AN INVESTIGATION OF PERIPHERAL BLOOD VOLUME AND OXYGEN SATURATION CHANGE IN OBSTRUCTIVE SLEEP APNEA

by

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DEDICATION

This thesis is dedicated to my parents, brother and sister in law.

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ABSTRACT

AN INVESTIGATION OF PERIPHERAL BLOOD VOLUME AND

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SLEEP APNEA

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Obstructive sleep apnea (OSA) is a type of sleep disordered breathing in which the airway collapse partially or fully and causes arousal to resume breathing. In a 2009 National sleep foundation poll of 1000 people, 63% of men and 50% of the females showed signs of sleep apnea. It also showed that subjects with sleep apnea have high risk of high blood pressure, stroke and mental disorders such as depression especially in female. Also by another group of researcher it has been shown that the prevalence of OSA is 4% in male and 2% in female. It has been also shown that 1 out of 20 adults are undiagnosed of OSA and this leads to cardiovascular morbidity.

This investigation employed pulse oximetry to see the changes in the peripheral blood flow and the percentage oxygen saturation during simulated OSA. The effect of

gravity (posture) on the peripheral blood flow and oxygen saturation was also studied. Features such as peak, nadir, peak to peak time, area under the curve, the amplitude of the photoplethysmography waveform and the rate of drop of oxygen saturation were analyzed. In addition, data were also collected from sleep apnea patients during sleep.

The results shows that there is a difference in the area under the curve and the peak to peak time between the simulated apnea and normal breathing. For Sitting protocol A the average and the standard deviation for baseline is 0.4±0.098 (A.U.) and for the simulated apnea it is 0.57±0.087 (A.U.). The increase in the area under the curve is observed for rest of the protocol/positions. Similarly the peak to peak increase in breath hold as compared to baseline. For sitting protocol A, the average and the standard deviation are 0.41±0.084 (s) for baseline and 0.56±0.078 (s) for breath hold. But for the actual sleep apnea study these trends were not observed which might be due to less number of subjects. The drop in the oxygen saturation was quite different for simulated and the actual sleep apnea. The average and the standard deviation for the normal breathing was found to be -0.0015±0.002 and for apnea it was -0.2669±.044. Also these features were significantly different. Also there was no gravity effect and the effect of frequency of apnea observed.

Hence we may say that the heart rate decreases (peak to peak time increases), the peripheral volume increases (area under the curve increases) and there is a drop in the oxygen saturation during apnea.

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CHAPTER 1

INTRODUCTION

1.1 Sleep apnea

Sleep apnea consists of repetitive reduction or the cessation of breathing during sleep. The breathing pauses last few seconds to over a minute. This leads to a decrease in oxygen saturation by 4% or more as well as sleep fragmentation [1, 2].

In 2009, the National Sleep Foundation poll, one thousand random subjects (equal number of male and female) were chosen for telephonic interview. Results revealed that 63% of male showed signs of sleep apnea at least a few nights in a week in the previous month of study than 50% of the females and from these 56% of the subjects were obese. It also showed that subjects with sleep apnea have high risk of high blood pressure, stroke, mental disorders such as depression especially in female [3]. The prevalence of OSA is 4% in male and 2% in female. It has been also shown that 1 out of 20 adults are undiagnosed of OSA and this leads to cardiovascular morbidity [4].

There are basically two main types of sleep apnea: central sleep apnea (CSA) in which there is a lack of respiratory effort and obstructive sleep apnea (OSA) which occurs when the throat muscle relaxes. There is yet another type known as complex sleep apnea which is the combination of both obstructive and central sleep apnea [5].

1.1.1 Central sleep apnea

Central sleep apnea occurs when there is a lack of respiratory effort which is controlled by the brain stem [5]. CSA can be classified into 1) idiopathic CSA, 2) Cheyne-Stokes respiration: caused mainly by congestive heart failure or stroke, 3) High-altitude periodic breathing: caused above an altitude of 15,000 feet due to change in barometric pressure and 4) Drug induced apnea: caused by consumption of certain drugs such as opiod. Various adverse effects of CSA include abrupt awakening due to the lack of breathing, day time sleepiness, difficulty in concentrating and cardiovascular risks [5, 6].

1.1.2 Obstructive sleep apnea

Obstructive sleep apnea occurs when the throat muscles temporarily relax, the airway is either narrowed or closed and there is an interruption in breathing. Figure 1.1 shows the site of obstruction during OSA [5].

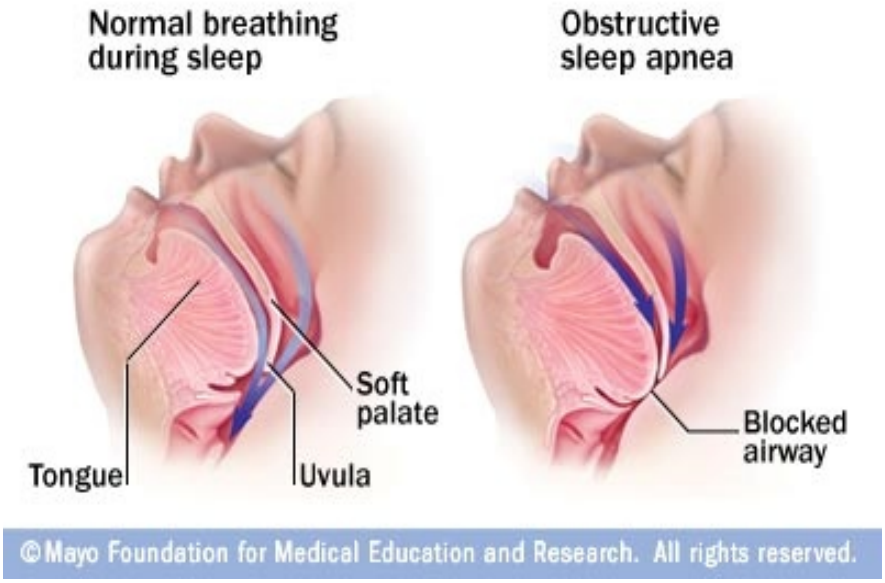


Figure 1.1 Site of obstruction during OSA [5]

The apnea hypopnea index (AHI) quantifies the frequency in reduction or cessation of airflow with sleep apnea. The main symptoms of OSA are similar to those from CSA include excessive day time sleepiness and fatigue. It has been shown that AHI correlates with day time sleepiness [7].

OSA may lead to many cardiovascular diseases like hypertension, heart failure, stroke, cardiac arrhythmia, etc. In OSA 1) Hypertension is caused or exaggerated by the activation of chemoreflex which is followed by the increase in the sympathetic activation. 2) The chronic increase in blood pressure contributes to heart failure. 3) The causes of stroke include less blood flow during an apnea event and hypertension. 4) The cardiac arrhythmia is caused due to the increase in the vagal tone due to apnea and hypoxemia [1].

1.2 Photoplethysmography

Photoplethysmography (PPG) can be used to detect blood volume changes in the micro vascular bed of tissue. It consists of two parts 1) Pulsatile part (AC) which represents the cardiac synchronous change in the blood volume for each heart beat and 2) Slowly varying baseline (DC) which represents sympathetic nervous system activity, respiration and thermoregulation.

Figure 1.2 shows the AC component of the PPG which indicates the increase in the attenuation of light proportional to the increase in the volume of the blood in the microvasculature of the tissue. Almost all the PPG waveforms are inverted before they are displayed on the pulse oximeter monitor.

Figure 1.2 Pulsatile component of PPG waveform [8]

Clinical applications of PPG include deriving blood oxygenation, cardiac output, heart rate and systolic pressure by utilizing the pulse transit time which is the time lag between R peak of ECG and foot of PPG waveform [8].

PPG is easily obtained from pulse oximeters. Along with the percentage of oxygen saturation, pulse oximeters also display the pulsatile component of the PPG waveform.

1.3 Arterial oxygen saturation

The arterial oxygen content equals the sum of oxygen bound to hemoglobin and the oxygen dissolved in blood (PaO_2). Hemoglobin is the main carrier of oxygen in the blood. When oxygen binds to hemoglobin, oxyhemoglobin is formed. Arterial oxygen saturation (SaO_2) equals the ratio of oxyhemoglobin to the total hemoglobin [9].

$$SaO_2 = \frac{HbO_2}{HbO_2 + Hb}$$

Where, SaO_2 is oxygen saturation

HbO_2 is oxyhemoglobin

Hb is reduced hemoglobin

The normal range of oxygen saturation is from 96% to 100% but decreases below the normal range depending on many factors such as PaO_2, pH of the blood, temperature of the body, and structure of hemoglobin. Pathological reduction in the oxygen content of the blood is known as hypoxemia. Hypoxemia is one of the common causes of hypoxia which is the deficiency of the oxygen reaching the tissue. Hypoxia is very dangerous as it not only affects the function of the tissues and organs but also can create irreversible damage to the tissues and organs [9-11].

The arterial oxygen saturation is measured using a pulse oximeter which works on the principle that the absorption coefficient of fully oxygenated hemoglobin and reduced hemoglobin is different. Wavelengths are chosen such that the absorption of both components has big difference i.e. when the absorption of one of the component is highest the other is lowest and vice-versa. Further detail of the principles of operation for the pulse oximeter will be provided in the Method chapter of this thesis.

1.4 Physiological effects of OSA on oxygen saturation and peripheral blood flow

As mentioned earlier, the closure of the airways causes cessation of breathing which in turn stops the air flow during the apneic event. This leads the oxygen to deplete from the blood and causes reduction in the oxygen saturation.

In addition to the decrease in the oxygen saturation, there is also a decrease in the heart rate due to the bradycardia reflex with high negative intrathoracic pressure [12]. Hence the time interval between two pulses in the PPG waveform increases.

1.5 Current Detection method

Polysomnography is presently the gold standard for detection of sleep apnea. However this method is costly and not always readily available[13]. Nocturnal pulse oximetry is simple to apply, cost effective, reliable, and noninvasive. Hence, it is suited for multiple testing and home tests [14].

Many approaches have been used to detect sleep apnea using pulse oximetry signal. Visual inspection of the oxygen saturation drop is the simplest technique of all [15]. Time domain features, frequency domain features and non-linear features have been used to diagnose OSA. Different classifiers such as multilayer neural networks, pattern recognition and support vector machine have also been implemented to diagnose OSA. These all methods have varied range of sensitivity and specificity.

1.6 Specific Aims

Pulse oximeter is the simplest and cheapest of all techniques used in sleep apnea study. The percentage oxygen saturation which is displayed on the pulse oximeter is used in all sleep apnea diagnostics, but the PPG waveform from the pulse oximeter has not been used to study sleep apnea. Hence in this study we aim to investigate the feasibility and efficacy of using the percentage oxygen saturation as well as the PPG waveform and to detect and quantify the physiological changes due to apnea. Specifically, new features from the PPG waveform will investigated to establish whether the waveform can be effectively used to discern between normal breathing and apnea. The features from the waveform have been detected during simulated sleep apnea which mimics the actual

sleep apnea in which the subject holds their breath for as long as they can. The same features are also tested in the data obtained from the actual sleep apnea patients.

Hence the hypothesis of this study was

1) To see if changes are observed between baseline and the breath holds.

2) To study the gravity effect.

3) To study the effect due to different frequency of apnea.

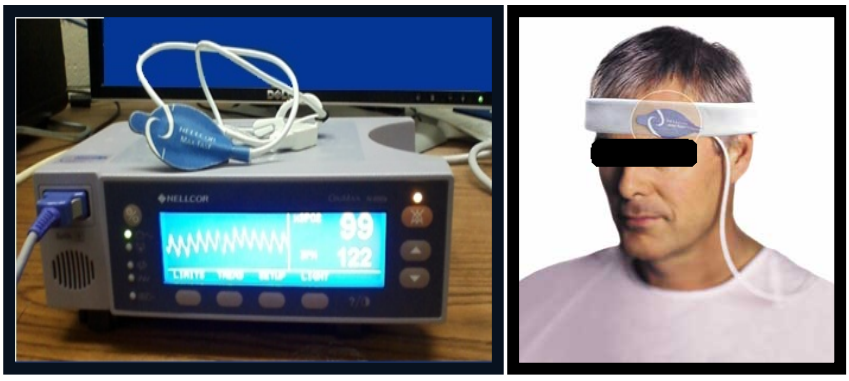
CHAPTER 2

MEANS AND METHODS

As explained earlier, two investigations i.e. the simulated sleep apnea study and the actual sleep apnea study were conducted to investigate the physiological changes in the PPG waveform and percentage oxygen saturation. The subject information, instrumentation setup, protocols and the analysis of the data for the two studies are explained in this chapter.

2.1 Pulse oximetry

The oxygen saturation and the PPG waveform can be obtained from the pulse oximeter.



(a) (b)

Figure 2.1 (a) Pulse oximeter monitor and forehead sensor (b) Site of placement of the sensor on forehead [16]

A Nellcor oximax N-600x pulse oximeter (Nellcor Inc.,Pleasanton, CA) was used for the study. A forehead sensor was used in conjunction with the pulse oximeter. The figure 2.1 (a) shows the pulse oximeter as well as the forehead sensor.

The forehead sensor works on the principle of reflectance from the illuminated area. Figure 2.1 (b) shows the sensor as placed on the left side of the forehead. A head band is used to avoid the venous pulsation which leads to a lower oxygen saturation reading. Hence applying positive pressure might help to avoid the venous pulsation [17]. Venous pulsation is caused by retro transmitted heart movement. It is transmitted backwards which causes pooling of the arterial and venous blood. [18]

2.1.1 Principle of pulse oximeter

The pulse oximeter works on the principle of spectrophotometry and difference in the absorption spectra for different components of the blood. Spectrophotometry depends on Beer-Lambert's law which gives information of the light transmitted for a given concentration of solute [19].

$$I = I_o * e^{-\varepsilon cl} \quad \text{---------- (1)}$$

$$A = \log\left(\frac{I_o}{I}\right) = \varepsilon cl \quad \text{---------- (2)}$$

where A is the optical density, I is the intensity of the light transmitted, I_o is the intensity of the light incident, ε is the extinction coefficient, c is the concentration of solute and l is the optical path length [19-21].

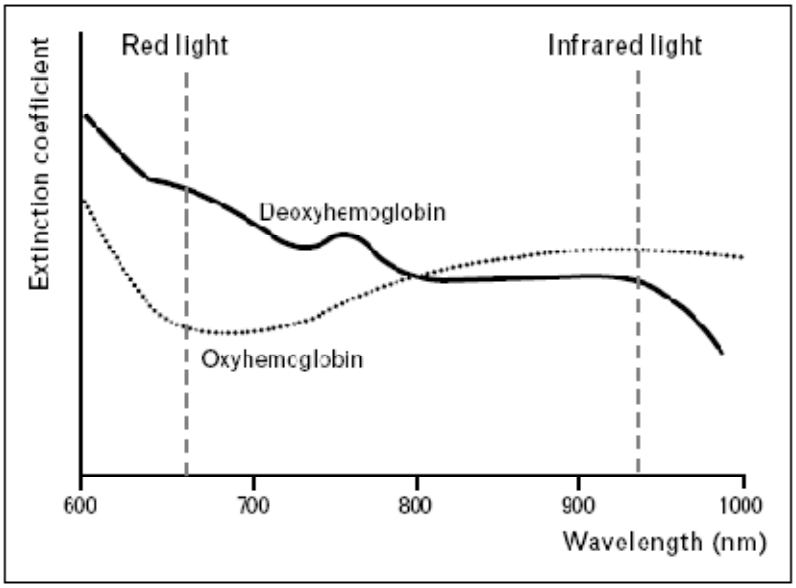


Figure 2.2 Absorption spectra of oxyhemoglobin and deoxyhemoglobin [22].

The absorption coefficients of the two components of the blood which are oxyhemoglobin and deoxyhemoglobin are different for different wavelength. Hence the wavelength of the light is chosen such that there is a maximum difference in the extinction coefficients of the two components. As shown in the figure 2.2 at 660 nm and 940 nm the difference in the extinction coefficient is highest and is in reverse direction for the two wavelengths [22].

As seen from figure 2.2, extinction coefficient is dependent of the wavelength of the light chosen. Optical density (A) for red and infrared wavelengths can be described in terms of oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) as follows.

$$A_R = (\varepsilon_{R,Hb} * c_{Hb} * l) + (\varepsilon_{R,Hbo2} * c_{Hbo2} * l) \quad \text{---------- (3)}$$

$$A_{IR} = (\varepsilon_{IR,Hb} * c_{Hb} * l) + (\varepsilon_{IR,Hbo2} * c_{Hbo2} * l) \quad \text{---------- (4)}$$

The oxygen saturation (%SaO_2) is the concentration of oxyhemoglobin divided by the sum of the concentration of oxyhemoglobin and deoxyhemoglobin. Hence by solving equations (3) and (4) we can find %SaO_2

$$\%SaO2 = \frac{\varepsilon_{R,Hb} - (\varepsilon_{IR,Hb} * \frac{A_R}{A_{IR}})}{(\varepsilon_{R,Hb} - \varepsilon_{R,Hbo2}) - ((\varepsilon_{IR,Hb} - \varepsilon_{IR,Hbo2}) * \frac{A_R}{A_{IR}})} * 100\% \quad \text{---------- (5)}$$

The value of A_R and A_{IR} can be calculated from equation (3) and (4). Also the values of each parameter described in the above equation are readily available. Hence the %SaO_2 value can be calculated [20, 23, 24].

2.1.1.1 Reflectance Pulse oximetry

The fore head sensor which was used the study works on the principle of reflectance. Reflectance pulse oximetry uses the same principle as in the transmission mode. When the tissue is illuminated by the light, a portion of it is absorbed and the photodetector measures the reflected light. In contrast to the transmission mode, the amount of light reaching the photodector is less. The reflectance spectra for the oxyhemoglobin and deoxyhemoglobin are shown in figure 2.3 which is similar to the the absorption spectra hence the same wavelength of LEDs are used as in the transmission mode [21, 22].

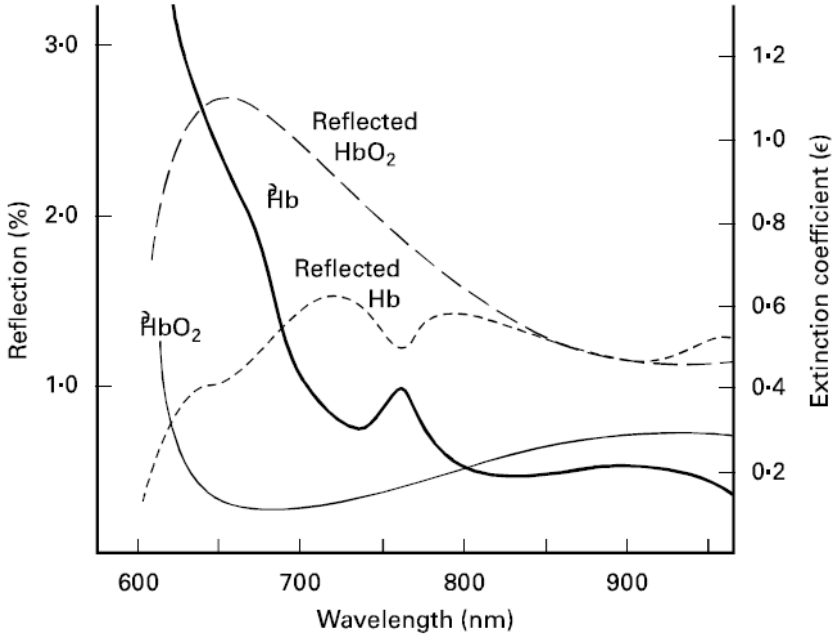


Figure 2.3 Reflection spectra for oxyhemoglobin and deoxyhemoglobin [21].

The sensor consists of the two light emitting diodes (LEDs) and a photodetector. One of the LEDs give out the red wavelength of light and the other one gives infrared wavelength of light respectively. In the reflectance pulse oximeter both the LEDs and the photodetector are placed in the same plane which is shown in figure 2.4. As the sensor components are in the same plane, the sensor can be placed at many different sites of the body and need not be placed on the periphery as in the case of transmission mode. This is one of the advantages of using the sensor in the reflectance mode.

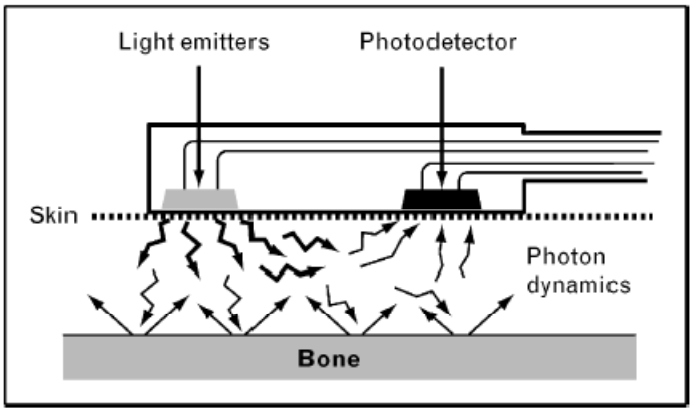


Figure 2.4 Placement of the LED and the photodetector [22].

2.1.1.2 Accuracy of pulse oximeters

For the calculation of oxygen saturation the absorption by the carboxyhemoglobin (CoHb) and the methemoglobin (MetHb) are neglected as they are present in very small amount. But if they are present in appreciable amount this might lead to erroneous reading of oxygen saturation.

The amount of CoHb is about 2% in non smokers and it can around 10-20% in heavy smokers. Also CoHb has similar absorption spectra as HbO. Hence this might cause the pulse oximeter to give a higher estimate of oxygen saturation [25]. To overcome this problem other alternative methods like co-oximeters should be used.

2.1.2 Calibration of pulse oximeter

The calibration of pulse oximeter is done using a co-oximeter which is considered the gold standard method. Co-oximetry uses the principle of spectrophotometry as in a pulse oximeter but it operates in the visible wavelength range. It provides the oxygen content of the blood at the time when the blood is drawn out from the body.

Co-oximeters from different manufacturers use different wavelengths, but the principle of operation used in detecting the oxyhemoglobin is the same. In the AVL Omni co-oximeter (AVL Scientific Corporation, Roswell,GA), a small volume of blood is drawn into the port of the co-oximeter. This sample is hemolysed by ultrasound and the resulting solution is drawn into a cuvette. A tungsten-halogen lamp is used as a light source which gives out wide bandwidth of light from 500 nm to 700 nm. This wide bandwidth is converted into a monochromatic light and the wavelength is increased by a stepper motor in discrete steps. The light is then shone on to the cuvette and the output from the cuvette is detected by a photodiode. It is then amplified and converted to digital form. The digital output is fed to a microprocessor which calculates different parameters like oxyhemoglobin, carboxyhemoglobin, methemoglobin and other chromophores using Beer-Lambert law.

2.2 Experimental Setup

2.2.1 For Simulated sleep apnea data collection

The pulse oximeter gives out the analog output of the oxygen saturation as well as the PPG waveform. As shown in the figure 2.5, the analog output can be collected from the data port which is on the rear panel of the pulse oximeter.

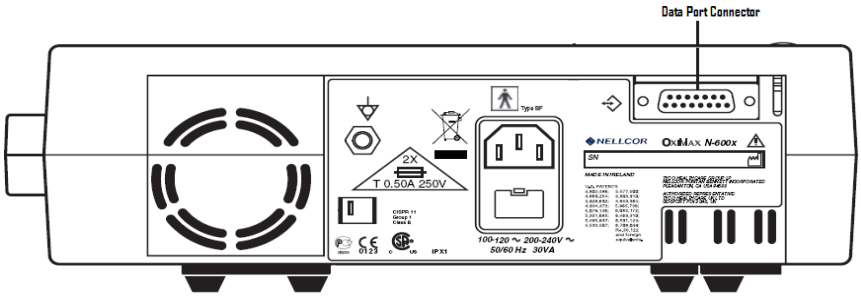


Figure 2.5 Rear Panel of Nellcor oximax N-600x pulse oximeter [26].

Table 2.1 Pin configuration

Pin Number	Signal
6	Analog oxygen saturation
10	Ground signal
14	Analog PPG waveform

The pin configuration of the data port is given in the table 2.2.

The analog output from the pulse oximeter is fed to NI CB-68 LP through a cable which has DB 15 connector at one end and free open wires on the other side. DB 15 side is connected to the pulse oximeter and the free open wires are directly screwed into NI CB-68 LP. This is shown in figure 2.6 (a).

NI CB-68 LP has 68 screw terminals which can easily connect to NI DAQcard-6024E. DAQcard-6024E has two 12-bit analog output, eight digital input/output lines and two 24-bit counters. The DAQ converts the analog signal to digital signal with a help of LabVIEW 8.6 at a rate sampling rate of one thousand hertz (1 kHz). Figure 2.6 (b) shows the CB-68 LP and figure 2.6 (c) shows the DAQcard-6024E.

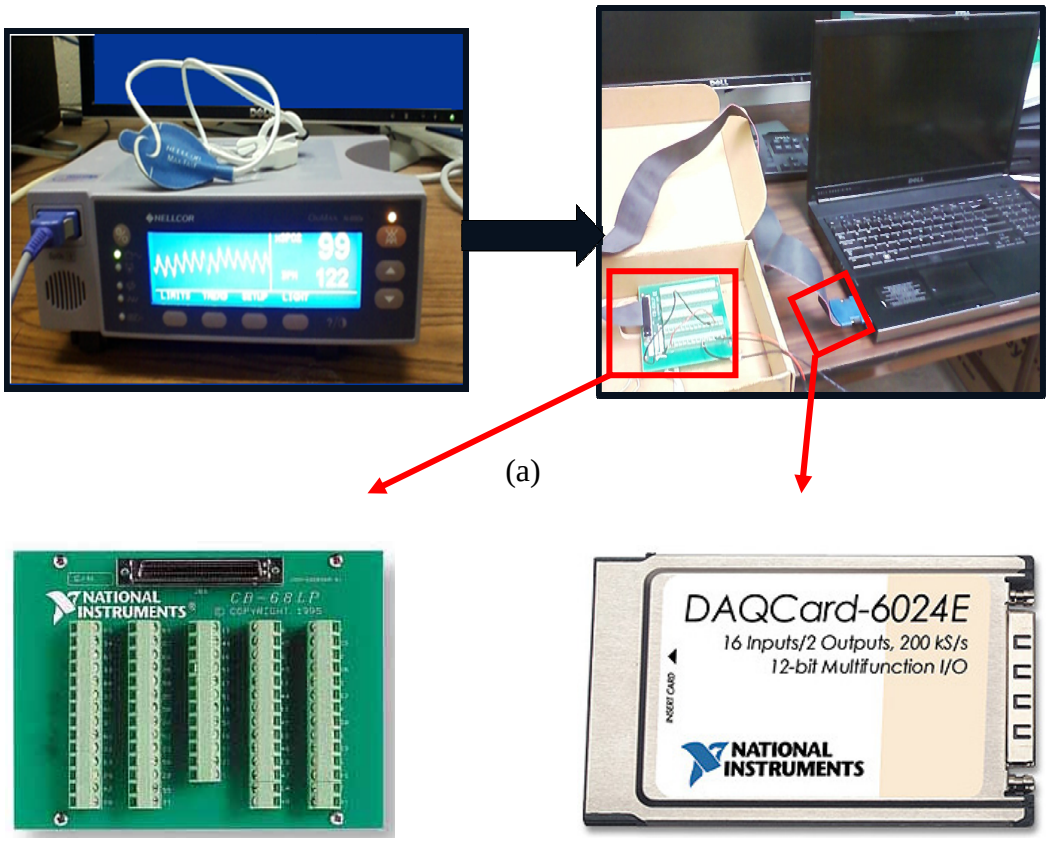


Figure 2.6 Instrumentation set up: (a) Connection between pulse oximeter and the LabVIEW, (b) CB-68 LP and (c) DAQcard-6024E.

Along with the pulse oximeter, data were also collected from

1) Arterial Blood Pressure (ABP) monitor: ABP was measured non-invasively using Nexfin, BMEYE (BMEYE B.M., Amsterdam, Holland). A finger cuff is used to inflate pressure and monitor the ABP.

2) CO_2 Monitor: CO_2 was monitored using a nasal cannula by Capnograph, Respironics (Philips, Netherlands).

3) Transcranial Doppler (TCD): TCD was used to measure the velocity of blood flow by Doppler-Box (Compumedics Germany GmbH). The velocity of blood flowing to the brain was measured from the cerebral medial artery.

4) Electrocardiograph (ECG): ECG is collected using 100 C, BIOPAC MP 150 (Biopac System Inc.,Goleta, CA). Surface electrodes in Lead I configuration are used to collect the signal.

5) On-off Pulse signal (Event Marker): The on-off device is a simple switch that gives out binary output. When the switch is turned on it gives a pulse of 5 mV and when it is in off mode it had 0 mV as output. The switch was turned on when the subject started holding his/her breath and switched off when the subject started breathing. This served as a marker to indicate the period for which the breath was held.

Using this setup, data from the seven channels were collected simultaneously by custom-designed software using the LabVIEW 8.6 graphics software.

2.2.2 For actual sleep apnea patient data collection

An eight hour polysomnography (PSG) was done at Sleep Consultant Inc., Fort Worth, TX. The PSG includes

1) Electroencephalogram (EEG) for the measuring brain electrical activity during sleep. This is used to score data into different stage of sleep and to detect cortical arousal from sleep.

2) Electrooculogram (EOG) for measuring the eye movement. This is particularly useful to determine the Rapid Eye Movement (REM) sleep stage where sleep apnea is more likely to occur.

3) Electromyogram (EMG) for measuring the muscle tension in the body and the chin and leg movements.

4) Electrocardiogram (ECG) for measuring the electrical activity of the heart.

5) Respiration monitoring bands used for recording respiratory efforts by measuring the chest and abdomen movement.

6) Pulse oximeter for measuring the oxygen saturation level.[27, 28]

The polysomnography is done using Sandman

Along with the polysomnography, data were also acquired from the devices as explained in section 2.2.1. The time stamp from the laptop was given to the Sandman as input to allow the data synchronization from both the systems.

2.3 Experimental Protocol and subject group

As described earlier, simulated sleep apnea requires subjects to hold their breath as long as they can. Two different protocols were designed to mimic the severity of sleep apnea and these protocols were performed in two different postures. All the four data sets were collected on the same day one after the other. The protocols as well as the postures were randomized for all the subjects.

2.3.1 Protocol A

In protocol A, before the start of the breath hold there was a period of at least 60s of breathing naturally and at rest which acted as the baseline. The experimenter signaled the start of the breath hold by a countdown of 5 second. The subjects were instructed to breath out normally before every breath hold begun. At the same time, as the breath hold

begun (1) the experimenter placed a nose clip on the subject's nose to avoid any unintentional breathing through the nose, and (2) the marker was switched on. The subjects were asked to hold their breath for as long as possible.

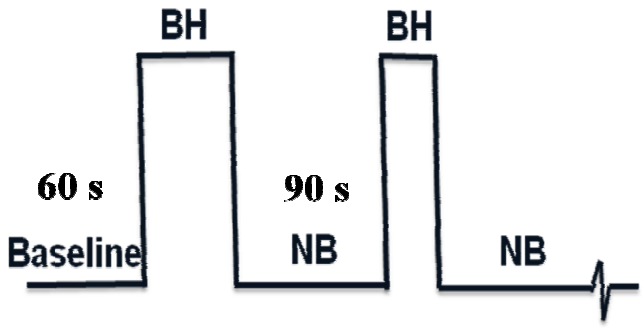


Figure 2.7 Protocol A sequence of breath hold (BH) and normal breathing (NB). Baseline signifies the 60s natural breathing that precedes the breath hold maneuvers.

When the subjects were no longer able to hold their breath, they were asked to indicate by tapping their feet or by inhaling air through their mouth. At this time the noseclip was taken off and the marker was switched off. A period of 90 seconds of normal breathing (NB) preceded the second breath hold (BH). This combination of breath hold and breathing was carried out 5 times. Figure 2.7 shows the protocol design where BH indicates the breath hold and NB indicated the normal breathing.

2.3.2 Protocol B

Protocol B is similar to protocol A with the only difference that the time period of breathing in between the two breath holds was 30s. This protocol mimics the severe sleep apnea condition where apnea episodes occur three times more frequently. Figure 2.8 indicates the design of protocol B where BH indicates the breath hold and NB indicated the normal breathing.

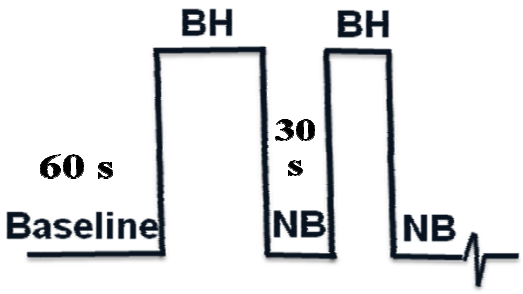
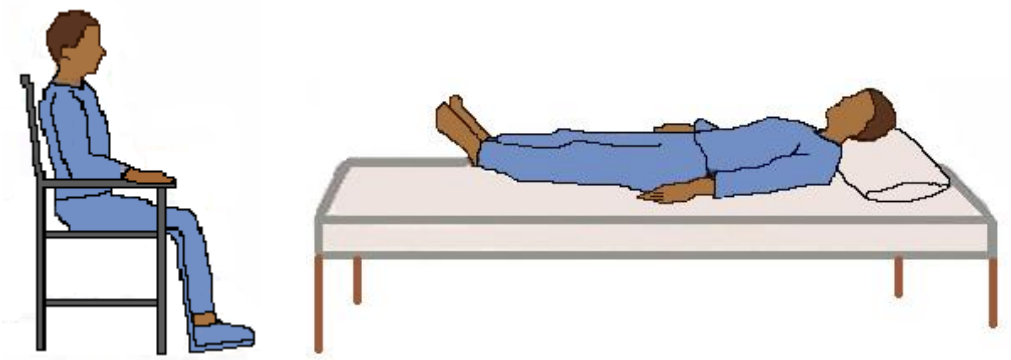


Figure 2.8 Protocol B sequence of breath hold (BH) and normal breathing (NB). Baseline signifies the 60s natural breathing that precedes the breath hold maneuvers.

2.3.3 Posture

Data were collected in two different postures that are the sitting and the supine position.



(a) (b)

Figure 2.9 Different positions used in simulated sleep apnea. (a) Sitting, (b) Supine

Figure 2.9 (a) indicates the sitting posture and 2.9 (b) indicates the supine postures. Both the protocols were performed in both the positions.

2.3.4 Subjects for Simulated sleep apnea data collection

A group of sixteen volunteers were recruited for the simulated sleep apnea study. All the subjects were normal healthy subjects with no history of sleep apnea.

Table 2.2 Subject Demography

Number	Age	Gender	Height (cm)	Weight (kg)	BMI (kg/m^2)
1	34	M	165	59	21.7
2	28	M	170	60	20.8
3	23	M	168	78	27.6
4	29	M	178	68	21.5
5	23	F	157	43	17.4
6	22	F	155	47	19.6
7	25	F	155	50	20.8
8	23	M	182	118	35.6
9	35	M	165	73	26.8
10	30	M	180	91	28.1
11	38	M	165	78	28.7
12	31	M	175	75	24.5
13	30	F	167	54	19.4
14	29	F	152	46	19.9
15	29	F	160	74	28.9
16	35	F	160	61	23.8
Mean	29.00	-	165.88	67.19	24.07
Standard deviation	4.89	-	9.28	19.31	4.84

There were seven females and nine males. The age group was 29.00 ± 4.86 years, height was 165.88 ± 9.28 cm, weight 67.19 ± 19.31 kg and BMI was 24.07 ± 4.84 kg/m^2. For females, age group was 27.57 ± 4.54 years, height was 158.00± 4.9 cm, weight 53.57

± 10.78 kg and BMI was 21.40± 3.83 kg/m^2. For males, age group was 30.11 ± 5.11 years, height was 172.00 ± 6.86 cm, weight 77.78 ± 17.98 kg and BMI was 26.14 ± 4.68 kg/m^2.The details of each subject are given in the Table 2..

A written informed consent form approved by IRB detailing the instruments and the procedures to be used was handed out to each subject Along with this an instructor also briefed the details about the study.

2.3.5 Subjects for actual sleep apnea patient data collection

Five subjects were chosen for the polysomnography study. Four subjects underwent a full eight hours of study and one underwent about two hours of study. All the five subjects were already diagnosed with obstructive sleep apnea. The age group was 53.60±7.40 yr, height was 166.10±6.60 cm, weight was 93.00± 23.00 kg and the BMI 33.66 ± 7.27 kg/m^2.

2.4 Feature detection and analysis

2.4.1 Data clipping

The data obtained from LabVIEW is in text file (.lvm) format and the length of each protocol is also long which makes the file size rather large. Therefore, it occupies a lot of memory and takes a longer time to analyze it. To overcome these problems, the data were split into smaller seggments and stored in binary file (.mat) format with the help of a graphic user interface (GUI) program in MATLAB developed by Gauri Bhave.

As explained earlier, the markers indicate the breath hold phase and normal breath phase. Data were clipped based on these markers that yielded five normal breath phase files and five breath hold phase files.

A mixed effect of normal breath and breath hold during the first few and last few seconds of the normal breaths were observed. The reasons are as briefed below.

1) The physiological parameters do not return to a baseline immediately once the subject resumes normal breathing after a breath hold maneuver. Thus, the effect of breath hold might be observed in first few seconds of recovery. To eliminate this effect one more set of data is clipped such that we skip the first few seconds of the normal breath.

2) Also as the experimenter started the countdown, it was observed that the subjects will react by either taking a deep breath or stiffening their body (i.e. large musculoskeletal group recruitment) affecting the physiological response due to mild, but noticeable, anxiety. Therefore, by discarding the final five seconds of normal breath this effect was eliminated.

By following the above procedure, the new set of data for Protocol A was clipped off from 55 seconds to 85 seconds from the entire 90 seconds normal breath phase (Fig. 2.7). For Protocol B, data was clipped off from 5 seconds to 25 seconds (Fig. 2.8). These clips were denoted as pre breath hold phase clips. For both protocols, data was clipped off from 25 to 55 seconds from the baseline which was treated as pre breath hold phase 1 clip.

Hence three different type of data set were clipped for 1) Breath hold phase which would be of variable time, 2) Normal breath phase which would include the baseline and the recovery period and 3) 30 s of normal breath which was the clipping from the recovery period.

For oxygen saturation, the data was considered as a whole due to the delay observed in the calculation of SaO_2. The drop in the SaO_2 was considered from the point the SaO_2 starts dipping to the point where it starts recovering. This would be possible with the clipping as seen from the figure 2.10 on the next page.

2.4.2 Feature selection

2.4.2.1 Percentage oxygen saturation

Figure 2.10 shows the drop in the oxygen saturation observed when the subject held his/her breath. Initially the oxygen saturation is constant at 98%. The green blocks indicate the breath hold phase. After a delay of few seconds from the start of breath hold, the oxygen saturation starts dropping. The drop may itself be one of the features. The rate of change in slope can be considered as another feature to detect simulated apnea.

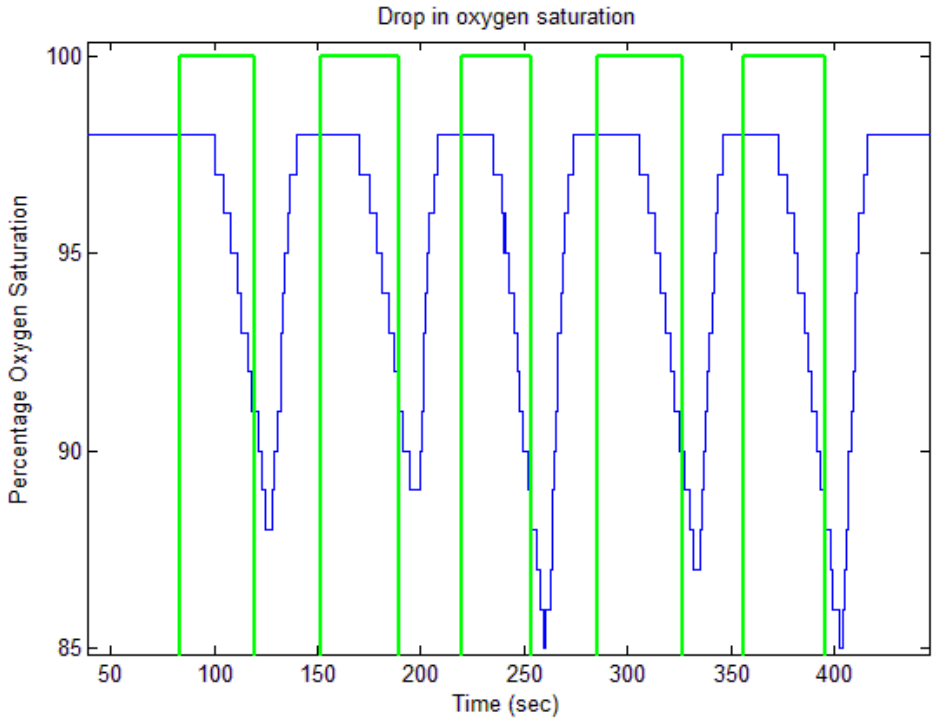


Figure 2.10 Drop in the percentage oxygen saturation

2.4.2.2 PPG waveform

Five features were extracted from the PPG waveform. They were 1) Peak, 2) Valley,3) Area under the curve, 4) Amplitude and 5) Peak to Peak time as shown in figure 2.11. These features were detected for the time period of normal breath and breath hold. A statistical comparison of the mean of these features was conducted to establish if these feature were sensitive to breath hold.

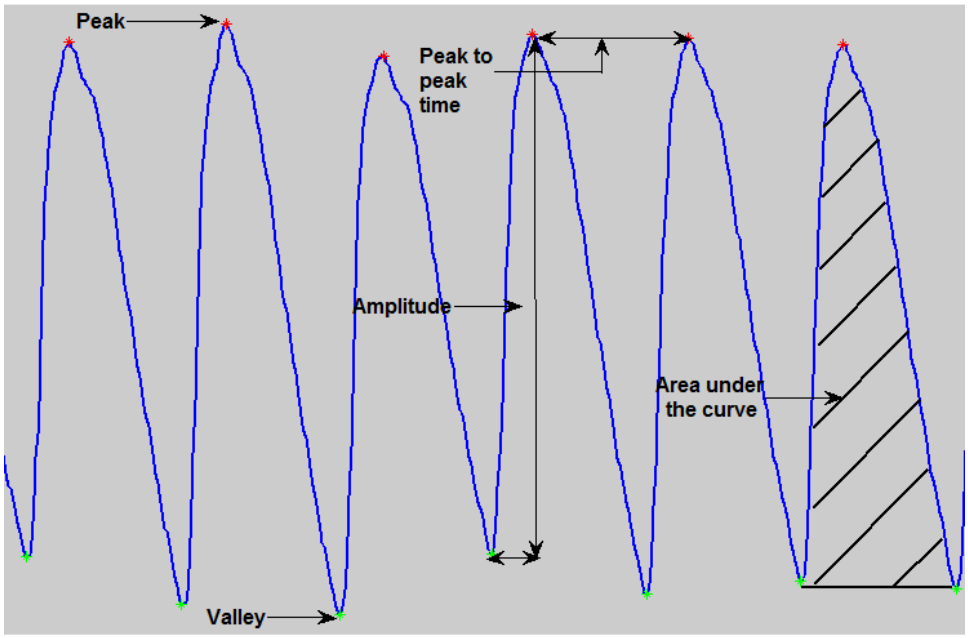


Figure 2.11 Different features of the PPG waveform

2.4.3 Algorithm for the feature detection

The algorithm for the feature detection is described in the flow chart shown in figure 2.12 each step is described below. A copy of the MATLAB-based program developed for this purpose is provided in Appendix A and B

2.4.3.1 Loading the clipping into MATLAB

The three types of data clips were loaded one after the other into MATLAB using "load" function. The data clips had signals from all the seven channels but only the oxygen saturation, PPG waveform and the pulse signal were used for the analysis.

2.4.3.2 Detecting peaks and valleys of the PPG waveform

Detecting the peaks and valleys correctly is very important. For detecting the peak and valley, an algorithm developed by Raichel Mary Alex was used. The algorithm includes setting up of two thresholds: one for the temporal distance and another for the height of the pulse

2.4.3.3 Calculating the amplitude, area under the curve and the peak to peak time between two pulses

1) Amplitude is the vertical distance between a peak and a valley preceding the peak.

2) Area under the curve is the integration of all the points between two consecutive valleys. A rectangular integration was used.

3) Peak to peak time is the time between two consecutive peaks.

Once the peaks and valleys are inspected visually for any errors the above mentioned parameters are calculated using the respective formulae for the entire data set.

2.4.3.4 Calculating the slope of the oxygen saturation drop

The percentage oxygen saturation from the pulse oximeter is given out every 2 seconds. Hence, the signal was resampled at 0.5 Hz using the "decimate" function which

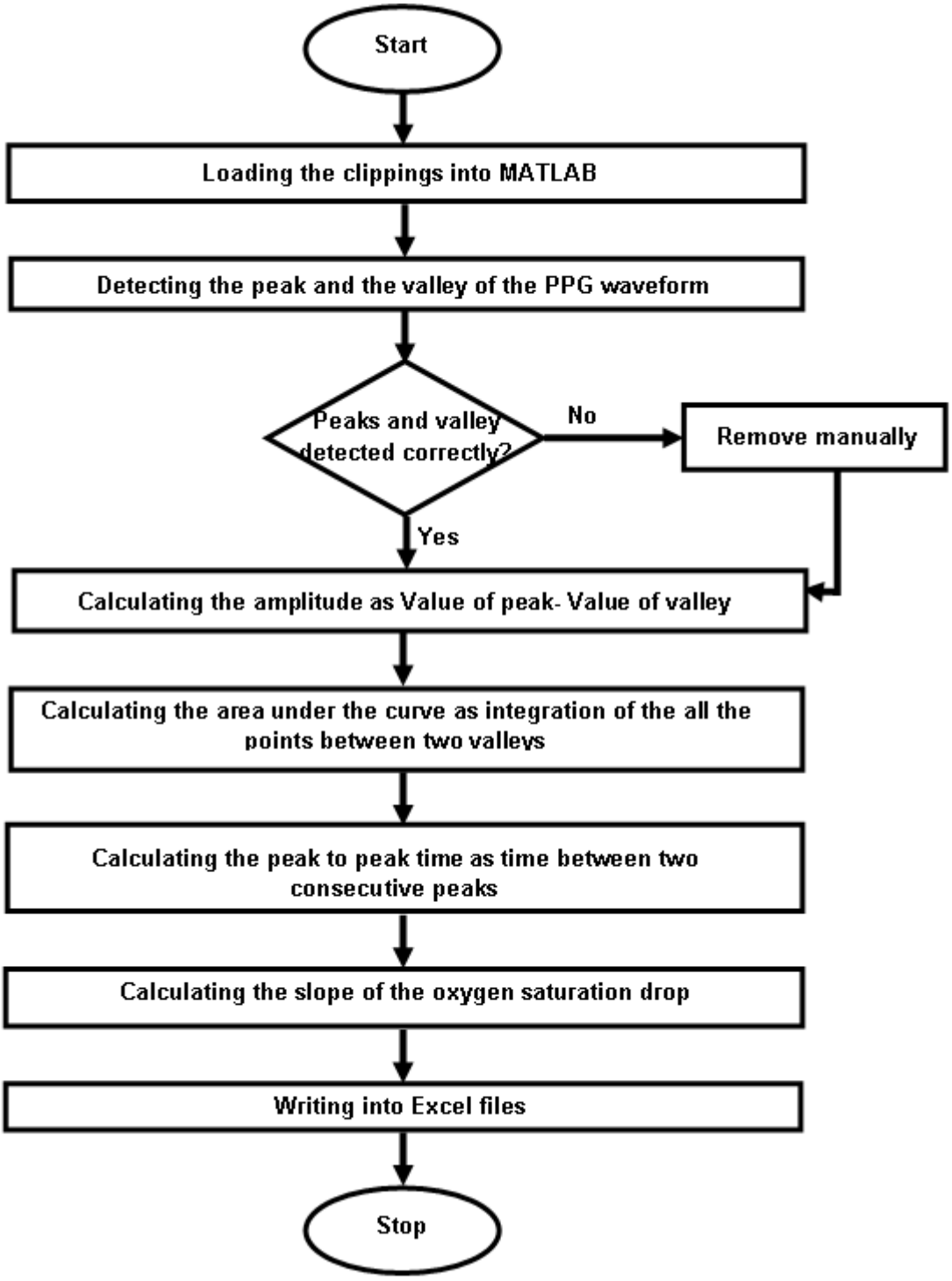


Figure 2.12 Flow chart of the algorithm developed to detect features of PPG waveform and percentage oxygen saturation

is inbuilt in MATLAB. After resampling the starting and the ending points of the slope were found out and the slope between two consecutive samples were found. These slopes were then averaged and the rate of drop in the oxygen saturation was obtained. The difference between two consecutive samples can be found using “diff” function of MATLAB which finally gives out the average of the differences.

2.4.3.5 Writing into Excel File

Finally when all the parameters were obtained, they were written into Microsoft excel file using “xlswrite” function of MATLAB.

2.4.4 Statistical Analysis

2.4.4.1 Mixed linear model

To see the effect of all breath hold, protocols and postures a mixed linear model analysis was performed. The mixed linear model is used to analyze the data in which repeated measures are made with fixed and the random effects which is called the mixed effect. In our study, the combination of the breath hold and the resting period is repeated 5 times for the different protocols and positions. Hence a multi level mixed linear model is used here to study the changes in the features with each other.

The model is represented as $Y=\beta X+\gamma Z+\varepsilon$ where Y would be the dependent variable which would in our case different features, X and Z are the regressors, β is the fixed effect parameter and γ is the random effect parameter.

The expected mean square for this model is calculated and the hypothesis is tested for the variance component for random effect to be equal to zero [29].

2.4.4.2 Tukey-Kramer method

It is a multiple comparison procedure used in conjunction with ANOVA. It is used to test the null hypothesis that the pair of sample means is equal. This is also used for testing unequal number of samples.

The test uses a single value with which it compares all the difference in the mean of the two samples. The single value is given as

$$q_{\alpha,k,N-K} * \sqrt{\frac{MSE}{2} * \left(\frac{1}{n_i} + \frac{1}{n_j}\right)}$$

Where k is the number of means in the study, N is the total number of observation in the study, n is the number of observation for a given group example number of samples of a feature for apnea, MSE is the error within the group and q is the studendized range statistics.

After finding this single point for each group, the difference between two sample mean is compared. The mean that exceed this point is considered significant. From SAS, we can get the confidence interval for the same. If zero is in between the confidence interval then that comparison is not considered significant [30].

CHAPTER 3

RESULTS

The average value and the standard deviation of each feature for baseline and the breath holds are indicated. Also the p-value from the linear mixed model analysis to see the gravity effect and the frequency of apnea effect are shown.

3.1 PPG waveform features for simulated sleep apnea study

The results for all the five features are shown here. The breath hold effect, gravity effect and the apnea frequency effect are tested here.

3.1.1 Amplitude

Figure 3.1 shows the average and the standard deviation of amplitude during the baseline and the breath hold phase. It shows the average for sitting protocol A, sitting protocol B, Supine protocol A and Supine protocol B.

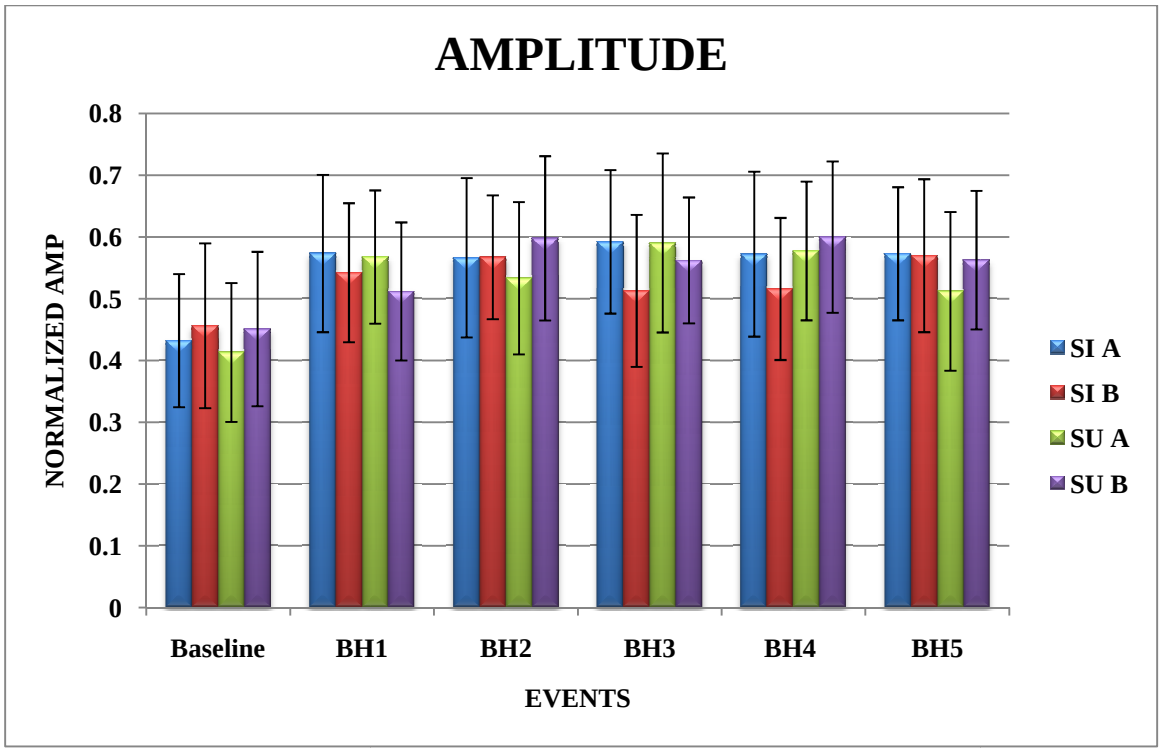


Figure 3.1 Average of the amplitude for both protocol and postures.

A mixed linear model was performed to see the effect of breath hold on the changes of the amplitude. The p-values of the same are shown in Table 3.1 below.

Table 3.1 p-values from the mixed linear model for amplitude for the breath hold effect

Amplitude				
	Sitting A	Sitting B	Supine A	Supine B
Baseline vs BH1	0.0004	<0.0001	0.001	0.2623
Baseline vs BH2	0.0015	0.0023	0.0027	0.0233
Baseline vs BH3	0.0868	<0.0001	0.0011	0.0747
Baseline vs BH4	0.0218	0.0024	0.042	0.0584
Baseline vs BH5	0.1067	<0.0001	0.0546	0.221

(Yellow blocks indicate significance)

Also the mixed linear model shows the comparison between the protocols for a given posture and the comparison between the postures for the given protocols. For example the baseline of sitting A is compared with sitting B. Similarly other events are

compared. Table 3.2 shows the p-values for the same. It also shows the percent of times when the comparisons were significant.

Table 3.2 p-values indicating gravity effect and effect of frequency of apnea on amplitude

Amplitude				
	Si A vs Si B	Su A vs Su B	Si A vs Su A	Si B vs Su B
Baseline	0.9521	0.8917	0.7361	0.6055
NB2	0.2941	0.6632	0.7177	0.8066
NB3	0.4313	0.8294	0.5093	0.9634
NB4	0.5005	0.6613	0.6271	0.8331
NB5	0.9079	0.5867	0.7436	0.4791
BH1	0.9682	0.877	0.9554	0.9616
BH2	0.6033	0.8179	0.9706	0.7228
BH3	0.6389	0.9961	0.7062	0.8874
BH4	0.843	0.8749	0.9397	0.9873
BH5	0.6315	0.8956	0.9092	0.7344
Percent	0	0	0	0

3.1.2 Area under the curve

Figure 3.2 shows the average and the standard deviation of area under the curve during the baseline and the breath hold phase. It shows the average for sitting protocol A, sitting protocol B, Supine protocol A and Supine protocol B.

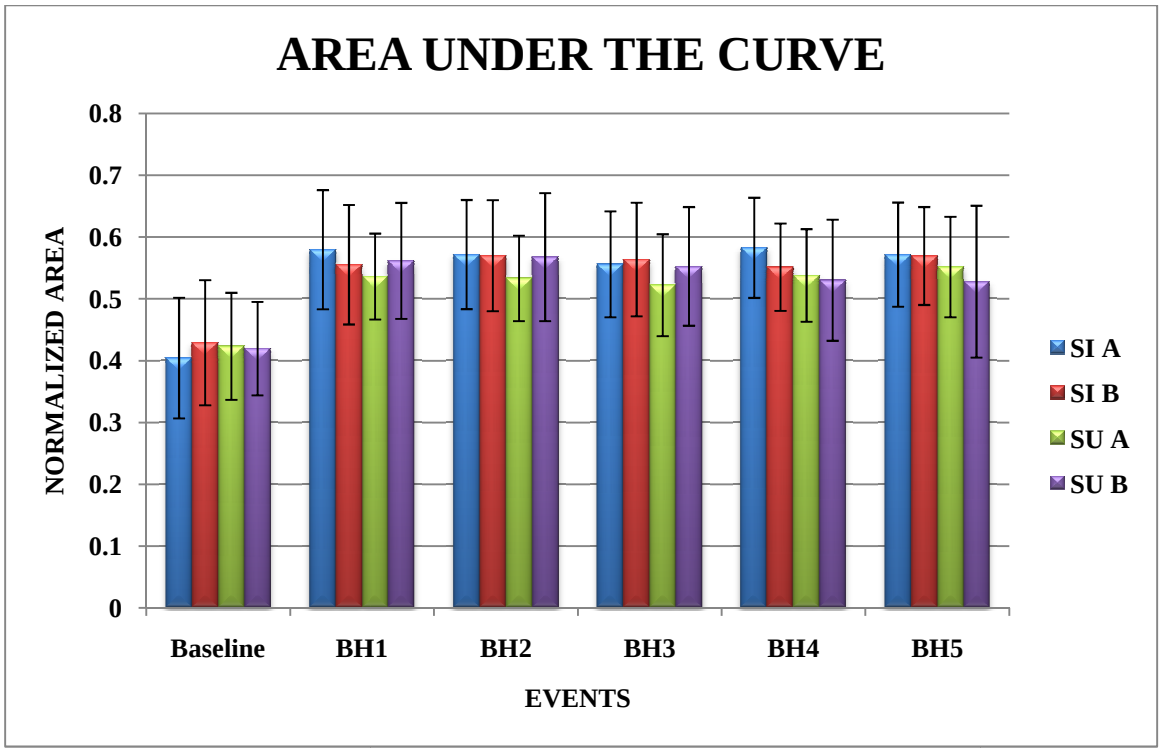


Figure 3.2 Average of the area under the curve for both protocol and postures.

A mixed linear model was performed to see the effect of breath hold on the changes of the area under the curve. The p-values of the same are shown in Table 3.3 below.

Table 3.3 p-values from the mixed linear model for area under the curve for the breath hold effect

Area under the curve				
	Sitting A	Sitting B	Supine A	Supine B
Baseline vs BH1	<0.0001	<0.0001	0.0036	0.0017
Baseline vs BH2	<0.0001	<0.0001	0.019	0.0066
Baseline vs BH3	0.0005	<0.0001	0.0086	0.0389
Baseline vs BH4	<0.0001	0.0002	0.0037	0.3784
Baseline vs BH5	<0.0001	<0.0001	0.0006	0.2618

(Yellow blocks indicate significance)

Also the mixed linear model shows the comparison between the protocols for a given posture and the comparison between the postures for the given protocols. For example the baseline of sitting A is compared with sitting B. Similarly other events are compared. Table 3.4 shows the p-values for the same. It also shows the percent of times when the comparisons were significant.

Table 3.4 p-values indicating gravity effect and effect of frequency of apnea on area under the curve

Area under the curve				
	Si A vs Si B	Su A vs Su B	Si A vs Su A	Si B vs Su B
Baseline	0.9218	0.2424	0.2151	0.8643
NB2	0.8469	0.4056	0.3442	0.8269
NB3	0.6609	0.2585	0.2755	0.63
NB4	0.6869	0.1193	0.2386	0.9961
NB5	0.4543	0.2242	0.4926	0.8926
BH1	0.9626	0.4495	0.5511	0.9178
BH2	0.9702	0.4043	0.5786	0.76
BH3	0.8429	0.4617	0.3171	0.9684
BH4	0.8273	0.5137	0.448	0.8032
BH5	0.997	0.6831	0.393	0.663
Percent	0	0	0	0

3.1.3 Peak to peak time

Figure 3.3 shows the average and the standard deviation of peak to peak time during the baseline and the breath hold phase. It shows the average for sitting protocol A, sitting protocol B, Supine protocol A and Supine protocol B.

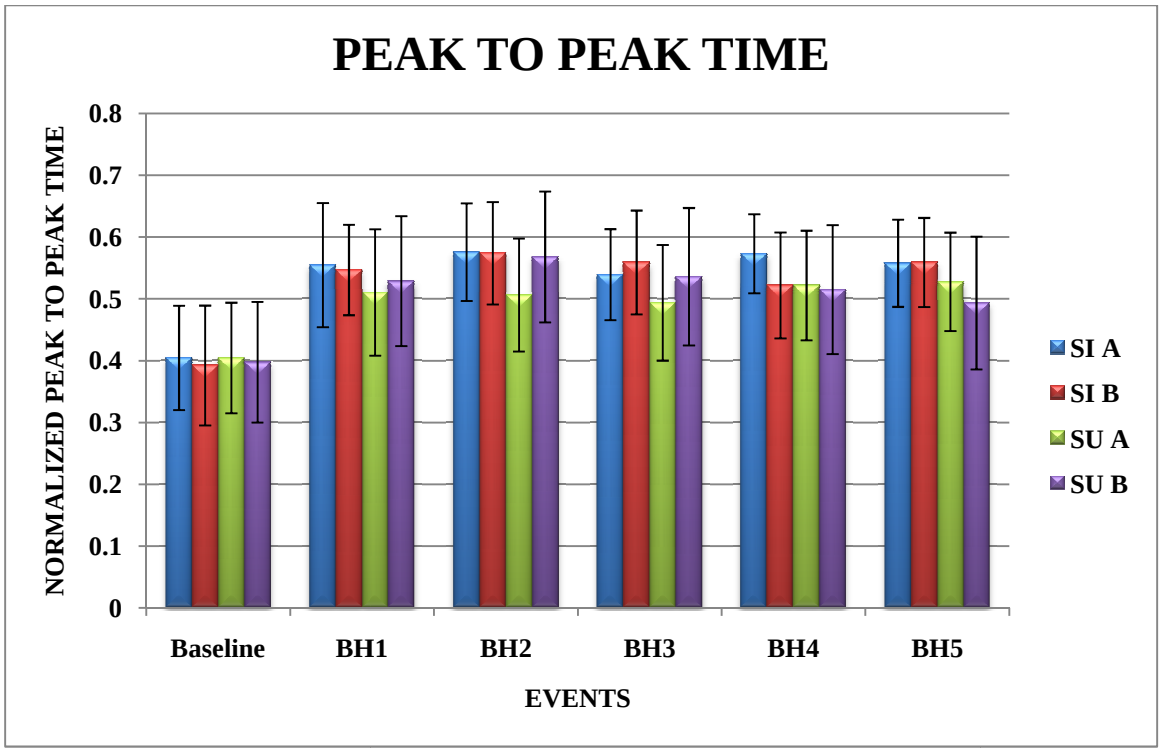


Figure 3.3 Average of the peak to peak time for both protocol and postures.

A mixed linear model was performed to see the effect of breath hold on the changes of the peak to peak time. The p-values of the same are shown in Table 3.5 below.

Table 3.5 p-values from the mixed linear model for peak to peak time for the breath hold effect

Peak to peak time				
	Sitting A	Sitting B	Supine A	Supine B
Baseline vs BH1	<0.0001	<0.0001	0.0472	0.0189
Baseline vs BH2	<0.0001	<0.0001	0.0318	0.0083
Baseline vs BH3	0.0034	<0.0001	0.0492	0.1207
Baseline vs BH4	<0.0001	0.0031	0.0098	0.2236
Baseline vs BH5	0.0001	<0.0001	0.002	0.3999

(Yellow blocks indicate significance)

Also the mixed linear model shows the comparison between the protocols for a given posture and the comparison between the postures for the given protocols. For

example the baseline of sitting A is compared with sitting B. Similarly other events are compared. Table 3.6 shows the p-values for the same. It also shows the percent of times when the comparisons were significant.

Table 3.6 p-values indicating gravity effect and effect of frequency of apnea on peak to peak time.

Peak to peak time				
	Si A vs Si B	Su A vs Su B	Si A vs Su A	Si B vs Su B
Baseline	0.9105	0.8934	0.1943	0.2401
NB2	0.8983	0.8904	0.3171	0.441
NB3	0.8958	0.7124	0.1958	0.2765
NB4	0.7003	0.9805	0.2565	0.1339
NB5	0.4928	0.6841	0.4063	0.2823
BH1	0.8919	0.9154	0.4233	0.4123
BH2	0.9136	0.6606	0.455	0.3086
BH3	0.7107	0.9776	0.2849	0.4693
BH4	0.8197	0.8152	0.3784	0.428
BH5	0.8179	0.6704	0.2845	0.6833
Percent	0	0	0	0

3.1.4 Peak

Figure 3.4 shows the average and the standard deviation of peak during the baseline and the breath hold phase. It shows the average for sitting protocol A, sitting protocol B, Supine protocol A and Supine protocol B.

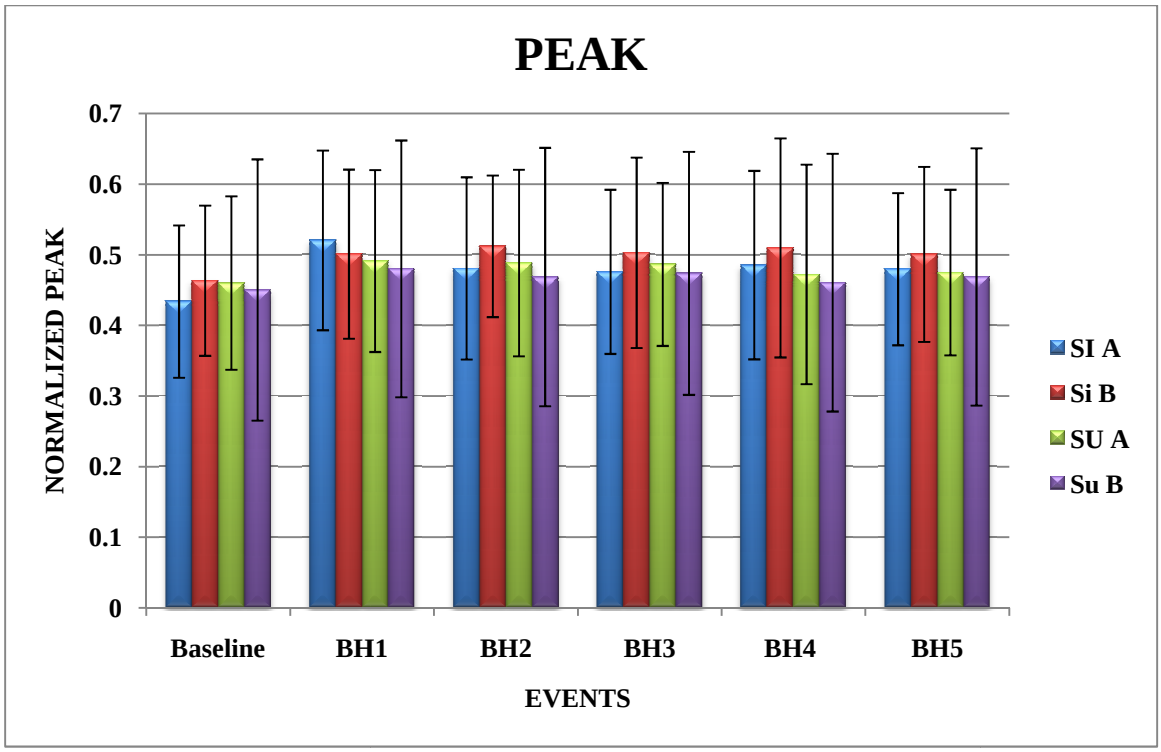


Figure 3.4 Average of the peak for both protocol and postures.

A mixed linear model was performed to see the effect of breath hold on the changes of the peak. The p-values of the same are shown in Table 3.7 below.

Table 3.7 p-values from the mixed linear model for peak for the breath hold effect

Peak				
	Sitting A	Sitting B	Supine A	Supine B
Baseline vs BH1	<0.0001	0.0002	0.056	0.2937
Baseline vs BH2	0.032	0.002	0.0257	0.3598
Baseline vs BH3	0.0207	<0.0001	0.4967	0.5241
Baseline vs BH4	0.0004	0.0026	0.1639	0.0991
Baseline vs BH5	0.0183	<0.0001	0.2732	0.174

(Yellow blocks indicate significance)

Also the mixed linear model shows the comparison between the protocols for a given posture and the comparison between the postures for the given protocols. For example the baseline of sitting A is compared with sitting B. Similarly other events are

compared. Table 3.8Table 3.2 shows the p-values for the same. It also shows the percent of times when the comparisons were significant.

Table 3.8 p-values indicating gravity effect and effect of frequency of apnea on peak.

Peak				
	Si A vs Si B	Su A vs Su B	Si A vs Su A	Si B vs Su B
Baseline	0.9105	0.9975	0.9887	0.9167
NB2	0.6183	0.8384	0.68	0.7564
NB3	0.8112	0.6246	0.7863	0.9252
NB4	0.6431	0.7814	0.8532	0.6338
NB5	0.4675	0.9054	0.5859	0.8207
BH1	0.8079	0.951	0.4767	0.6077
BH2	0.7974	0.7718	0.9636	0.5042
BH3	0.7523	0.991	0.6811	0.4059
BH4	0.9521	0.7204	0.5247	0.6693
BH5	0.895	0.8849	0.6525	0.5881
Percent	0	0	0	0

3.1.5 Valley

Figure 3.5 shows the average and the standard deviation of valley during the baseline and the breath hold phase. It shows the average for sitting protocol A, sitting protocol B, Supine protocol A and Supine protocol B.

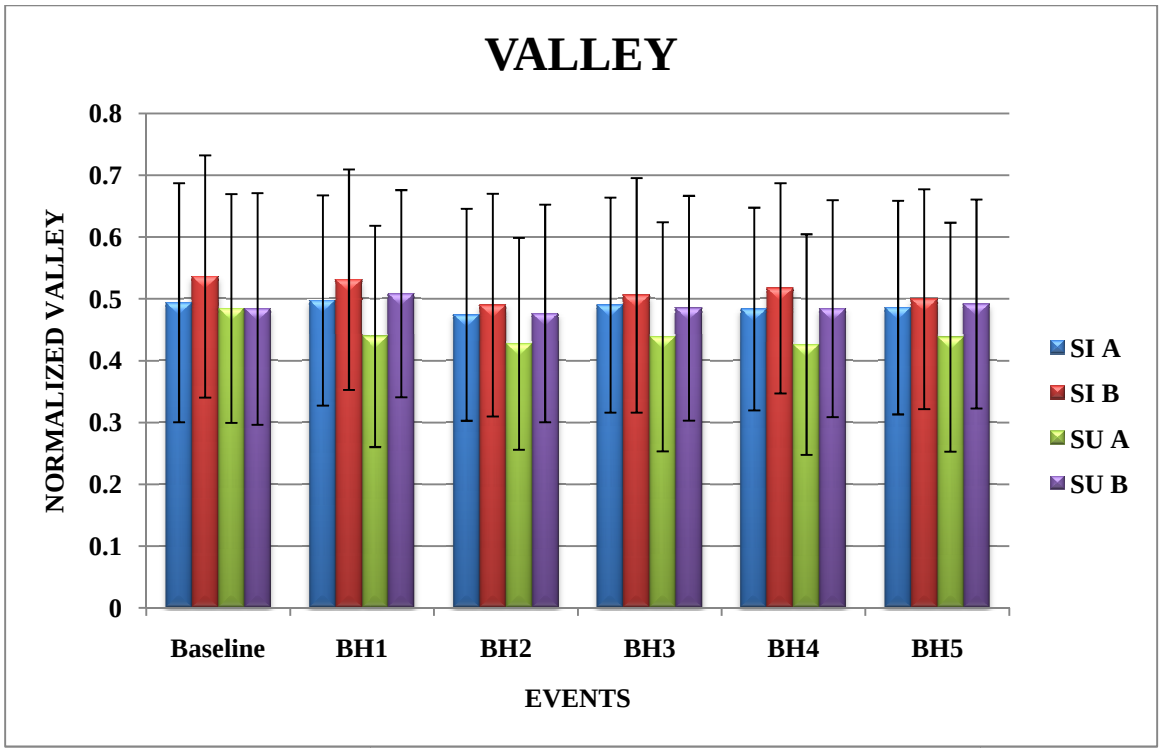


Figure 3.5 Average of the valley for both protocol and postures.

A mixed linear model was performed to see the effect of breath hold on the changes of the valley. The p-values of the same are shown in Table 3.9 below.

Table 3.9 p-values from the mixed linear model for valley for the breath hold effect

Valley				
	Sitting A	Sitting B	Supine A	Supine B
Baseline vs BH1	0.7735	0.2376	0.6396	0.3381
Baseline vs BH2	0.2263	0.0582	0.3942	0.0002
Baseline vs BH3	0.9012	0.0117	0.1712	0.4968
Baseline vs BH4	0.8529	0.1087	0.6236	0.2806
Baseline vs BH5	0.9049	0.005	0.631	0.4929

(Yellow blocks indicate significance)

Also the mixed linear model shows the comparison between the protocols for a given posture and the comparison between the postures for the given protocols. For example the baseline of sitting A is compared with sitting B. Similarly other events are

compared. Table 3.10 shows the p-values for the same. It also shows the percent of times when the comparisons were significant.

Table 3.10 p-values indicating gravity effect and effect of frequency of apnea on valley

Valley				
	Si A vs Si B	Su A vs Su B	Si A vs Su A	Si B vs Su B
Baseline	0.9523	0.8234	0.5102	0.3679
NB2	0.369	0.6939	0.705	0.9317
NB3	0.1908	0.5522	0.2292	0.6219
NB4	0.7177	0.4105	0.4218	0.2606
NB5	0.5234	0.9712	0.774	0.7402
BH1	0.8195	0.7795	0.4055	0.7142
BH2	0.3493	0.49	0.6455	0.8233
BH3	0.5218	0.8606	0.3086	0.7725
BH4	0.7318	0.7102	0.4776	0.4695
BH5	0.3706	0.7634	0.4972	0.9306
Percent	0	0	0	0

3.1.6 Duration of Breath hold

Figure 3.6 shows the average and the standard deviation of valley during the baseline and the breath hold phase. It shows the average for sitting protocol A, sitting protocol B, Supine protocol A and Supine protocol B.

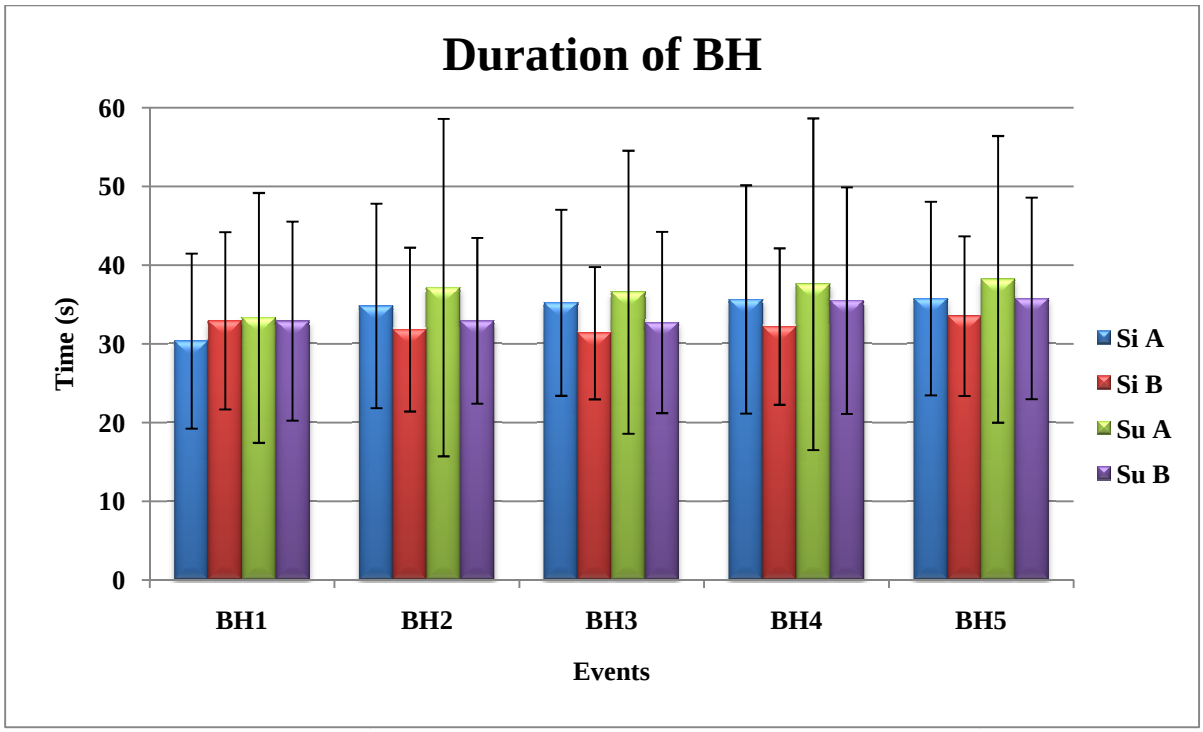


Figure 3.6 Average of the duration of BH for both protocol and postures.

A mixed linear model was performed to see how duration of breath hold differs with the order of breath hold for sitting A. The p-values of the same are shown in Table 3.11Table 3.9 below.

Table 3.11 Comparison of duration of BH for Sitting A

	Sitting A				
BH	1	2	3	4	5
1	-	0.001	0.0074	0.0161	0.003
2	0.001	-	0.7605	0.6322	0.5064
3	0.0074	0.7605	-	0.7521	0.6811
4	0.0161	0.6322	0.7521	-	0.9421
5	0.003	0.5064	0.6811	0.9421	-

(Yellow blocks indicate significance)

A mixed linear model was performed to see how duration of breath hold differs with the order of breath hold for sitting B. The p-values of the same are shown in Table 3.12 below.

Table 3.12 Comparison of duration of BH for Sitting B

	Sitting B				
BH	1	2	3	4	5
1	-	0.3783	0.3265	0.6115	0.5972
2	0.3783	-	0.734	0.7011	0.2664
3	0.3265	0.734	-	0.4803	0.1514
4	0.6115	0.7011	0.4803	-	0.215
5	0.5972	0.2664	0.1514	0.215	-

A mixed linear model was performed to see how duration of breath hold differs with the order of breath hold for Supine A. The p-values of the same are shown in Table 3.13 below.

Table 3.13 Comparison of duration of BH for Supine A

	Supine A				
BH	1	2	3	4	5
1	-	0.0366	0.009	0.0225	0.0004
2	0.0366	-	0.6662	0.5485	0.5023
3	0.009	0.6662	-	0.4359	0.2053
4	0.0225	0.5485	0.4359	-	0.685
5	0.0004	0.5023	0.2053	0.685	-

(Yellow blocks indicate significance)

A mixed linear model was performed to see how duration of breath hold differs with the order of breath hold for Supine B. The p-values of the same are shown in Table 3.14 below.

Table 3.14 Comparison of duration of BH for Supine B

	Supine B				
BH	1	2	3	4	5
1	-	0.9626	0.9177	0.0959	0.0699
2	0.9626	-	0.8496	0.051	0.0168
3	0.9177	0.8496	-	0.0144	0.0004
4	0.0959	0.051	0.0144	-	0.8359
5	0.0699	0.0168	0.0004	0.8359	-

(Yellow blocks indicate significance)

Also the mixed linear model shows the comparison between the protocols for a given posture and the comparison between the postures for the given protocols. For example the baseline of sitting A is compared with sitting B. Similarly other events are compared. Table 3.15 shows the p-values for the same. It also shows the percent of times when the comparisons were significant.

Table 3.15 p-values indicating gravity effect and effect of frequency of apnea on duration of BH

	Si A Vs Si B	Su A Vs Su B	Si A Vs Su A	Si B Vs Su B
BH1	0.4692	0.9300	0.5119	0.9898
BH2	0.4338	0.4474	0.6862	0.7471
BH3	0.2430	0.4398	0.7851	0.6834
BH4	0.3931	0.7232	0.7421	0.4146
BH5	0.5389	0.6420	0.6331	0.5480

3.2 Oxygen saturation during simulated sleep apnea

As explained earlier, the rate of drop of the oxygen saturation is calculated for all five breath hold phase for a given subject, protocol and posture. Rate of drop of oxygen saturation for all sixteen subject for a given protocol and posture were compared with each other to see if they differed from each other using t-test. For instance, Breath hold 1

of all sixteen subjects were compared with breath hold 2. Also the average of the drop for a given protocol and position for the five breath holds are indicated.

Figure 3.7 shows the avergae drop in oxygen saturation for sitting A.

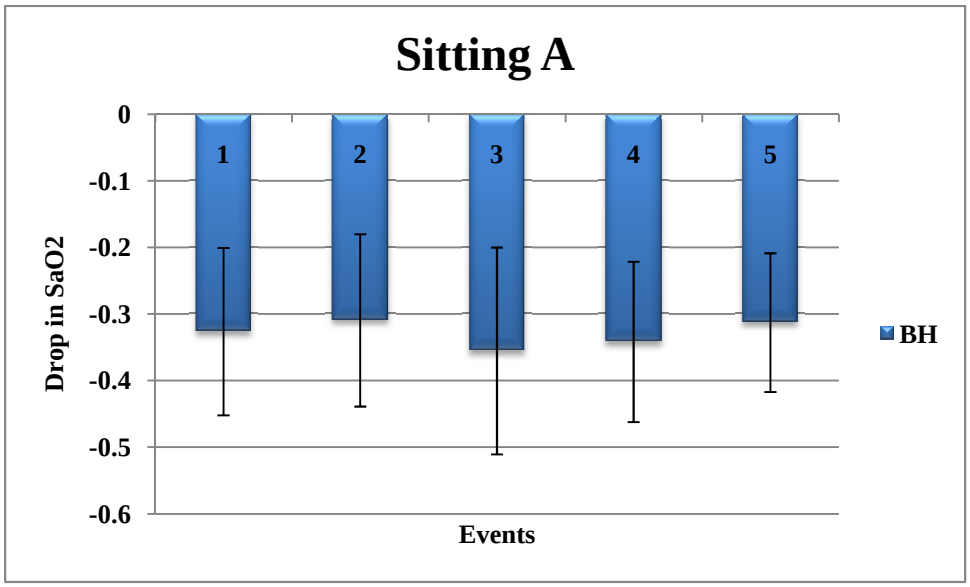


Figure 3.7 Drop in oxygen saturation due to breath hold for Sitting A

The p-value for the t-test for sitting A is shown below in Table 3.16

Table 3.16 p-value from comparison of the rate of drop of oxygen saturation for all breath holds for Sitting A where BH is the breathhold

	Sitting A				
BH	1	2	3	4	5
1	-	0.744856	0.622823	0.763148	0.774239
2	0.744856	-	0.439732	0.530926	0.942814
3	0.622823	0.439732	-	0.814831	0.44009
4	0.763148	0.530926	0.814831	-	0.534404
5	0.774239	0.942814	0.44009	0.534404	-

Figure 3.8 shows the avergae drop in oxygen saturation for sitting B.

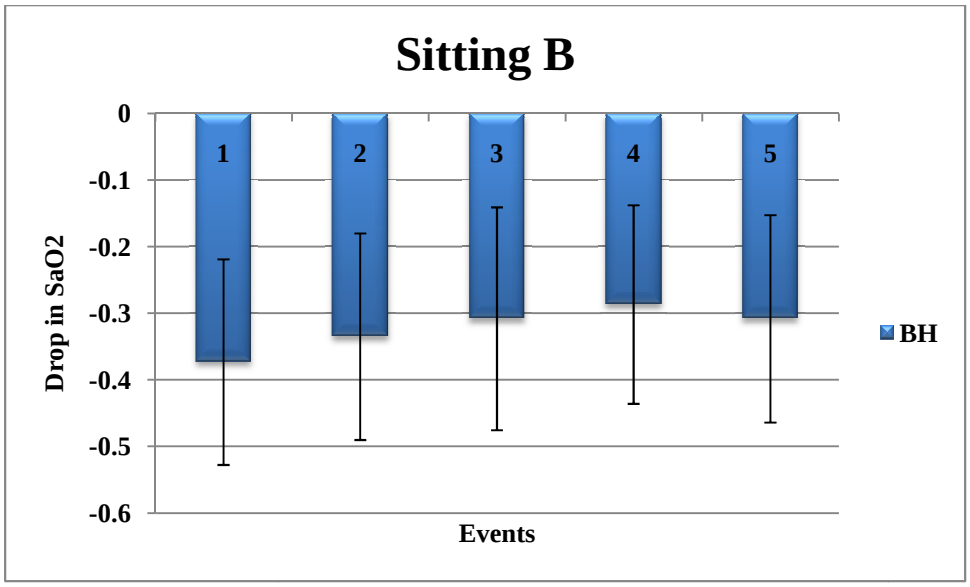


Figure 3.8 Drop in oxygen saturation due to breath hold for Sitting B

The p-value for the t-test for comparison of the breath holds for sitting B are shown in Table 3.17

Table 3.17 p-value from the comparison of the rate of drop of oxygen saturation for all breath holds for Sitting B where BH is the breath hold

	Sitting B				
BH	1	2	3	4	5
1	-	0.744856	0.622823	0.763148	0.774239
2	0.744856	-	0.439732	0.530926	0.942814
3	0.622823	0.439732	-	0.814831	0.44009
4	0.763148	0.530926	0.814831	-	0.534404
5	0.774239	0.942814	0.44009	0.534404	-

Figure 3.9 shows the avergae drop in oxygen saturation for supine A.

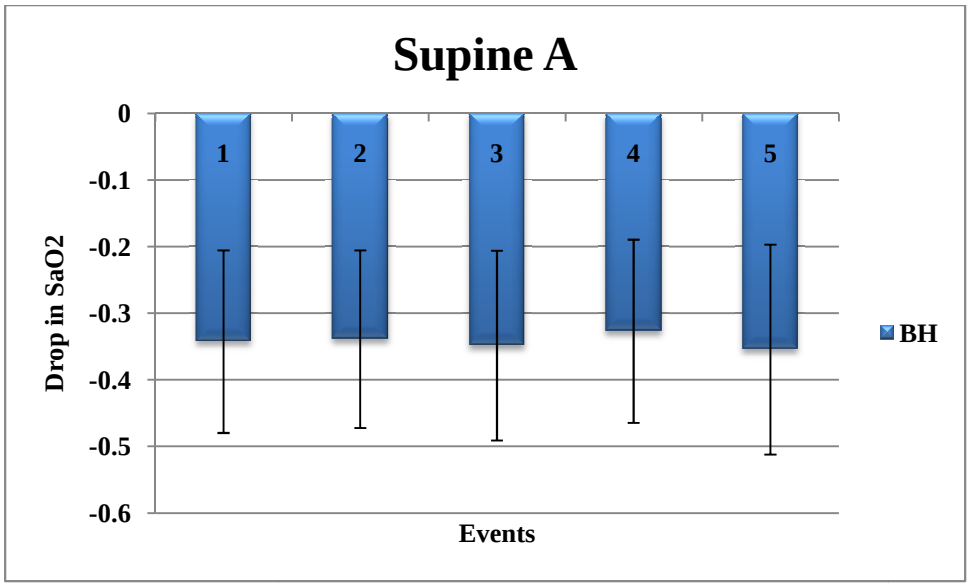


Figure 3.9 Drop in oxygen saturation due to breath hold for Supine A

The p-value for the t-test for comparison of the breath holds for supine A is shown below in Table 3.18

Table 3.18 p value for the comparison of the rate of drop of oxygen saturation for all breath holds for Supine A

	Supine A				
BH	1	2	3	4	5
1	-	0.945301	0.914058	0.774677	0.839703
2	0.945301	-	0.859874	0.824484	0.788656
3	0.914058	0.859874	-	0.697926	0.921493
4	0.774677	0.824484	0.697926	-	0.640586
5	0.839703	0.788656	0.921493	0.640586	-

Figure 3.10 shows the avergae drop in oxygen saturation for supine B

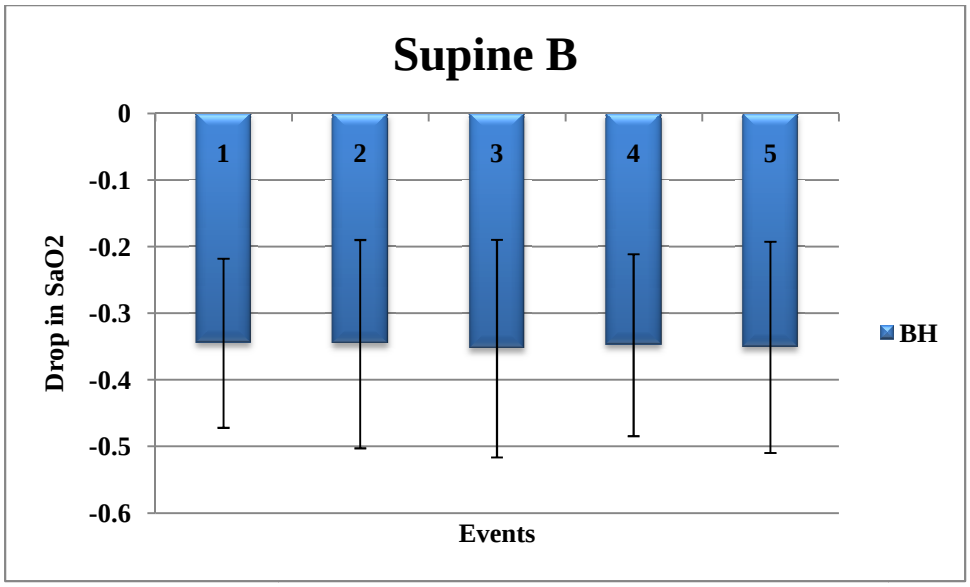


Figure 3.10 Drop in oxygen saturation due to breath hold for Supine B

The p-value for the ttest for comparison of the breath holds for for supine B is shown below in table Table 3.19

Table 3.19 Comparison of the rate of drop of oxygen saturation for all breath holds for Supine B

	Supine B				
	1	2	3	4	5
1	-	0.979955	0.882405	0.954032	0.908955
2	0.979955	-	0.910043	0.978134	0.934973
3	0.882405	0.910043	-	0.925697	0.974109
4	0.954032	0.978134	0.925697	-	0.952459
5	0.908955	0.934973	0.974109	0.952459	-

3.3 Sleep apnea study

The same features that were analyzed for simulated sleep apnea were analyzed for actual sleep apnea study too.

3.3.1 Amplitude

Figure 3.11 shows the average value of the amplitude for different events i.e. during normal breathing, apnea and hypopnea.

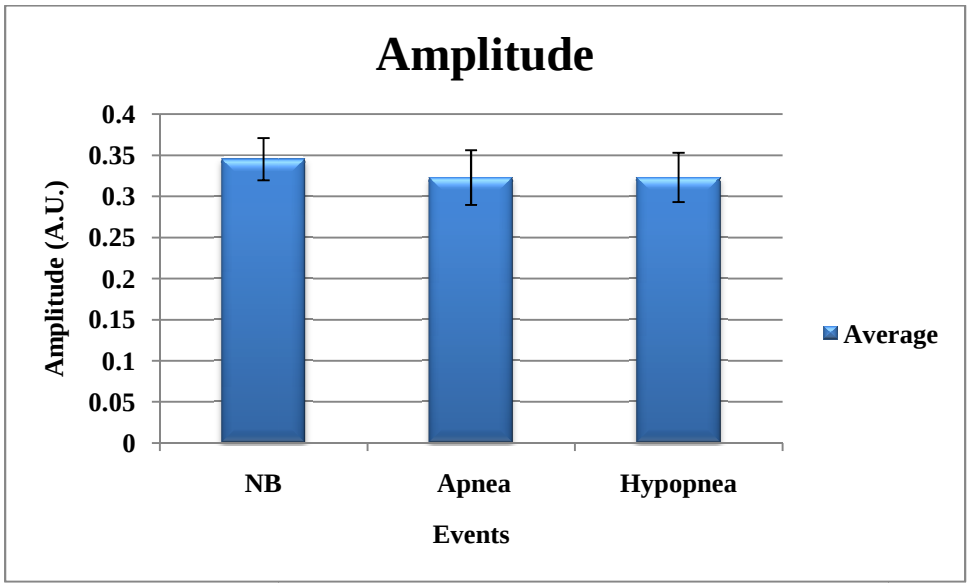


Figure 3.11 Average of amplitude for different events for sleep study.

The Tukey-Kramer test compares different events and the confidence limit for each are as shown in Table 3.20 where *** indicates significance

Table 3.20 Tukey-Kramer comparison for amplitude

Amplitude			
Comparison	Confidence limits		
Nb vs Apnea	0.01874	0.02937	***
Nb vs Hypopnea	0.0231	0.03313	***
Hypopnea vs Apnea	-0.0092	0.00107	

3.3.2 Area under the curve

Figure 3.12 shows the average value of the area under the curve for different events i.e. during normal breathing, apnea and hypopnea.

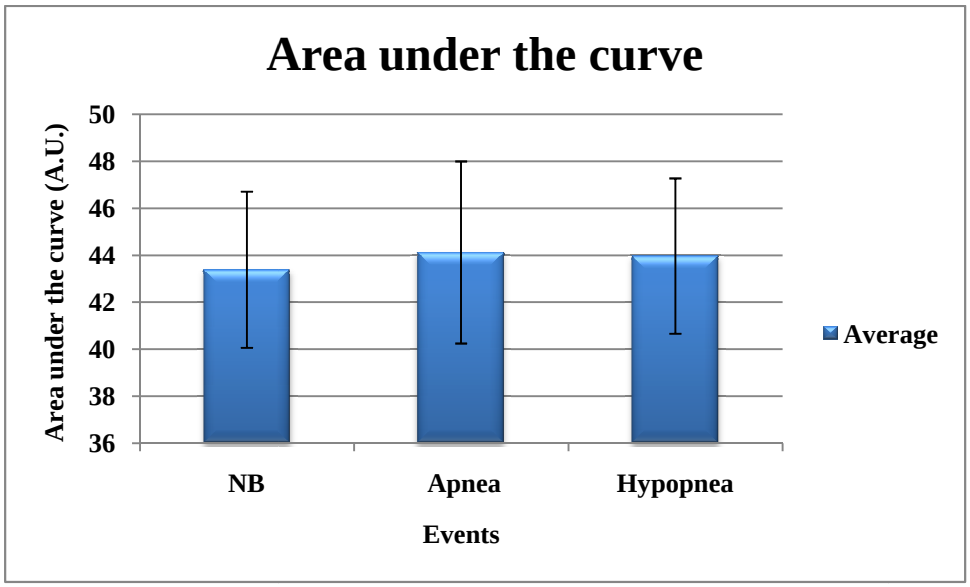


Figure 3.12 Average of area under the curve for different events for sleep study.

The Tukey-Kramer test compares different events and the confidence limit for each are as shown in Table 3.21 where *** indicates significance

Table 3.21 Tukey-Kramer comparison for area under the curve

Area under the curve			
Comparison	Confidence limits		
Nb vs Apnea	-1.0687	0.2917	
Nb vs Hypopnea	-0.4243	0.8594	
Hypopnea vs Apnea	-1.2617	0.0494	

3.3.3 Peak to peak time

Figure 3.13 shows the average value of the peak to peak time for different events i.e. during normal breathing, apnea and hypopnea.

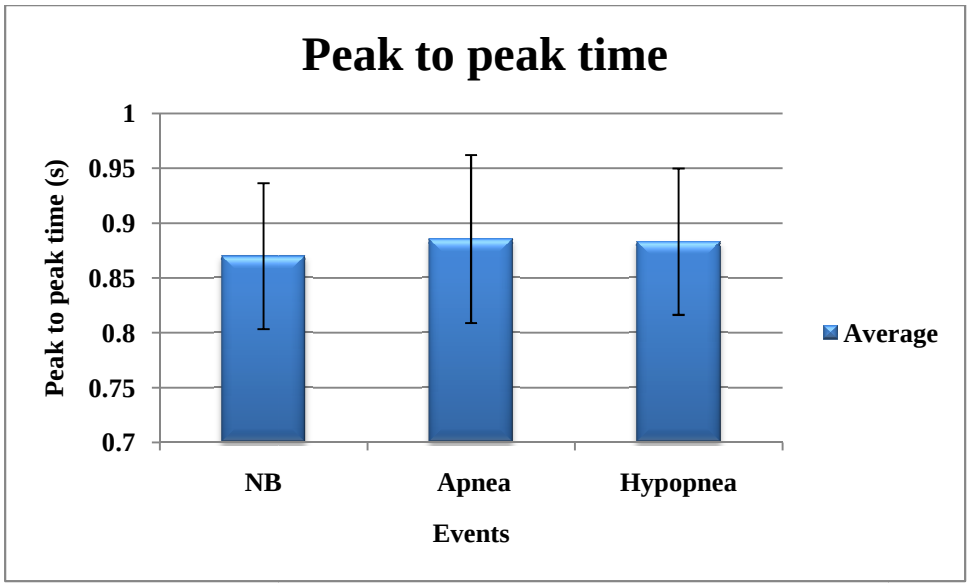


Figure 3.13 Average of peak to peak time for different events for sleep study.

The Tukey-Kramer test compares different events and the confidence limit for each are as shown in Table 3.22 where *** indicates significance

Table 3.22 Tukey-Kramer comparison for peak to peak time

Peak to peak time			
Comparison	Confidence limits		
Nb vs Apnea	-0.0313	0.00255	
Nb vs Hypopnea	-0.0089	0.01363	
Hypopnea vs Apnea	-0.0233	-0.0002	***

3.3.4 Peak

Figure 3.14 shows the average value of the peak for different events i.e. during normal breathing, apnea and hypopnea.

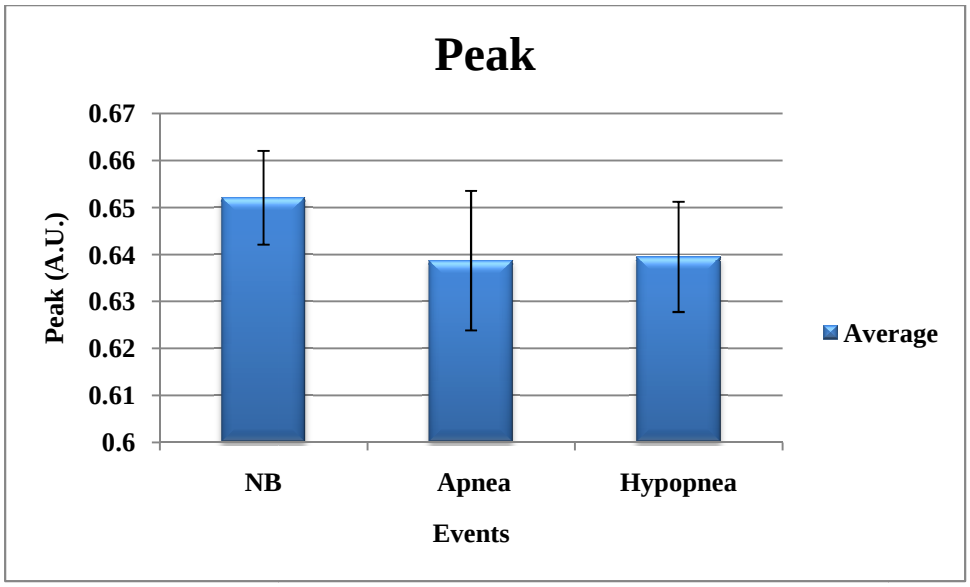


Figure 3.14 Average of peak for different events for sleep study.

The Tukey-Kramer test compares different events and the confidence limit for each are as shown in Table 3.23 where *** indicates significance

Table 3.23 Tukey-Kramer comparison for peak

Peak			
Comparison	Confidence limits		
Nb vs Apnea	0.00906	0.01925	***
Nb vs Hypopnea	0.01045	0.02007	***
Hypopnea vs Apnea	-0.006	0.00381	

3.3.5 Valley

Figure 3.15 shows the average value of the valley for different events i.e. during normal breathing, apnea and hypopnea.

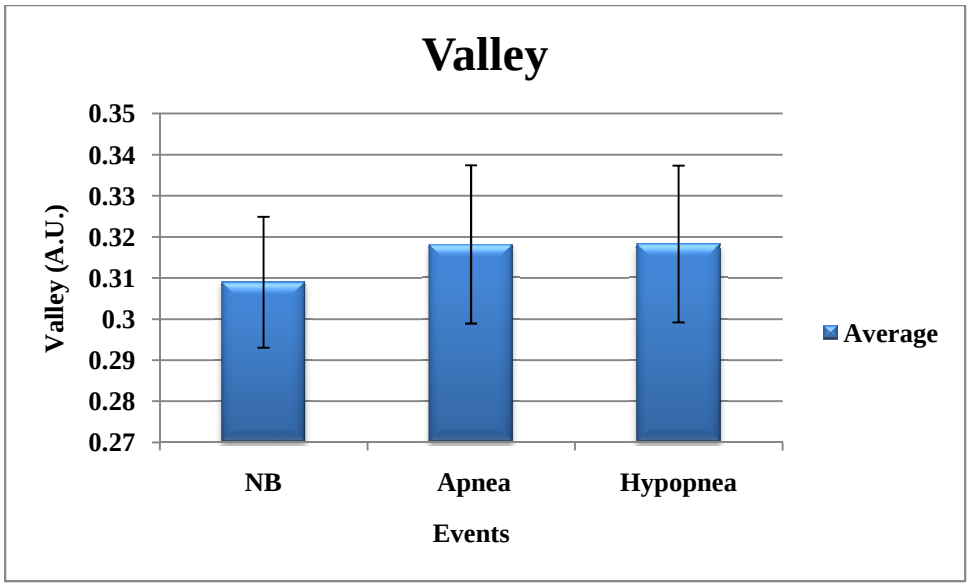


Figure 3.15 Average of valley for different events for sleep study.

The Tukey-Kramer test compares different events and the confidence limit for each are as shown in Table 3.24 where *** indicates significance

Table 3.24 Tukey-Kramer comparison for valley

Valley			
Comparison	Confidence limits		
Nb vs Apnea	-0.0145	-0.0054	***
Nb vs Hypopnea	-0.0167	-0.008	***
Hypopnea vs Apnea	-0.002	0.00682	

3.3.6 Drop in oxygen saturation

Figure 3.16 shows the average value of the drop in oxygen saturation for different events i.e. during normal breathing, apnea and hypopnea.

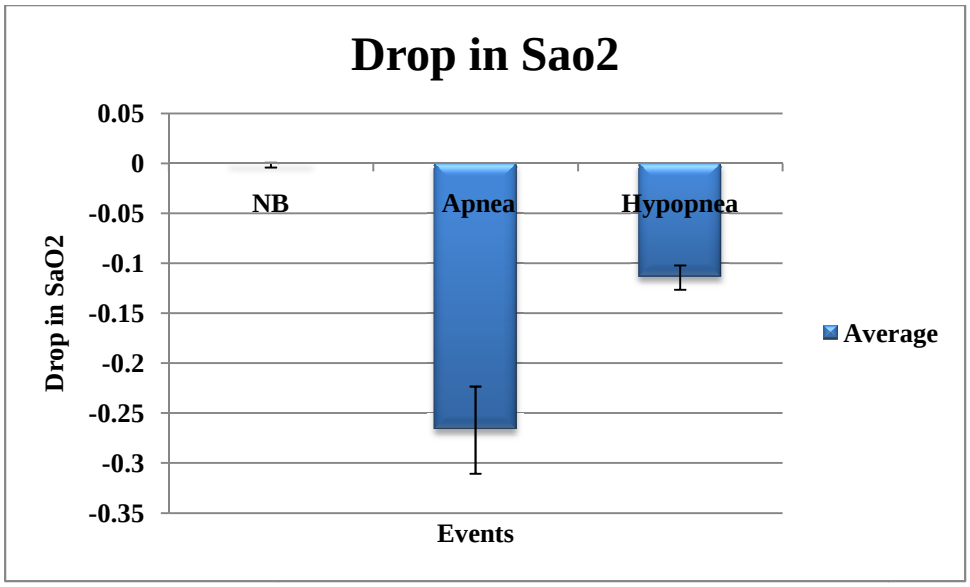


Figure 3.16 Average of drop of oxygen saturation for different events for sleep study.

The Tukey-Kramer test compares different events and the confidence limit for each are as shown in Table 3.25 where *** indicates significance

Table 3.25 Tukey-Kramer comparison for drop in oxygen saturation

Drop in SaO2			
Comparison	Confidence limits		
Nb vs Apnea	0.0772	0.14966	***
Nb vs Hypopnea	0.22892	0.30241	***
Hypopnea vs Apnea	0.1161	0.18836	***

CHAPTER 4

DISCUSSION AND CONCLUSION

4.1 PPG waveform from the simulated sleep apnea for study

Visually inspecting the average of all the features, we can see from figure 3.1 through figure 3.3, the amplitude, area under the curve and the peak to peak time increases as compared to the baseline.

These finding are confirmed from table 3.1, 3.3 and 3.5. The p-values from the mixed linear model also show that the amplitude, area under the curve and the peak to peak time are significantly different during breath hold when compared with the baseline.

The change in amplitude indicates the pulsatile flow increase during the breath hold, the volume of blood in every bolus has increased during the breath hold which is indicated by the area under the curve parameter and the peak to peak time which can be considered as the inverse of heart rate increases. This means that the heart rate decreases during the breath hold. We can say that as the heart rate decrease the heart pumps more volume of blood to maintain the cardiac output constant.

Table 3.2, 3.4, 3.6, 3.8 and 3.10 indicate the comparison of each parameter to see the gravity effect (posture effect) and the effect due to different frequency of apnea (protocol effect). This table indicates that there is no protocol effect i.e. there is no effect of the change in the frequency of apnea. This might be due to the reason that the 30 s rest

period in protocol B was enough for the physiological parameters to come back to normal as the subject chosen for this study all young and healthy subject.

It also shows there is no gravity effect i.e. there is no effect due to the change in the posture. Mainly the changes due to the posture are regulated by the carotid sinus reflex. But the reflex might weaken because of the fatigue or mental excitement [29]. This might the cause that we did not see any postural effect.

The duration of breath hold is another factor which is indicated in figure 3.6 and in tables 3.11 through 3.16. The table shows that for the sitting A and supine A there is a difference in the duration between breath hold 1 and all other breath holds. This might be due to the fact that the resting period in protocol A is quite enough for the physiological parameters to come back to baseline and the subject can hold their breath as much as they did during breath hold 1 or more. But for protocol B there is less time between the two breath holds which might cause fatigue. This might indicate the fact that subjects are not able to hold their breath longer.

4.2 Oxygen saturation during simulated sleep apnea

Table 3.16 indicates the p value of comparison of the rate of drop of oxygen saturation for all the breath holds for sitting A and figure 3.7 indicates the average rate of drop of oxygen saturation during Sitting A. Similarly table 3.17 indicates the comparison of the breath hold for sitting B, table 3.18 for supine A and table 3.19 for supine B and the figures 3.8 through 3.10 indicate the average value.

The figures and the tables indicated that the rate of drop of the oxygen saturation is not different for different breath holds and order in which the maneuver was done. This

might be because of the reason that the resting period in both the protocols was enough for the physiological parameters to be back to normal.

4.3 Conclusion

Five new features are proposed for quantifying the effects of sleep apnea on cardiovascular response. Simulated apnea tests in healthy subjects demonstrated that the peak to peak time and the area under the curve from the PPG waveform are the best features that show a significant difference between normal breathing and the breath hold. The rate of drop of oxygen saturation is another feature that showed promise for to differentiating between normal breathing and breath hold. However there is no difference in the rate of drop of oxygen saturation from one breath hold to the next breath hold.

Also there is posture effect on the peak to peak time i.e. there is a difference in heart rate while sitting versus supine. The two protocols did not make much difference in any of the features which shows 30 seconds is enough for the physiological parameters to back to normal.

4.4 Sleep apnea study

The same features as analyzed in simulated sleep apnea were analyzed for the actual sleep study too. The average of all the parameters during normal breathing, hypopnea and the apnea are shown in the figure 3.11 through 3.16 and the results from Tukey-Kramer comparisons between all these three events are shown in table 3.20 through 3.25.

For the actual sleep data study amplitude, peak and the valley show a significant difference between normal breathing and hypopnea and also between normal breathing

and apnea. This can be seen from both the graphical representation and the Tukey-Kramer comparison.

The peak to peak time and the area under the curve were the least significant features. If we compare sleep apnea data with the simulated sleep apnea data, we see that the peak to peak time and the area under the curve that were highly significant in the simulated study are not at all significant in sleep study. Also, peak and valley were not significant in the simulated sleep study were highly significant in the actual sleep study. This might be due to the fact that clippings were not fair enough to show the actual changes due to apnea or hypopnea. For example, there might be a mixed effect of the apnea and normal breathing in the same clip. The effect of normal breathing hence might suppress the effect of apnea. Also there were only 5 subjects for this study which is less. This might be also one of the causes that we see a difference between the simulated sleep study and the actual sleep study.

4.5 Future Work

Some of the features like upstroke time, down stroke time and slope of the up stroke edge from the PPG waveform can be studied in more detail. The combination of new features like peak to peak time and area under the curve from PPG waveform and the spectral analysis of the oxygen saturation [31] could be a very good diagnostic tool which would be simple and also cost effective. The PPG waveform features can also be combined with arterial blood pressure, electrocardiogram and other techniques for reliable diagnosis of obstructive sleep apnea.

APPENDIX A

MATLAB PROGRAM FOR FEATURE DETECTION FROM PPG WAVEFORM

```
clear all;
close all;
clc;
%Loading the data clipping into MATLAB
A=load('6235_10-02-01_1730_midmin5.mat');
d2=A.viru1(:,1); d1=A.viru1(:,3);
d3=A.viru1(:,6);



max = [];
min = [];
delta=0.05;

mn = 0; mx = 0;
mnpos = 0; mxpos = 0;

lookformax = 1;

% Finding Peak and Valley
for i=1:length(d1)
   a1 = d1(i);
 if a1 > mx, mx = a1; mxpos = i;
 end
 if a1 < mn, mn = a1; mnpos = i;
 end

 if lookformax
  if a1 < mx-delta
    max = [max ; mxpos mx];
    mn = a1; mnpos = i;
    lookformax = 0;
  end
```

```
  else
    if a1 > mn+delta
      min = [min ; mnpos mn];
      mx = a1; mxpos = i;
      lookformax = 1;
    end
  end
end

v1=max(:,2);
index=max(:,1);
v2=min(:,2);
val=min(:,1);
t1=d2(index);
t2=d2(val);
figure
plot(d2,d1);
hold on
plot(t1,v1,'r*')
hold on
plot(t2,v2,'g*')
hold on
plot(d2,d3)

%%Finding FWHM
j=1;
if t1(j)<t2(j)
   for i=1:length(v1)
   if i==length(v1)
      break
   end
      amp(i,1)=v1(i+1)-v2(i); %Finding the amplitude of the PPG waveform
```

```
        half(i,1)=(v1(i+1)-v2(i))/2;
        FWHM(i,1)=half(i,1)+v2(i);
        amptime(i)=t1(i+1);
    end
else
    for i=1:length(v1)
        amp=v1(i)-v2(i);
        half(i,1)=(v1(i)-v2(i))/2;
        FWHM(i,1)=half(i,1)+v2(i);
    end
    amptime(i)=t1(i);
end

d_valley=diff(t2);
d_peak=diff(t1); %Finding the peak to peak time of the PPG waveform

%Finding the area under the curve of the PPG waveform
for i=1:(length(val))
    if i==length(val)
        break
    end
    m=val(i);
    n=val(i+1);
    area=0;
for j=m:n
    area=area+d1(j);
end
auc(i,1)=abs(area);
end

%Writing into excel file
```

```
xlswrite('amp.xlsx',amp,'6235 Si B','A');
xlswrite('peak.xlsx',v1,'6235 Si B','A');
xlswrite('valley.xlsx',v2,'6235 Si B','A');
xlswrite('area.xlsx',auc,'6235 Si B','A');
xlswrite('difference.xlsx',d_peak,'6235 Si B','A');
```

APPENDIX B

MATLAB PROGRAM FOR DETECTION OF RATE OF DROP OF OXYGEN SATURATION

```
close all
clear all
clc
a=load('1986_10-02-01_1838.lvm');
t1=a(:,1);s1=a(:,2);w1=a(:,3);p1=a(:,6);
a1=decimate (t1,2000);
a2=decimate (s1,2000);
a3=decimate (w1,2000);
a4=decimate (p1,2000);
a2_new=roundn(a2,-2);
plot (a1,a2_new)
hold on
% plot (a1,a3,'r')
% hold on
a4_new=round(a4);
plot (a1,a4_new,'g')

%Finding end points of BH

j=1;
for i=1:length(a1)
   if i==length(a1)
         break
   end
   if (a4_new(i)>a4_new(i+1)) & (a4_new(i+1)==0)
      bh_end_time(j)=i;
      j=j+1;
   end
end

%Finding point from which the oxygen saturation starts rising
```

```
n=1;
for i=1:length(bh_end_time)
   k=bh_end_time(i);
   for m=k:length(a1)
      if a2_new(m)<a2_new(m+1)
         oxy_up(n)=m;
         n=n+1;
         break
      end
   end
end

% End Time delay

for i=1:length(bh_end_time)
   end_delay(i)=a1(oxy_up(i))-a1(bh_end_time(i));
   least_oxy(i)=(roundn(a2(oxy_up(i)),-2)*100);
end

% Finding starting point of BH

j=1;
for i=1:length(a1)
   if i==length(a1)
         break
   end
   if (a4_new(i)<a4_new(i+1)) & (a4_new(i)==0)
      bh_start_time(j)=i+1;
      j=j+1;
   end
end
```

```
% Start point of the lowest saturation

n=1;
for i=1:length(oxy_up)
   k=oxy_up(i);
   for m=k:-1:0
      if (a2_new(m)<a2_new(m-1))
         lowoxy_start(n)=m;
         n=n+1;
         break
      end
   end
end

hold on
plot(a1(lowoxy_start),(least_oxy/100),'b*')


% Start of downfall
for i=1:length(lowoxy_start)
   m=lowoxy_start(i);
   for x=m:-1:bh_start_time(i)
      if a2_new(x)>a2_new(x-1) | x==bh_start_time(i)
         plat_start(i)=x;
         break
      end
   end
end

for i=1:length(plat_start)
   x=plat_start(i);
   for m=x:bh_end_time(i)
```

```
        if a2_new(m)>a2_new(m+1) & a2_new(m-1)==a2_new(m)
            slope_start(i)=m;
            i=i+1;
            break
        end
    end
end

hold on
plot(a1(slope_start),a2_new(slope_start),'r*')
% hold on
% plot(a1(plat_start),a2_new(plat_start),'m*')


% New slope
for i=1:length(slope_start)
    a=slope_start(i);
    b=lowoxy_start(i);
    w=1;
    y=[];
    x=[];
    for m=a:b
        x(w)=a1(m);
        y(w)=a2_new(m);
        w=w+1;
    end
    diff_y=diff(y);
    diff_x=diff(x);
    new_slope(i)=(diff(y)/diff(x));
    two_slope(i)=(a2_new(a)-a2_new(b))/(a1(a)-a1(b));
end
```

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BIOGRAPHICAL INFORMATION

Swathi Iyer was born in Ahmedabad, India in the year of 1987. She is the second child of the family. She graduated with a degree of Bachelors of Engineering in Biomedical in the year 2008. Her keen interest in pursuing higher studies helped her to recieve Dean's Fellowship at the Bioengineering Department at University of Texas at Arlington. Her interest in signal processing led her to serve as a Graduate teaching assistant for Biological Digital signal processing and Process control in Biotechnology. This in turn gave her an impetus in the research carried out for the detection of sleep apnea which included collection of physiological signals and processing of the signals by developing several algorithms.