15 classified correctly (TP)
- The misclassified participants with AHI>15 (FN)
- The misclassified participants with AHI<15 (FP)

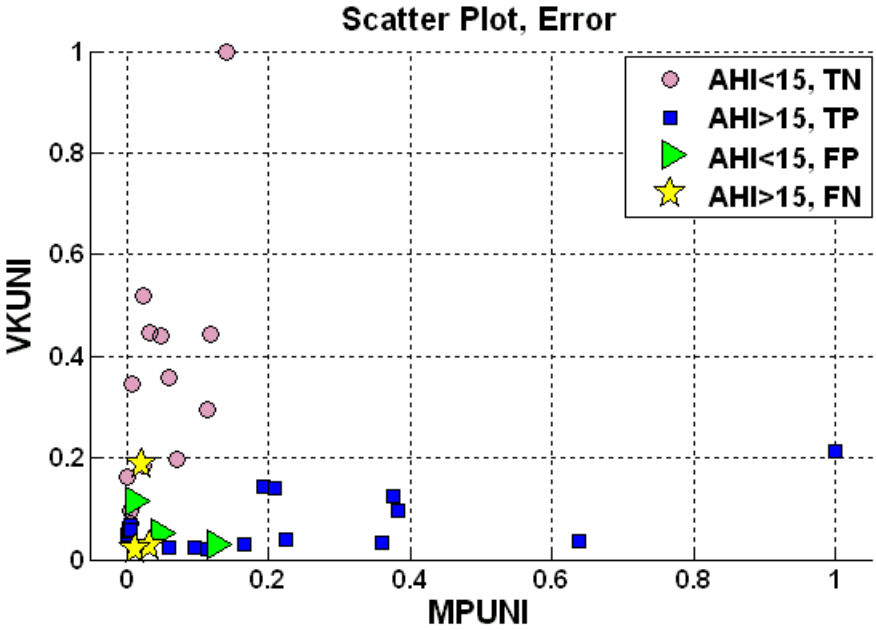


Figure 4.5: *The 2-D scatter plot (MPUNI, VKUNI) for participants with AHI<15 and AHI>15. The figure shows four different groups: the participants with AHI<15 classified correctly (TN); the misclassified participants with AHI<15 (FP); the participants with AHI<>5 classified correctly (TP); the misclassified participants with AHI>15 (FN).*

4.2 Discussion

People with OSA disorder usually have smaller and more collapsible pharynx than healthy individuals [15, 48, 21, 49, 50]. It is known that muscle tone naturally decreases during sleep. In a non-OSA individual, the decrease in dilator muscle activity does not obstruct the airway. However, in people with OSA a decrease in dilator muscle activity leads their airway to collapse and obstruct the airflow as the dilator muscle activity is not enough to maintain the pharynx sufficiently open during sleep [18, 51]. In the other words, OSA is a product of decrement in muscle activities superimposed upon abnormal airway anatomy. The level of dilators muscles activation to maintain adequate ventilation is determined by the passive pharynx properties. Pharynx is connected to bone and cartilage (larynx) at it extremes upper and lower ends. Therefore, its area varies with luminal pressure [7, 18, 21, 49-52]. There is a certain lumen pressure, in which the pharynx is closed (Pclose). Above the Pclose, the pharynx area increases by increasing in the pressure; the relation between pressure and area is nonlinear [7]. When negative pressure is applied to one end of a pharynx, air flow increases as a function of the applied pressure.

In addition, it has been shown that the pharyngeal muscles respond to the change in the local upper airway milieu during wake time. The most important local stimulus to pharyngeal dilator muscle activity is negative intraluminal airway pressure [7]. The increased negative airway pressure stimulate upper airway muscle activity; hence, dilate the pharyngeal airway and maintain reasonable level of airflow resistance during wakefulness.

In the other words, people with OSA compensate for their more collapsible airway by an increased activity of their the dilator muscles during wakefulness and the increased dilator muscle activity represents the increased negative pressure of the pharynx [7].

On the other hand, the intensity of tracheal breath sounds represents the pharyngeal pressure almost linearly during normal breathing (no flow limitation condition) [53]; this has been the premise of the acoustic flow estimation method [30]. Given the above mentioned facts and knowing that the tracheal sounds intensity represents the pharyngeal pressure, we hypothesized that there must be some notable differences between the breath sounds of people with different OSA severity during wakefulness.

The goals of this study were to investigate the above hypothesis, and offer a simple and non-invasive method to identify people with different OSA severity during wakefulness. We focused on classifying participants with AHI>30 from those with AHI<5 and also people with AHI>15 from those with AHI<15. The main objective was to find a robust feature set for classifications of different AHI ranges.

The results on the selected features are congruent with physiological facts about airway structure associated with OSA as mentioned above. The MPUNI is a feature derived from average power of the breath sounds during inspiratory phase of nose breathing, when the pharyngeal pressure is more negative. The higher MPUNI values in the people with OSA represent more negative pressure and turbulence of air in their airway (Figures 4.1(a) and 4.4(b)); this result is congruent with the above mentioned physiological change in airway

structure due to OSA.

The other selected features were MKSNI and VKUNI, which are median and variance of the kurtosis during inspiratory nose breathing. Kurtosis, in general, is a measure of peakedness of the distribution of the random variables respect to normal distribution. As we calculated the kurtosis in 50 ms windows, we had a vector of kurtosis for each signal. Therefore, higher values of variance and median of kurtosis may represent higher variation in flatness and non-flatness of distribution of signal in different windows, respectively. In other words, higher variation in distribution of signal is related to the higher complexity of the signal. Studies on biological signals have often reported an association between the pathological signals and loss of complexity [54, 55]. The lower variability of the kurtosis in our OSA data may also be due to lower complexity of pathological signals (Figures 4.1(b), 4.1(c) and 4.4(c)).

The clusters obtained from non-OSA participants (AHI<5) and those with severe OSA (AHI>30) are more distinguishable due to the gap between the AHI range of participants. Thus, the classification results were expected to be better for the mentioned groups as opposed to when classifying two groups below and above the threshold of AHI=15 (Table 4.3, 4.2, 4.5 and 4.4).

As it can bee seen, the classification results show higher sensitivity values than specificity. This could be due to two reasons. First, the number of subjects in each group was not balanced. We recorded data from 17 healthy participants and 35 patients with different

severity of OSA. Therefore, a shift in the classification boundary toward the apneic subjects was expected, which results in higher specificity. Second, our non-OSA data included data from simple snorers, whom airway might be similar to the patients with OSA.

Since the classification results were very similar for 2D and 3D classifiers (the one with 2D was slightly better), we used the results of 2D classification for further investigation. In general the smaller size of the feature set, the more robust is the classification result in terms of a change in population. In other words, we may achieve a higher accuracy using more features for this particular population, but then the chance to achieve the same accuracy with the same feature set in a larger population is less. Therefore, in pilot studies with small population, it is recommended to select the smaller feature sets and simple classifications.

Except for two misclassified subjects, the AHI of the rest of misclassified cases were very close to the boundaries of the classification (Fig. 4.5). Note that in determining our classification accuracies, we only used the AHI values and not the overall diagnosis of the participants. Obviously, one cannot say the severity of the OSA of a person with AHI of 14 is indeed different from the one with AHI of 16. The AHI values can be slightly different depending on who scores the PSG.

It should be noted that in the hospital (in Winnipeg), where we recorded our data, the PSG is assessed manually. Manual assessment of PSG is considered to be more accurate than automatic scoring; though it is expected to have slight differences in the AHI values

depending on who scores the PSG [56]. Nevertheless, while the AHI is one of the most important factors in diagnosis of OSA, it is not yet the only factor determining the severity of OSA. Therefore, we expected to have some misclassified cases especially for those with AHI close to the boundaries. Moreover, due to the small size of our study subjects, we did not group the subjects in terms of their anthropometric parameters, i.e. gender, BMI, height, as well as their smoking history that have an impact on the tracheal respiratory sounds. These are important parameters that should be considered in future studies.

Chapter 5

Conclusion & Future Work

5.1 Summary & Conclusion

In this study a novel method using breath sound analysis has been proposed for OSA severity assessment during wakefulness. We showed that, features representing average power and kurtosis of the sound signals are characteristic features that can be used for screening OSA severity. We tested our proposed method on 42 subjects; the preliminary results showed a good separability between the groups with different severity of OSA. The results show over 88% and 77% sensitivity and classification accuracy (for classifying participants with different degrees of OSA severity), respectively.

The results of this study are encouraging, and pave the way for a simple, non-invasive, and inexpensive screening tool for people suspected of OSA; it estimates the degree of severity of the OSA during wakefulness.

5.2 Suggestion For Feature Works

A number of open problems must be solved to allow the development of a screening apnea device. First, it is desirable to create a data bank of 500 participants based on the body mass index, gender, age and smoking condition of subjects. Second, the result of unsupervised clustering should be reevaluated; third, the quality of recording breathing sound signals with different microphones should be compared and their effect on OSA detection should be investigated.

Age, gender, obesity are major factors contributing to narrowing, increased resistance and collapsibility of the upper airway. Currently, we are in the process of creating a data bank of 500 participants based on the subjects' body mass index, gender, age and smoking condition.

The accuracy of the diagnosis method during wake time can be improved through enhancing the classification algorithms. As a future study, the method has to be tested in a double blind study.

In our proposed sleep apnea detection system, we record breathing sound signals using a Sony microphone (ECM-77B) which is fairly expensive. In order to commercialize our method, we need to test cheaper microphones. Therefore, the recorded sound signals with different microphones must be compared with each other.

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Appendix

Appendix A

One-Way Anova

One-Way ANOVA is needed to compare different variables or different levels of a single variable. Suppose we have n observations and the response from each of these observations is a random variable. Table A.1 shows the observations; for example, y_{ij} represents the jth observation taken under factor level i. In this study, we had two states: (AHI<5 & AHI>30) and (AHI<15 & AHI>15). The total number of observation was 52 (number of subjects). It is useful to denote the observation with the following models:

Table A.1: *DATA FOR A SINGLE-FACTOR EXPERIMENT.*

Treatment Level	Observation			
1	y_{11}	y_{12}	$\cdots$	y_{1n}
2	y_{21}	y_{22}	$\cdots$	y_{2n}
$\vdots$	$\vdots$	$\vdots$	$\vdots\vdots$	$\vdots$
a	y_{a1}	y_{a2}	$\cdots$	y_{an}

$$y_{ij} = \mu_i + \epsilon_{ij}\{i = 1, 2, ..., a; j = 1, 2, ..., n\}, \tag{A.1}$$

$$y_{ij} = \mu + \tau_i + \epsilon_{ij}\{i = 1, 2, ..., a; j = 1, 2, ..., n\}. \tag{A.2}$$

Where y_{ij} is the ijth observation, μ_i is the mean of ith factor, and ϵ_{ij} is a random error. In eq. A.2, the mean of each factor (μ_i) is estimated with the overall mean (μ), and ith treatment effect (τ_i). The observed variable y_{ij} is a linear function of the model parameters.

Equation A.1 is called the means model, while eq. A.2 is called the effects model. They are also called one-way or single-factor analysis of variance model, because only one factor is investigated. The objective is to test appropriate hypotheses about the factors means and estimate them. The model errors are assumed to be normally and independently distributed random variables with zero mean and variance (σ^2). This implies that the observations to be mutually independent and have the following form:

$$y_{ij} \sim N(\mu + \tau_i, \sigma^2). \tag{A.3}$$

A.1 Analysis

Assume that y_i represent the sum of observations of the ith factor, and $y_{..}$ represents the some of all observations:

$$\begin{aligned} y_i &= \Sigma_{j=1}^{n} y_{ij}; i = 1, 2, ..., a, \\ y_{..} &= \Sigma_{i=1}^{a} \Sigma_{j=1}^{n} y_{ij}. \end{aligned} \tag{A.4}$$

We are interested in testing the equality of the factors means. $E(y_{ij}) = \mu + \tau_i = \mu_i, i = 1, 2, ..., a$. The hypothesis is:

$$H_0 : \mu_1 = \mu_2 = ... = \mu_a,$$

$$H_1 : \mu_i \neq \mu_j \text{ for at least one pair (i,j).} \tag{A.5}$$

In the effects model (eq. A.2), we assume that $\mu_i = \mu + \tau_i$, where μ is the overall mean and calculated as follow:

$$\mu = \frac{\Sigma_{i=1}^{a} \mu_i}{a}. \tag{A.6}$$

This definition implies that $\Sigma_{i=1}^{a} \tau_i = 0$; therefore an alternative way for writing eq. A.9 is:

$$H_0 : \tau_1 = \tau_2 = ... = \tau_a,$$

$$H_1 : \tau_i \neq 0 \text{ for at least one pair (i,j).} \tag{A.7}$$

The appropriate procedure for testing the equality of a treatment mean is the analysis of variance.

Decomposition of the total sum of squares

The total corrected sum of squares is used as a measure of overall variability in the data;

$$SS_T = \Sigma_{i=1}^{a} \Sigma_{j=1}^{n} (y_{ij} - \bar{y}_{..})^2. \tag{A.8}$$

SS_T can be rewritten as:

$$\begin{aligned}\Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(y_{ij}-\bar{y}_{..})^2 &= \Sigma_{i=1}^{a}\Sigma_{j=1}^{n}[(\bar{y}_i-\bar{y}_{..})+(y_{ij}-\bar{y}_i)]^2 \\ &= n\Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(\bar{y}_i-\bar{y}_{..})^2+\Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(y_{ij}-\bar{y}_i)^2 \\ &\quad +2\Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(\bar{y}_i-\bar{y}_{..})(y_{ij}-\bar{y}_i). \qquad \text{(A.9)}\end{aligned}$$

As $\Sigma_{j=1}^{n}(y_{ij}-\bar{y}_i)=y_i-n\bar{y}_i=0$; therefore, we have:

$$\Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(y_{ij}-\bar{y}_{..})^2 = n\Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(\bar{y}_i-\bar{y}_{..})^2+\Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(y_{ij}-\bar{y}_i)^2. \qquad \text{(A.10)}$$

The first part of eq. A.10 shows the difference between the observed treatment averages and the grand average which is a measure between treatment means. On the other hand, the second part of eq. A.10 shows the difference of observations within a treatment from the treatment average which can be due only to random error. Hence, we have:

$$SS_T = SS_{Treatments} + SS_E. \qquad \text{(A.11)}$$

$SS_{Teatment}$ is the sum of squares due to treatment (between treatments), and SS_E is the sum of squares due to error(within treatment). There are N observations ($N=an$). We have:

$$SS_E = \Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(y_{ij}-\bar{y}_i)^2 = \Sigma_{i=1}^{a}[\Sigma_{j=1}^{n}(y_{ij}-\bar{y}_i)^2]. \qquad \text{(A.12)}$$

The term within the brackets, is the sample variance for the ith factor multiplied by $n-1$, or

$$S_i^2 = \frac{\Sigma_{j=1}^n (y_{ij} - \bar{y}_i)^2}{n-1} \; i = 1, 2, ..., a. \tag{A.13}$$

By combining the S_is, we have:

$$\begin{aligned} \frac{(n-1)S_1^2 + ... + (n-1)S_n^2}{(n-1) + ... + (n-1)} &= \frac{\Sigma_{i=1}^n [\Sigma_{j=1}^n (y_{ij} - \bar{y}_i)^2]}{\Sigma_{i=1}^a (n-1)} \\ &= \frac{SS_E}{(N-a)}, \end{aligned} \tag{A.14}$$

where $\frac{SS_E}{(N-a)}$ is a pooled estimate of common variance. In addition, we have $\frac{\Sigma_{i=1}^a (\bar{y}_i - \bar{y}_{..})^2}{a-1}$ is an estimate of σ^2/n (if there is no difference in the treatment means). Hence, $\frac{SS_{Treatment}}{a-1}$ estimates σ^2.

For further analysis, the quantities $MS_{Treatment} = \frac{SS_{Treatment}}{a-1}$ and $MS_E = \frac{SS_E}{N-a}$ aare called mean squares. The expected values of these mean squares value were calculated as follow:

$$\begin{aligned} E(MS_E) = E(\frac{SS_E}{N-a}) &= \frac{1}{N-a} E[\Sigma_{i=1}^a \Sigma_{j=1}^n (y_{ij} - \bar{y}_i)^2] \\ &= \frac{1}{N-a} E[\Sigma_{i=1}^a \Sigma_{j=1}^n (y_{ij}^2 - 2y_{ij}\bar{y}_i + \bar{y}_i^2)] \\ = \frac{1}{N-a} E[\Sigma_{i=1}^a \Sigma_{j=1}^n y_{ij}^2 - 2n\Sigma_{i=1}^a \bar{y}_i^2 + n\Sigma_{i=1}^a \bar{y}_i^2] \\ &= \frac{1}{N-a} E[\Sigma_{i=1}^a \Sigma_{j=1}^n y_{ij}^2 - \frac{1}{n}\Sigma_{i=1}^a y_i^2]. \end{aligned} \tag{A.15}$$

By applying the effect model, we obtain:

$$E(MS_E) = \frac{1}{N-a} E[\Sigma_{i=1}^{a}\Sigma_{j=1}^{n}(\mu + \tau_i + \epsilon_{ij})^2 - \frac{1}{n}\Sigma_{i=1}^{a}(\Sigma_{j=1}^{n}\mu + \tau_i + \epsilon_{ij})^2]. \quad \text{(A.16)}$$

By replacing ϵ_{ij}^2 and ϵ_i^2 byσ^2 and $n\sigma^2$, respectively and knowing that $E(\epsilon_{ij}) = 0$, eq. A.16 takes the following form:

$$\begin{aligned} E(MS_E) &= \frac{1}{N-a}[N\mu^2 + n\Sigma_{i=1}^{a}\tau_i^2 + N\sigma^2 - N\mu^2 - n\Sigma_{i=1}^{a}\tau_i^2 - a\sigma^2] \\ &= \sigma^2. \end{aligned} \quad \text{(A.17)}$$

Using the same approach, we have:

$$E(MS_{Treatment}) = \sigma^2 + \frac{n\Sigma_{i=1}^{a}\tau_i^2}{a-1}. \quad \text{(A.18)}$$

Therefore; $MS_E = SS_E/(N-a)$ estimates σ^2 and if there are no differences in the treatment means ($\tau_i = 0$), then $MS_{Treatment}$ also estimates σ^2. The test of hypothesis of equal means for each factor can be performed by comparing $MS_{Treatment}$ and MS_E. There are different methods for comparing these values [43]. In addition of the data in which the number of observations are not same (This study), the **unbalanced analysis of variance** is used [43]. There are slight differences in the balanced and unbalanced analysis.

Appendix B

Patents & Publications

B.1 Patent

- Moussavi, Z., A. Montazeri. SYSTEM AND METHODS OF ACOUSTICAL SCREENING FOR OBSTRUCTIVE SLEEP APNEA DURING WAKEFULNESS, U.S. Patent, Pending

B.2 Publications

B.2.1 Journal Papers

- Montazeri, A., Moussavi, Prediction of Obstructive Sleep Apnea and its Severity during Wakefulness , Annals of Biomedical Engineering (ABME), DOI: 10.1007/s10439-011-0456-5

B.2.2 Conference Papers

- Montazeri, A., Moussavi, Z., Prediction of Sleep Apnea and Its Severity Level during Wakefulness, The 33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2011)

- Moussavi, Z.,Montazeri, A., Obstructive Sleep Apnea Prediction by Breath Sound Analysis during Wakefulness, The 25th Annual Meeting of the Associated Professional Sleep Societies (Sleep 2011), Minneapolis, MN, USA, June 201

- Montazeri, A., Moussavi, Z., Acoustical Screening for Obstructive Sleep Apnea during Wakefulness, The 32nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2010), Buenos Aires, Argentina, August 201

- Montazeri, A., Moussavi, Z., Evaluation of Tracheal Respiratory Sounds at Different Body Positions in Healthy and Patients with Obstructive Sleep Apnea during Wakefulness, The 24th Annual Meeting of the Associated Professional Sleep Societies (Sleep 2010), San Antonio, TX, USA, June 201