INVESTIGATION OF END TIDAL CARBON DIOXIDE ($ETCO_2$) AND HEART RATE VARIATIONS DURING SLEEP APNEA

by

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Nothing is achieved in isolation.

July 13, 2010

ABSTRACT

INVESTIGATION OF END-TIDAL CARBON-DIOXIDE ($ETCO_2$)

AND HEART RATE VARIATIONS DURING

SLEEP APNEA

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Sleep Apnea is a sleep disorder where limitation or cessation of breathing occurs. It is characterized by abnormalities in the respiratory pattern and quantity of ventilation during sleep. According to a study 4% of men and 2% of women have sleep apnea, which is a sizable sector of the adult population.

To analyze end-tidal CO_2 and heart hate variations due to apnea, 8 hr polysomnography (Sleep Consultant. Inc, Fort Worth, Texas) was performed on limited sleep apnea subjects and breath hold maneuvers were performed in awake subjects. In the simulated apnea study, 16 volunteer subjects (age: 29 ± 5 yrs, BMI: 24 ± 5 kg/m^2, 9 Male and 7 Female) were recruited to participate in two experimental protocols, referred to as A and B. Both A and B protocols involved breath hold maneuvers in sitting as well as supine positions. The order of protocols and the positions within the protocols were randomized. Each protocol started with normal breathing and stable blood pressure for 60s, followed by voluntary breath hold that lasted as long as the subject could tolerate. In A, each breath hold was followed by 90s of recovery; in B this period was 30s. The cycle was repeated five times in both protocols.

The features extracted from the wave forms are End-Tidal CO_2, Exhaled Carbon dioxide concentration sum (ECCS), Inspiration Time/ Expiration Time Ratio, Peak-Peak Interval, and Heart Rate (ECG). The Mixed Linear Model and the Tukey Kramer analysis show that $etco_2$, IE ratio from CO_2 and heart rate from ECG respectively are significant parameters ($P < 0.05$) to distinguish apneic events both in simulated and sleep study. $ETCO_2$ changes from baseline (40.80 ± 2.4) mmHg to normal breathings (38.56 ± 3.2) mmHg for sitting A which follows the same for other protocols. IE ratio changes from baseline (0.85 ± 0.05) to normal breathings (0.80 ± 0.06) for sitting A which follows the same for other protocols. Heart Rate changes from baseline (1.32 ± 0.02) *60 b.p.m to breath holds (1.26 ± 0.02) *60 b.p.m for sitting A which follows the same for other protocols. During sleep study there is a significant change in $ETCO_2$ from normal breathings (40.85 ± 3.9) mmHg to apnea (43.57 ± 3.4) mmHg and hypopnea (39 ± 6.4) mmHg. There is a significant change in IE ratio from normal breathings (1.58 ± 1.58) to apnea (1.02 ± 0.66) and hypopnea (1.21 ± 0.62). Heart Rate is also significantly different from normal breathings (1.05 ± 0.28) *60 b.p.m to apnea (1.19 ± 0.5) *60 b.p.m and hypopnea (1.06 ± 0.31) *60 b.p.m. It implies that during the apneic events the accumulation of CO_2, change in breathing patterns (IE ratio) and change in heart rate are significantly different. The posture (effect of gravity), frequency of apnea (protocols), duration of the breath hold did not have any effect on these features. Gender had an effect on the $ETCO_2$. These significant features can be used to check the efficacy of apnea treatment.

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CHAPTER 1

INTRODUCTION

1.1 Sleep Apnea

1.1.1 Definition

Sleep apnea is repetitive reduction or cessation of breathing for 10 seconds or more during sleep. Sleep apnea is a common disorder which is estimated to occur in 6% of U.S adult population (around 18 million people). 17% of adult populations having sleep apnea are estimated to have mild or severe apnea. Cessation of breathing during obstructive sleep apnea occurs because of the collapse of the airway due to sleep induced muscle relaxation.

1.1.2 Types of Sleep Apnea

Sleep Apnea is of two types: obstructive sleep apnea (OSA) and Central sleep apnea (CSA). Obstructive sleep apnea occurs when the throat collapses and blocks the air from entering the lungs. Central sleep apnea occurs when the brain stem does not signal the body to breathe. It occurs generally to the people who have the brain stem injury which is a crucial part for the respiration.

1.1.3 Related Disorders

Sleep Apnea is associated with many cardiovascular disorders. Sleep apnea has been independently associated as a risk factor for hypertension, arrhythmia, myocardial infarction and TYPE- II diabetes. Central Sleep Apnea (CSA) is associated with internal carotid artery stenosis [1] and diabetes mellitus [2]. Brain stem is the main center for the ventilatory response. So any disease affecting brain stem has an influence of ventilatory problems [3]. An example of this is post polio syndrome in which medullary neurons are damaged [3]. The arterial pressures are elevated during OSA. OSA also results in ventricular ectopy [3].

1.1.4 Detection and Treatment

Sleep Apnea is diagnosed using a standard test called nocturnal polysomnography. This test includes an overnight study at a sleep lab with multiple physiological markers being measured simultaneously. The physiological markers which are measured during nocturnal polysomnography are Electroencephalography (electrical activity of brain), skeletal muscles electrical activity, eye movements, heart rate, arterial oxygen saturation, and respiratory flow. The severity of the sleep apnea is scaled with the Apnea-Hypopnea Index (AHI). AHI equals the number apneas and hypopneas in one hour of sleep, as averaged over a full night study. A person with AHI of 40 experiences 40 abnormal respiratory events per hour of sleep which is a severe level of disease. Continuous positive airway pressure (CPAP) is the treatment of choice for sleep apnea. CPAP applies pressurized air to the upper airway sufficient to prevent the upper airway from collapsing. CPAP is highly effective for treating sleep apnea. Other devices which are used to treat sleep apnea which include mandibular advancement devices, soft palate lift and tongue retaining device [4].

1.2 Effect of apnea on CO_2 production

Each sleep apnea event leads to CO_2 accumulation in the tissues. Therefore the breath after each sleep apnea episode contains elevated levels of carbon dioxide.

1.3 Effect of apnea on Heart Rate

During the apnea, the breathing stops which activates sympathetic nervous system (fight or flight) system. The nerve and adrenaline signals are sent to the blood vessels which constricts them thus making the heart work harder. During the vessel constriction the blood is pumped more to the brain and some important muscles. ECG is the best and cheap way to detect sleep apnea. With the help of ECG sleep apnea can be detected more accurately. The QRS and RR interval are the parameters with which sleep apnea can be classified among the normal patterns. Both Time domain and Frequency domain analysis is useful for detection of sleep apnea [9]. The heart rate decreases during sleep apnea[3].

1.4 Previous Studies

Depressed hypercapnic response is associated with Obstructive sleep apnea[6]. Study is performed on influence of carbon dioxide levels on the cerebral autoregulation in patients [12]. CO_2 reactivity and Cerebral Blood Flow (CBF) regulate the chemoreflex control of the breathing [13]. A model is developed based on mechanism of CBF and CO2 [13]. The ventilator responsiveness to CO2 below the eupnea is set as a determinant of ventilatory stability in sleep [14]. During apneic oxygenation preceded by acute respiratory hypocapnia , the rate of increase of arterial carbon dioxide is compared with that during apnea preceded by the respiratory eucapnia [15]. ECG based wavelet analysis was used to classify OSA from normal based on the QRS peak area and RR interval [8]. Different algorithms have been developed for ECG based sleep apnea detection which uses ECG pulse energy, spectral analysis of R wave amplitude using power spectral density, S wave amplitude and R duration [9].

1.5 Goals

The goal of the study is to determine the features which can quantitatively measure the CO_2 and Heart Rate variations in sleep apnea and determining their efficacy in detecting the apnea. In order to achieve this goal we propose the following hypothesis.

1. We hypothesize that "CO_2 and heart rate during sleep apnea are significantly different from normal breathing."
2. We hypothesize that " CO_2 and heart rate are influenced by the frequency of apnea episodes and posture."
3. We hypothesize that "Breath hold tolerance is greater in sitting posture compared to supine and greater in low frequency apnea compared to high frequency apnea "

To test the above hypothesis study is done on simulated apnea and actual sleep apnea.

1.6 Organization of Thesis

Chapter two describes the end-tidal CO_2, equipments, protocols, features extracted and algorithms used to detect them. Chapter three presents the results obtained from simulated apnea maneuvers and nocturnal polysomnography. Chapter four discusses the results presented in chapter three and draws conclusion based on the results and discussion.

CHAPTER 2

METHODS

This chapter describes the methods utilized to achieve the objectives of the study. Specifically, the metrics and means for quantifying CO2 production in response to apnea will be presented. It will be followed by the methods for obtaining and quantifying the cardiac response from ECG. As part of the experimental investigation, two protocols used for studying simulated sleep apnea will be described followed by a presentation of the methods of studying the CO2 production and cardiac response in apnea patient during sleep.

2.1 Quantification of CO2 production in response to apnea

2.1.1 End Tidal CO_2

End-tidal carbon dioxide ($ETCO_2$) is the maximum concentration or partial pressure of the CO_2 in the exhaled breath at the end of exhalation. The unit of its measurement is mmHg. Carbon dioxide is an important gas exhaled by the human body. The inhaled oxygen in the lungs is exchanged with the carbon dioxide in the alveoli capillaries. The normal end-tidal CO_2 range is 35-45 mmHg. In healthy subjects, the difference between arterial CO_2 ($PaCO_2$) and End-Tidal CO_2 ($ETCO_2$) is typically ± 5 mmHg [11]. Abnormally elevated CO_2 content in the blood constitutes hypercapnia. Hypoventilation or rebreathing exhaled carbon dioxide cause hypercapnia. Decreased content of CO_2 in the blood is called hypocapnia and results from ventilation in excess of that necessary to support the current metabolism. Hypocapnia causes cerebral vasoconstriction and systemic alkalosis. Figure 2.1 shows a typical respiratory CO_2 waveform[11].

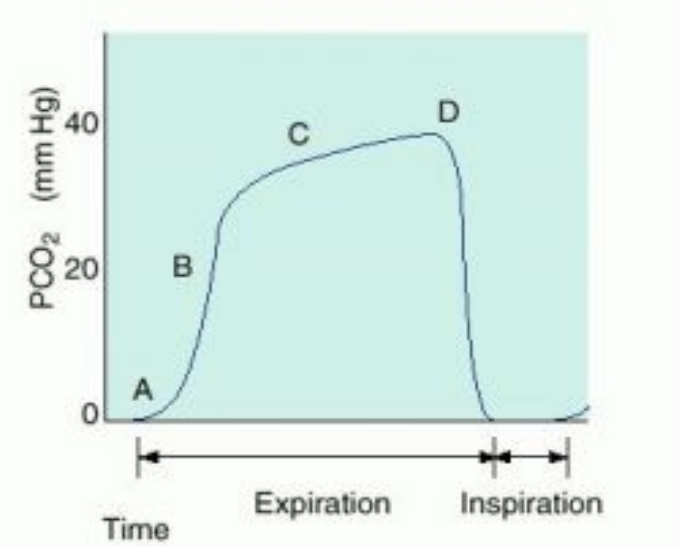

Figure 2.1 CO_2 waveform[11]

A to B is the inhalation phase and shows atmospheric [CO_2]. B to C is primary respiratory phase. C to D, exhalation of mostly alveolar gas (alveolar plateau). D is the end-tidal point, which is the maximum [CO_2] during the respiratory cycle, which is generally accepted as representing alveolar [CO_2]. D to E is the inspiration begins and carbon dioxide concentration rapidly falls to atmospheric levels (~0.03 %).

2.1.2 Exhaled CO_2 concentration area

The exhaled CO_2 concentration area represents the amount the CO_2 being exhaled during a single breath. Considering Figure 2.1, each point on the CO_2 curve represents the concentration of CO_2 during exhalation which reaches a maximum at point D which is called End-Tidal CO_2. The area under the CO_2 waveform gives the total exhaled CO_2 concentration. The exhaled CO_2 concentration area when plotted against the expired volume is called the effective alveolar ventilation [17].

2.1.3. Means for measuring exhaled CO_2

The exhaled CO_2 is measured using CO2 monitor (Model 1265, Novametrix Medical Systems INC. CT, USA) called capnogard. The exhaled gas is sampled via vacuum through cannula to

the equipment and the concentration of the CO2 is determined. The CO2 monitor takes about 30 seconds to warm up after it is turned ON. The Capnostat sensor is plugged in and unit is calibrated using the zero cell and reference cell. The pump in the unit which samples the air is turned ON and then the nasal cannula is attached to it and calibrated. The interface must be set to analog output module.

2.1.3.1 Principle of Operation

Capnography is a technique for monitoring Carbon dioxide levels in exhaled air. Capnography works on the principle of Beer Lambert's law with the use of a non-dispersive Infrared (NDIR) sensor [7]. Ratiometric measurement is used to measure the concentration of the CO_2. NDIR sensors detect the CO_2 concentration in the gaseous mixture using its characteristic optical absorption. An NDIR sensor consists of an infrared source, light tube or sample chamber, interference filter and infrared detector. The gas is sent into the sample chamber or light tube and its concentration is measured by its specific wavelength absorption in the IR spectrum. CO_2 absorbs IR wavelength in the range of 4 – 4.5 µm (typically at 4.2 µm). Capnostat (CO2 sensor) uses the beam splitter by which it measures the IR light at two wavelengths. Infrared light source is directly related to the wavelength which is not absorbed by CO_2 molecules. The absorbed wavelength is sent to the infrared detector by using the interference filter (wavelength filter). The CO_2 partial pressure is determined using the Beer Lambert's Law which is given as

$I=I_0 .e^{k*p}$

$I/I_0=e^{k*p}$

Applying natural logarithm on both sides of the above equation

$\ln(I/I_0)=k*p$

$p = (1/k)*\ln(I/I_0);$

Where I_0 is the measured intensity of the unabsorbed wavelength, I is the intensity of the light at the detector, k is the constant, p is partial pressure to be measured expressed in mmHg.

For determining Carbon dioxide (CO_2) concentration NDIR sensor is the reliable one [16] whose specifications are described in section 2.3.1.4. Infrared light is generated on one side of the U-shaped sensor shown in the Figure 2.2 and focused on the airway adapter. The light is detected at the other end. Carbon dioxide in the adapter which is placed between the source and detector absorbs some of this light energy. The amount of detected light energy is related to the amount of CO_2 in the sample cell and displayed on the monitor (Fig 2.3) . A proprietary adaptive digital detection algorithm system is used in the Capnogard to measure the CO_2 levels [7].

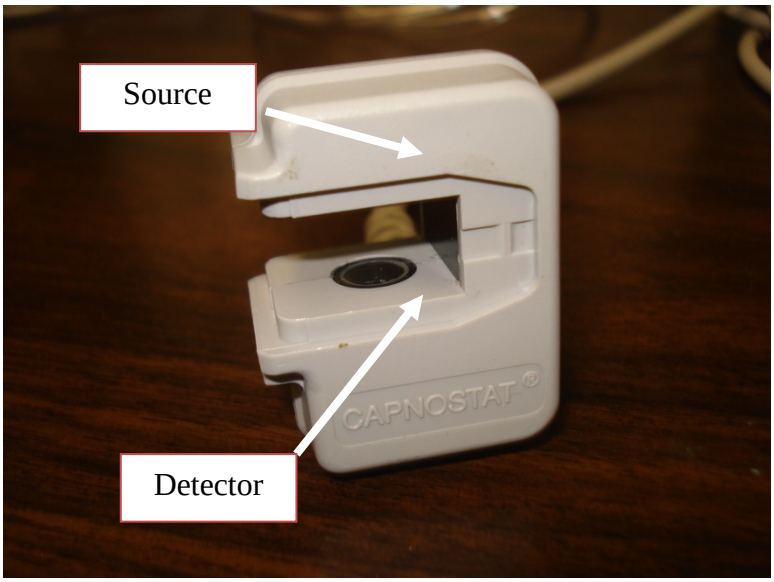

Figure 2.2 Capnostat Sensor

Figure 2.3 Capnoguard monitor and display unit

2.1.3.2. Catheters and Tubing

The Capnogard consists of nasal air sampling tube, NDIR sensor (Capnostat), CO_2 analyzer and analog output. Nasal sampling cannula samples air from the opening of the nasal cavity or mouth and sends it to the NDIR sensors which generates signal based on the light intensity at the detector and then sends the signal to the CO2 analyzer (Fig. 2.2) . The CO_2 analyzer determines the concentration of the gas. Sampling Cannulas are of two types nasal cannula and oral nasal cannula (Salter Labs, CA, USA) as shown in the Figure 2.4, 2.5.

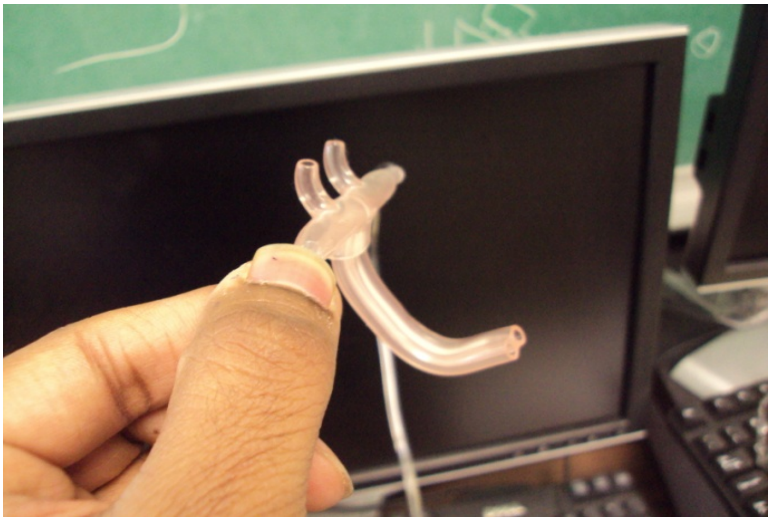

Figure 2.4 Oral Nasal Cannula

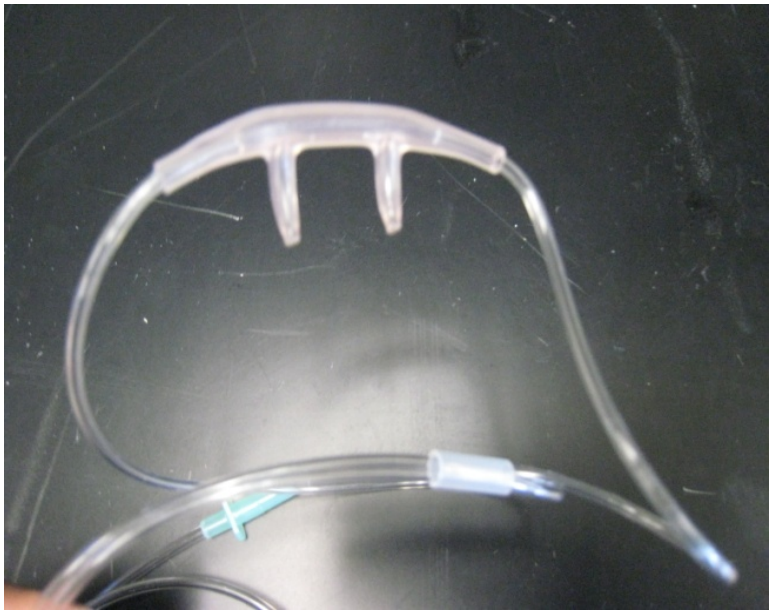

Figure 2.5 Nasal Cannula

2.1.3.3. Calibration

The calibration set up consists of placing the calibration cells (Fig. 2.6) within the sensor opening (Fig. 2.2). As show in in Fig. 2.6, the calibration cells are zero cell and reference cell. The zero cell is placed in the Capnostat until the timer goes off and the same is repeated with the reference cell. This sets the baseline of the readings. No air should be passed through the cannula when the calibration is in process [7].

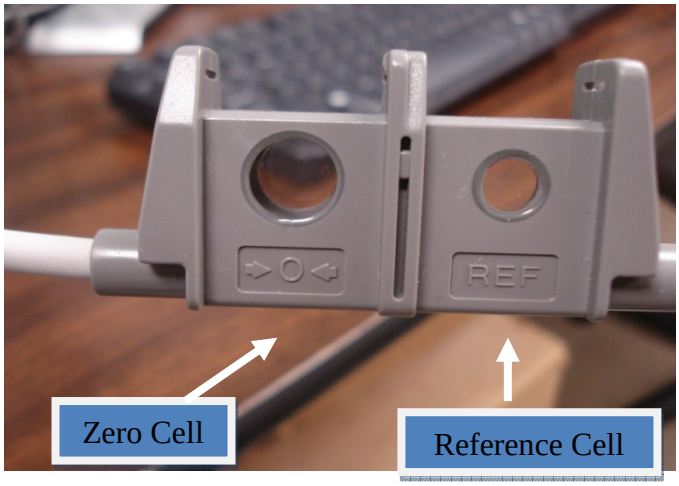

Figure 2.6 Calibration Set Up

2.1.3.4. Output Signals

The CO_2 monitor (Fig. 2.3) generates three signals that can be used for quantification of CO_2 production. They are End-tidal CO_2, instantaneous CO_2 waveform, and respiratory rate. Respiration is calculated by measuring the time interval between detected peaks of CO_2 waveform. The inverse of this measurement is displayed as respiratory rate. The Capnogard measures the respiratory rate in the range of 0-150 breaths/min and accuracy of ±1br/min. End-Tidal CO_2 indicates the CO_2 concentration at the end of each exhalation. CAPNOGARD measures $ETCO_2$ in the range of 0-99 mmHg. The system is accurate to ±2 mmHg from 0-40 mmHg, and to within 5% of reading from 40-99 mmHg [7]. The response time is 60 ms. These signals are acquired from the Analog Output module of the Capnoguard which is located at the rear of the unit. The interface must be set to Analog Output Module interface in the setting panel of the unit. A detail of the analog connection for Capnoguard is given in Appendix.

2.2 Quantification of cardiac response to apnea

2.2.1. Electrocardiography (ECG)

As part of the objectives of this thesis, the relationship between the cardiac response and CO_2 production was investigated. Specifically, the cardiac response was measure and quantified using electrocardiography.

2.2.1.1. Definition

Electrocardiography (ECG) is the measurement of the electrical activity of the heart with the help of surface electrodes. The electrodes can be placed in different configurations like Limb Lead configuration which includes Lead I, Lead II, Lead III or a chest electrode configuration like V1, V2, V3, V4, V5, V6 can also be used. A typical ECG wave consists of the P wave, QRS complex, and T wave. The figure 2.7 shows an idealized ECG wave with all the waves and intervals associated with it. The RR interval (the time interval between two consecutive R peaks) is the main parameter for measuring the heart rate (HR).

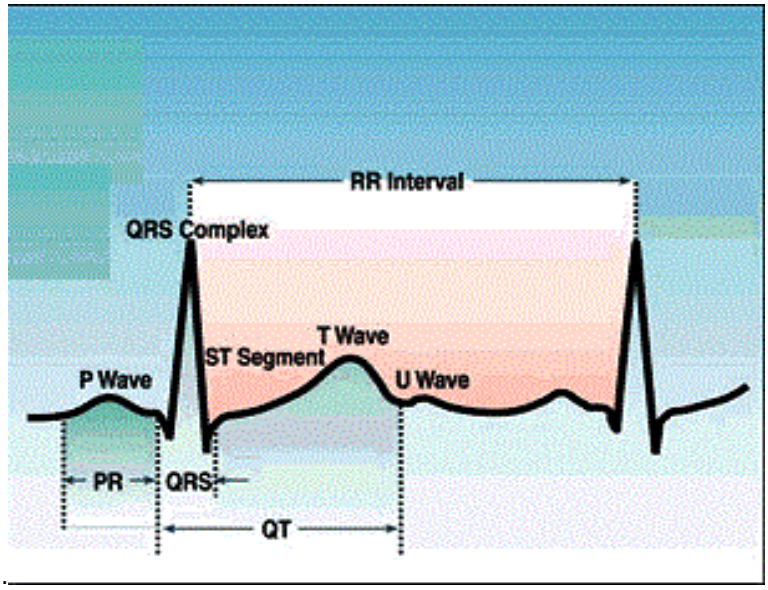

Figure 2.7 ECG wave [18]

2.2.1.2 Relation of ECG with sleep apnea

Studies have shown that cardiac response to sleep apnea can be quantified using ECG [8] [9]. The morphology of QRS and metrics derived from RR interval have been used to detect apnea. Both Time domain and Frequency domain analysis of these metrics have shown promise for detection of sleep apnea[9]. In particular, researchers have demonstrated that heart rate variability which is the variation in the time between the heart beats increases during sleep apnea. From the ECG waveform the heart rate is derived which is inverse of the RR intervals.

2.2.1.3 Means of acquiring ECG

Electrocardiography (ECG) is the measurement of electrical activity of heart. This electrical activity is recorded with the help of ECG electrodes which are placed on the skin at some specific locations based on the configuration used. The ECG recording unit used is the MP150 and ECG 100C (Biopac, CA, USA). All the ECG leads namely lead I, lead II, lead III can be used with the ECG unit. The analog output is taken from channel 1 whose details are given in Appendix B.

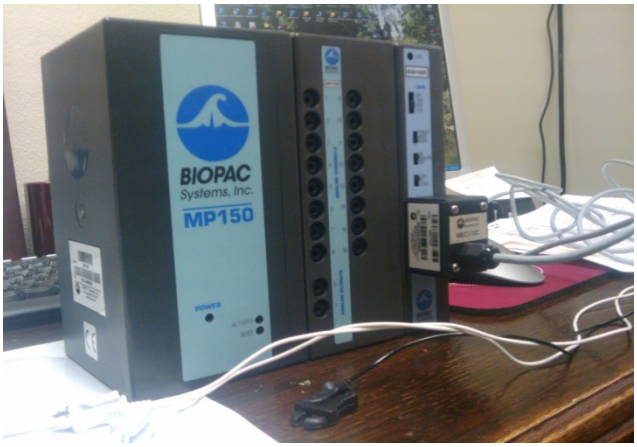

Figure 2.8 Electrocardiography Unit

2.2.2 Electrode Placement

The LEAD I configuration is used for placing electrodes on the chest. The positioning of the electrodes is shown in the Figure 2.9. The RA is the placement of electrode on Right Arm, LA is the placement of electrode on Left Arm, LL is the placement of electrode on Left Leg.

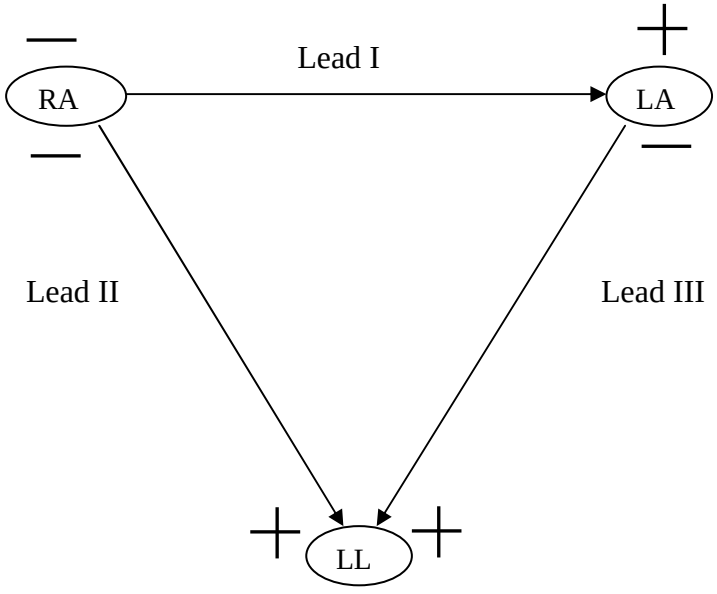

Figure 2.9 Lead I Configuration

The part of the skin used for placing electrodes is cleaning with cleansing solution to provide good contact between skin and electrode. The electrodes used are cloth electrodes which are shown in the figure 2.10. These have a circular contact area of 1cm diameter on a 2.5 cm square backing. These silver-silver chloride (Ag-AgCl) electrodes provides good transmission of surface biopotentials[].

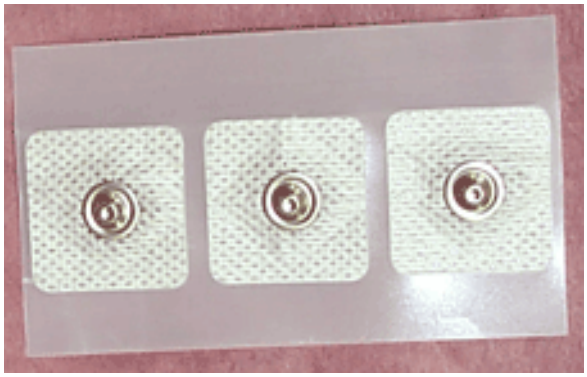

Figure 2.10 ECG Electrodes

2.2.3 Output Signals

The MP150 acquisition unit has analog output channels through which analog ECG signal can be sent to the Data Acquisition Device DAQ unit.

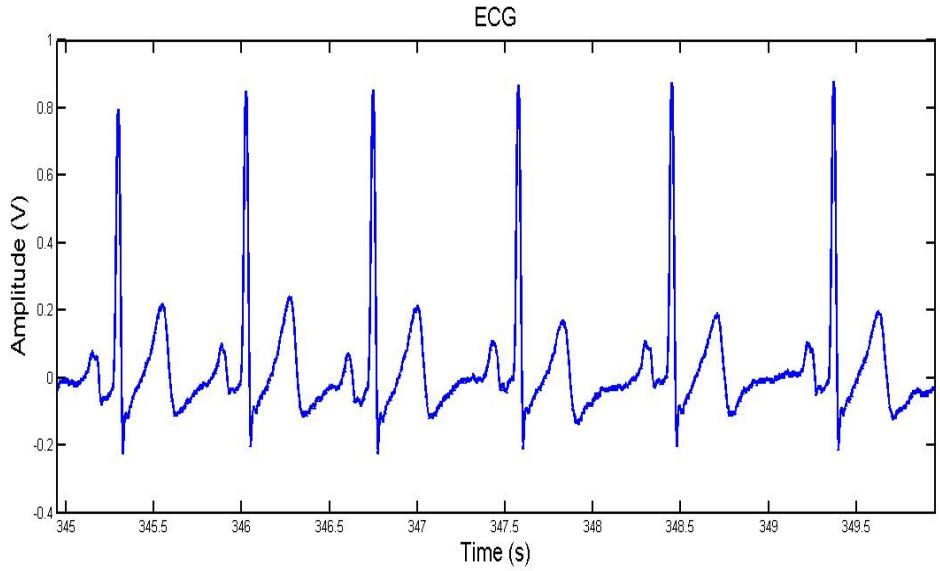

Figure 2.11 ECG signal

2.3 Experimental Methods

2.3.1 Simulated Apnea Study

One method to simulate sleep apnea is wakeful breath holding. During this maneuver a subject voluntarily holds his/her breath to simulate apnea. The breath hold maneuver is expected to elicit physiological responses that are similar to sleep apnea.

2.3.1.1. Simulated Sleep Apnea Protocol

In order to investigate the effect of apnea on the CO_2 dynamics, two experimental protocols namely Protocol A and Protocol B which uses breath holds to simulate apnea are used. The duration of breath holds and time duration between successive breath holds are different. The data is collected using these protocols in two different positions namely sitting and supine. The selection of these protocols for the study is randomized in order to eliminate bias in the results.

2.3.1.1.1 Protocol A

The subject breaths normally for 60s which is considered as baseline. When the subjects starts holding his/her breath a nose clip is placed on the nostrils. The subject was asked to signal with his hand when he/she can no longer hold his breath, then the nose clip is removed. The next breath hold was started after 90s. The protocol A was design to have 5 breath holds and two normal breathing (one preceding the breath hold 1 and another succeeding the breath hold 5). The timing diagram for the protocol A is shown in the figure 2.12. The Breath hold is represented as BH and normal breathing are represented as NB's.

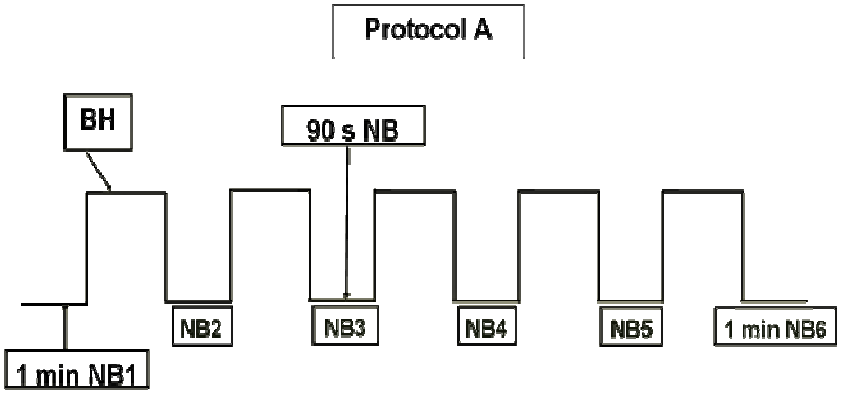

Figure 2.12 Timing Diagram for Protocol A (NB-Normal Breathing, BH-Breath hold).

2.3.1.1.2. Protocol B

The subject breaths normally for 60s which is considered as baseline. When the subjects starts holding his/her breath a nose clip is placed on the nostrils. The subject was asked to signal with his hand when he/she can no longer hold his breath, then the nose clip is removed. The next breath hold was started after 30s. The protocol B was design to have 5 breath holds and two normal breathing (one preceding the breath hold 1 and another succeeding the breath hold 5). The timing diagram for the protocol B is shown in the figure 2.13.

The difference between Protocol A and Protocol B is the inter-breath hold duration. For the Protocol B the inter-breath hold duration is 1/3 of the period of normal breathing between breath holds in Protocol A.

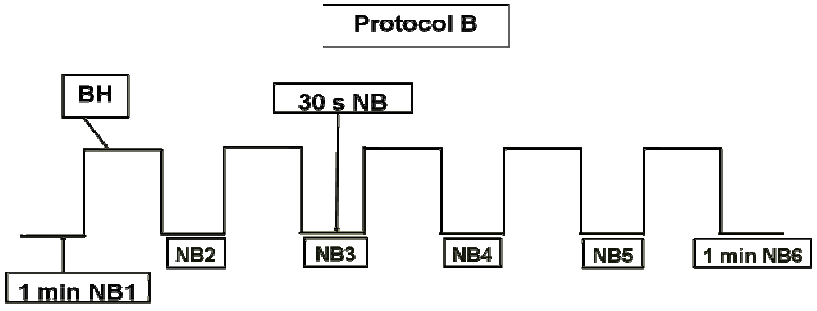

Figure 2.13 Timing Diagram Protocol B (NB-Normal Breathing, BH-Breath hold).

2.3.1.2 Postures

Both the Protocol A and Protocol B are performed under two different postures namely sitting and supine. So, totally we have 4 modes during experiment which are sitting A, sitting B, supine A, supine B. As mentioned earlier, the order of the protocols and the order of postures within each protocol were randomized.

2.3.1.2.1. Sitting

In this posture, the subject comfortably sits in a chair with upright postures with all the electrodes and cannula attached as shown in the Figure 2.14

Figure 2.14 Sitting Posture

2.3.1.2.2. Supine

In this posture, the subjects lays down on an inflatable mattress with all the electrodes and cannulas attached as shown in the Figure 2.15

Figure 2.15 Supine Posture

2.3.1.3 Experimental Setup

2.3.1.3.1. Data acquisition

The output signals from the CO_2 monitor is fed to the data acquisition system which consists of a DAQ 6024 E and CB-68 LP (National Instruments, Austin, Texas). DAQ 6024E is a 200 kS/s,12 Bit, 16 Analog Input Multifunction DAQ. It has two 12 bit analog output lines, 8 digital I/O lines, and two 24 bit counters. CB-68LP serves as the hardware interface between DAQ device and the CO_2 unit. CB-68LP is a 64 Pin I/O connector Block with slots for screwing analog cables into it. The signal from the DB15 connector of the analog output module is given to the CB-68LP by screwing the cable into it. From the CB-68LP, the End-Tidal CO_2 value and CO_2 waveform are passed on to DAQ which digitizes the signal. The digital signal is capture by a custom-designed data acquisitions program (DACP) using the LABVIEW 8.6 graphic programming language (National Instruments, Austin, Texas) . The signals are sampled at a rate of 1kHz.

Figure 2.16 DAQ 6024E for data acquisition

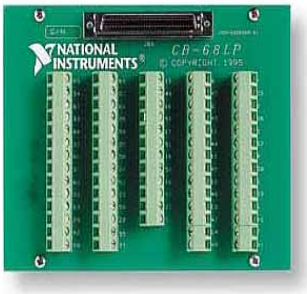

Figure 2.17 CB-68 LP (connector block)

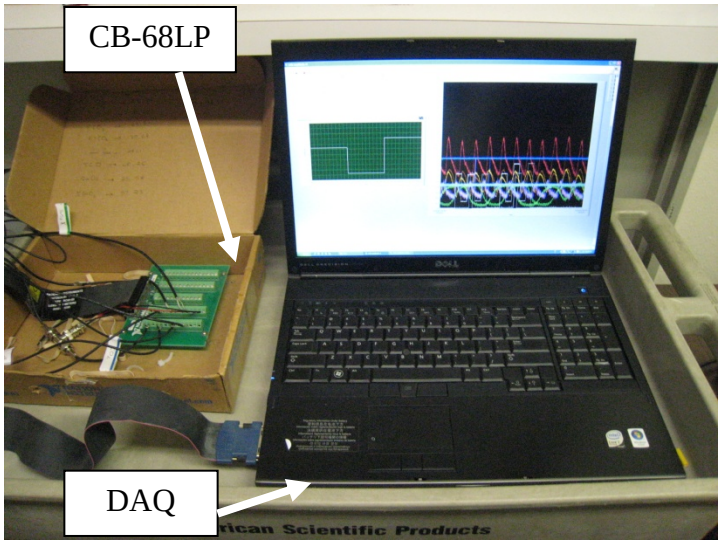

Figure 2.18 Data acquisition set up

2.3.1.3.2 Other Equipments

Cerebral Blood Flow monitor (DWL, Compumedics, Germany) collects the mean cerebral arterial blood flow.

2.3.1.3.3. Data Storage

The signals are converted to digital and then stored in the laptop using LABVIEW 8.6. The data is stored in the form of .lvm (LABVIEW Measurement) files. This format is used for one dimensional data and is a text based format file. These files store the data in a columnar format with each column having the values of the signal from a particular

channel of the board. The naming of the file follows with the subject number and the date the experiment is conducted.

2.3.1.4. Subjects

Sixteen volunteer healthy subjects (9 men and 7 women) participated in this study. The subjects presented that they did not have any respiratory or cardiac disorder. They also refrained from drinking caffeine or alcohol in the 24 hours before the time of study.

2.3.1.4.1 Subject Demographics

The demographics for the subject who participated in the simulated sleep apnea study are given in the table 2.1.

Table 2.1 Subject Demographics for Simulate Sleep Apnea Study

Subject	Age (mean ± σ) yrs	Height (mean ± σ) (cm)	Weight (mean ± σ) (kg)	BMI (mean ± σ) (kg/m^2)
9 M, 7 W	29 ± 4.89	165.88 ± 9.23	67.19 ± 19.31	24.07 ± 4.84
Men	30.11± 5.11	172 ± 6.86	77.78 ±17.99	26.14 ± 4.6 8
Women	27.57 4.54	158± 4.89	53.57± 10.78	21.4± 3.83

(σ = standard deviation)

2.3.2. Sleep Studies

The sleep study is done to monitor and diagnose the sleep disorders. In this section the protocols used and the experimental setup required for the sleep study are described.

2.3.2.1 Protocol

The protocol used for the sleep lab study is an 8hr nocturnal polysomnography.

2.3.2.2. Experimental Setup

The subjects who volunteer for study have been previously diagnosed as having sleep apnea. They are tested in the Sleep Consultants Inc (Fort Worth) which is an accredited sleep lab and being monitored by expertise lab personnel. The set up includes Capnogard, BP monitor, ECG, Cerebral blood Flow monitor, SaO2 monitor, Ultrasound Unit, EEG, EOG, EMG,

Nasal Pressure, leg movements, other equipment generally connected during polysomnography. The DACP also generates a synchronizing signal concurrent with the data acquisition which is fed back into the system and also to other units in the study. The synchronous signal takes the system time as input and generates three pulses corresponding to hours, minutes and seconds. The magnitude of the pulse is based on the value of the hours, minutes and seconds. The hours, minutes and seconds are converted to a particular voltage within the range of 0-1 V which is compatible with the sleep lab system. The corresponding voltages for hours, minutes and seconds are the amplitudes of the each of the square pulses. This signal is sent to the polysomnography unit as well as the DAQ board (3.1). This synchronous signal ensures that there is no time lag between different units.

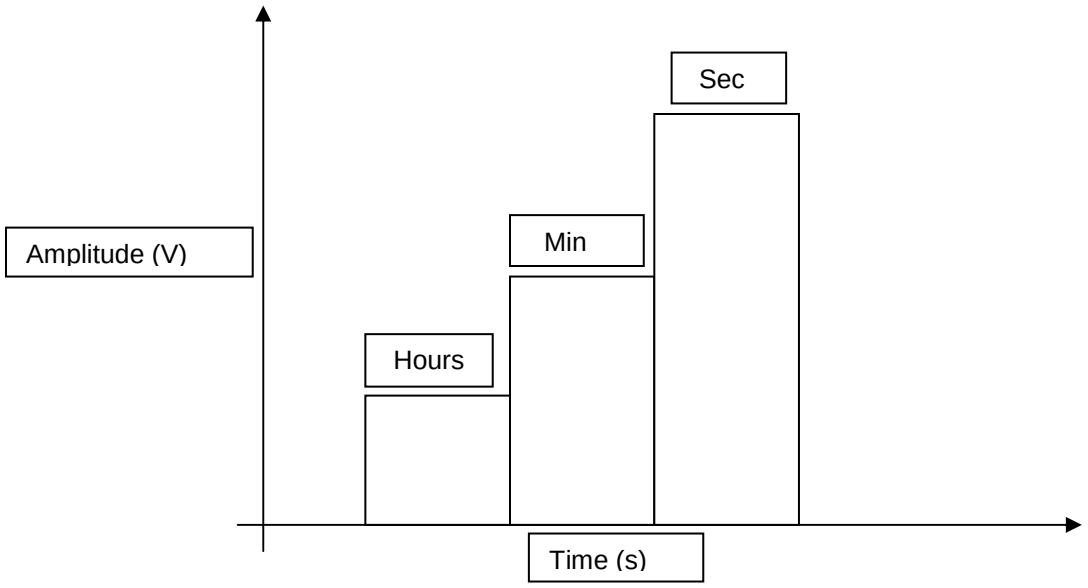

Figure 2.19 Synchronous Signal

2.3.2.3. Subjects

The total of 5 subjects who have been previously diagnosed with obstructive sleep apnea are recruited. An 8 hr nocturnal polysomnography study is performed on them (*- with exception to one subject who was studied during day time and for very short time).

Table 2.2 Subject Demographics for Sleep Study

Subject	Age (mean ± σ) yrs	Height (mean ± σ) (cm)	Weight (mean ± σ) (kg)	BMI (mean ± σ) (kg/m^2)
4 M *, 1 W	53.6 ± 7.4	166.1± 6.6	93.00±23.60	33.66 ± 7.27

(σ = standard deviation)

2.3.2.4 Sleep data scoring

The data obtained during the nocturnal polysomnography are scored by a certified sleep technician, blind to the objectives of this study.. The scoring is based on the sleep stages and the types of apnea they have experienced during the study. The details of this scoring is documented which is used to analysis of the exhaled CO_2 and ECG signals which is explained in details in section 2.4.1

2.4 Design of Feature Extraction Algorithm

The previous sections explained the CO_2 and its relation with sleep apnea, its instrument and experimental protocols. In this section, the metrics derived from CO_2 waveform that hold potential for assessment of metabolic variation are described.

2.4.1 Constructing Apneic Event and Sleep Stage Waveform

The scored polysomnography data obtained from the sleep lab contains information about the time of apnea, the sleep stage and their duration. Using this information, an event waveform and sleep stage waveforms are generated whose amplitudes describe the type of apnea and the sleep stage respectively and whose duration describes the duration of the apneic event and sleep stage respectively.

2.4.2 Data Clipping

The data obtained from the LABVIEW and polysomnography are clipped into normal breathings, breath holds in case of breath hold maneuvers and normal breathings, apneic events in case of polysomnography. The software used for clipping the data is MATLAB which loads the file and with the help of Graphics User Interface (GUI) it allows the user to clip the large files into required small files of normal breathings and apneic events. The naming convention of the clipped file is in accordance with the LABVIEW naming convention (as in 3.2.4) including the protocol and postures used.

2.4.2.1 Clipping data for simulated apnea studies

The data obtained from labview 8.6 is clipped into files of normal breathing and breath holds using MATLAB GUI. These files are used to analyze the data for comparison of breath holds and normal breathing for ECG and post breath hold values with the baseline.

2.4.2.2 Clipping data for sleep studies

The data obtained from labview 8.6 merged with the apnea events file, sleep stage file and ecg data obtained from the polysomnography. The merging is based on the synchronous signal such that the time stamps on both the data (labview and polysomnography) are same. The clipping of the data is then done using the Matlab GUI. The clipping is done based on the type of apnea from the data of events file and type of sleep stage from data of sleep staging file. The normal breathings are clipped from the REM sleep stage.

2.4.3 Filtering the signals and features extraction

The signal obtained from the CO_2 adds to the electrical interference noise which distorts the signal and makes it diffcult to analyse the signal.

2.4.3.1 Filtering the CO_2 waveform

The output signal received from the Capnogard contains some high frequency content which acts as a noise in the signal. Hence, the CO_2 signal is low pass filtered in order to remove the high frequency content and restore the low frequency content which is the actual signal. An FIR filter with 50 terms and the cut off frequency of 0.6 Hz was used to eliminate the

noise. In order to eliminate the phase shift in the filtered signal, both forward and backward filtering is done. Fig 2.20 shows the raw CO_2 signal without filtering and Fig 2.21 gives the filtered CO_2 signal.

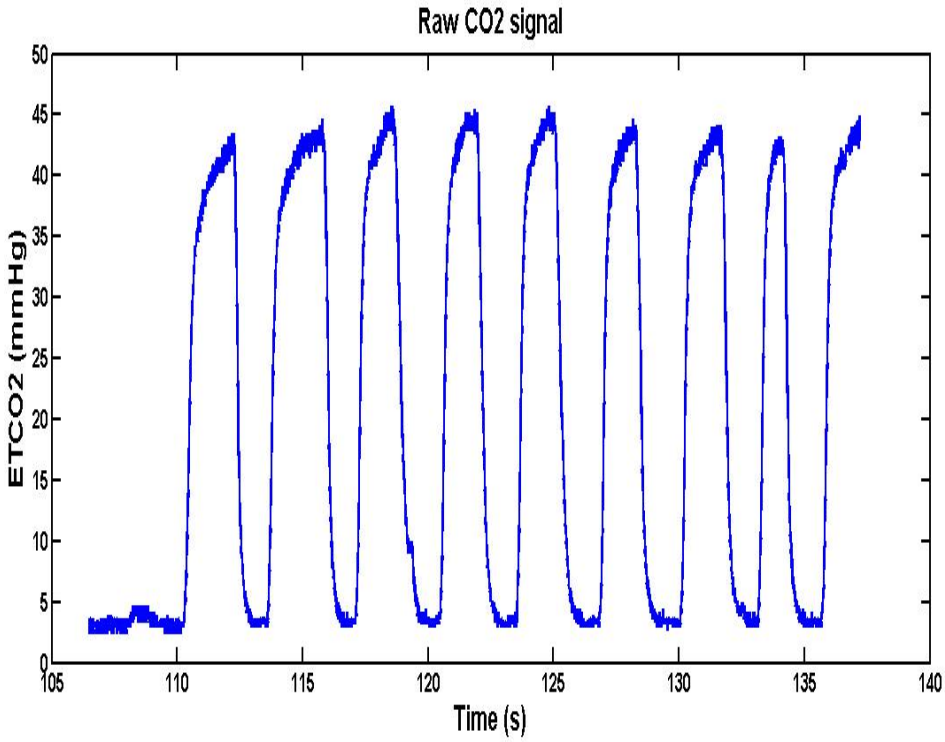

Figure 2.20 Raw CO_2 signal

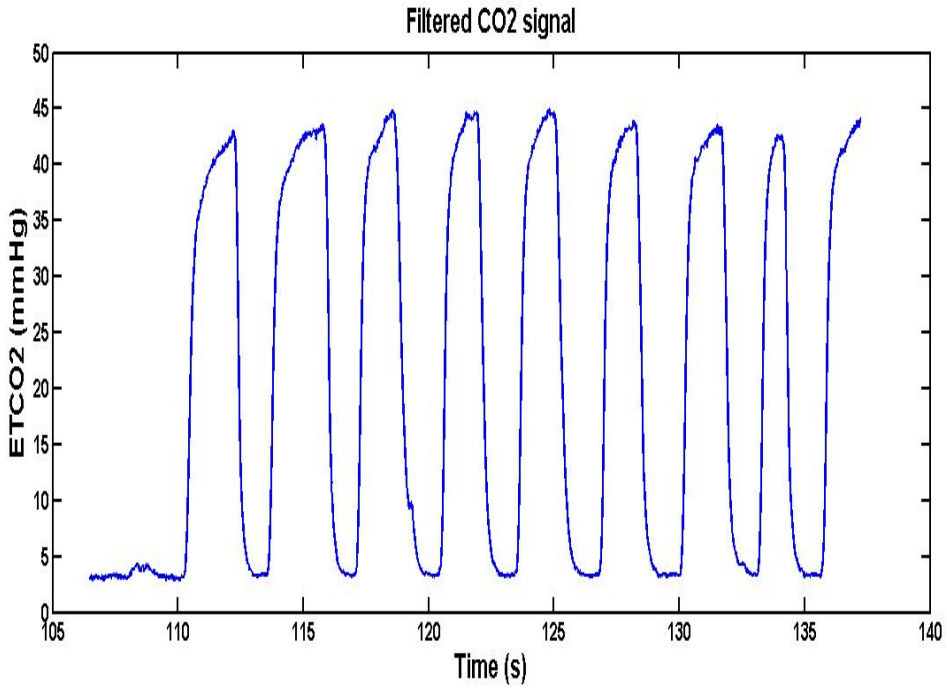

Figure 2.21 Results of filtering the signal shown in Figure 2.20

2.4.3.2 Features Extracted

The block diagram shown in the Fig 2.20 explains the features extracted from CO2 waveform.

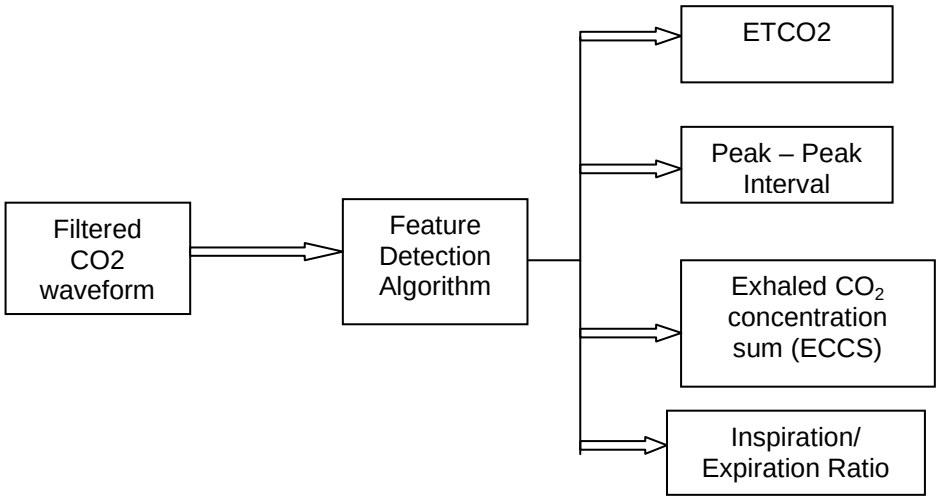

Figure 2.22 Flow Diagram of Features Extraction

The CO2 waveform can be related to the respiratory signal. The rising portion of the signal corresponds to the expiration and the falling portion of the signal corresponds to the inspiration. The $ETCO_2$ is detected by finding the maximum point of CO2 waveform [Fig 2.22] and the maximum is detected by comparing the samples in each peak with the preceding and succeeding samples which is repeated for all pulses. The Peak – Peak Interval is the time interval between two peaks in the CO_2 waveform. The ECCS of the pulse is determined by summation of the all data points in the pulse. The Inspiration / Expiration Ratio is the ratio of time it takes to inspire and time it takes to expire. The Figure 2.23 shows the graphical representation of the features being extracted.

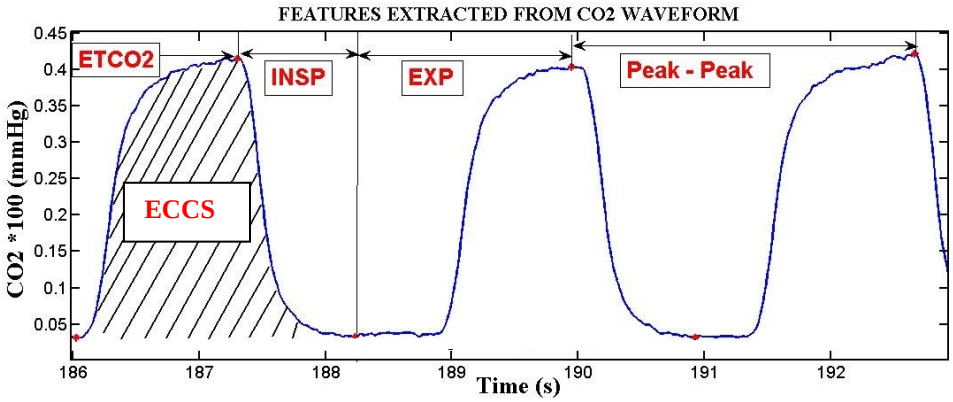

Figure 2.23 Graphical Representation of the features extracted.

The block diagram shown in the Fig 2.24 explains the feature extracted from ECG waveform. The R peaks are detected by comparing each sample with the preceding and succeeding values and check if its maximum. Then the maximum value is stored as the peak and the same procedure is repeated for other ecg pulses. The Heart Rate (HR) is found out by inverse of the RR interval

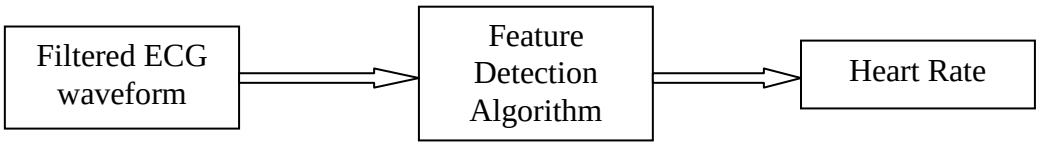

Figure 2.24 Block Diagram of feature extraction of ECG wave.

The figure 2.25 shows the ECG waveform with the R-R interval.

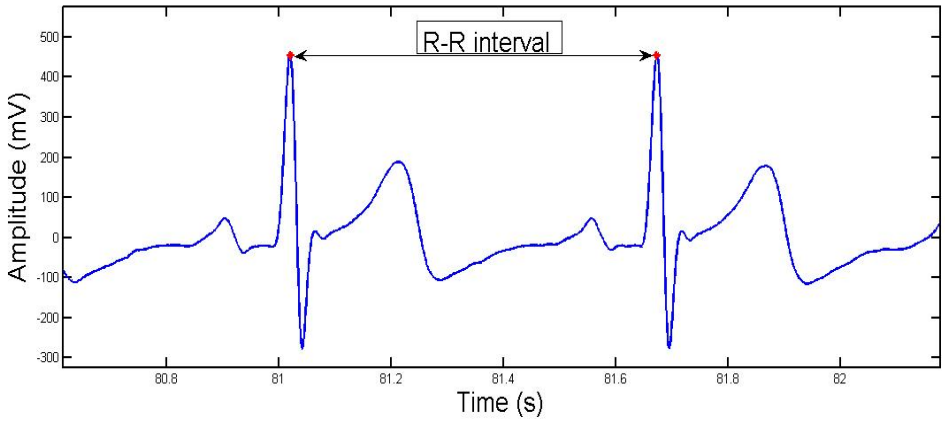

Figure 2.25 Graphical Representation of the features extracted from ECG.

The features extracted namely $ETCO_2$, ECCS, Peak-Peak Interval, Inspiration time to Expiration time ratio, Heart Rate from ECG are analyzed which is discussed in next chapter 3.

2.5 Mixed Linear Model

When the observations made are not independent then using a generalized linear model will lead to errors. Hence Mixed linear models is used to correct the correlated errors. Mixed Linear Model analyzes the Random effects, repeated measures and heirarchial effects which is best suited to actual biological data. The mathematical representation of the Mixed linear models is as shown below.

$$Yij= (\beta_1.x_{1ij} + \ldots\ldots\ldots\ldots + \beta_p.x_{pij}) + (b_{i1}.z_{1ij} + \ldots\ldots\ldots + b_{p1}.z_{1pj}) + \varepsilon_{ij}.$$

In a matrix form the above equation can be written as $Y=\beta X+bZ+\varepsilon$

Where Y = response variable (observations), β = fixed effect coefficients, X= matrix of fixed effect regressors, b= random effect coefficients, z= matrix of random effect regressors, ε= error in the observation [20]. In Statistical Analysis Software (SAS), the procedure used for MLM is PROC MIXED. In our study, interactions between protocols and postures are taken to be random effects. The normal breathings, breath holds, protocol, postures, gender are considered as fixed effects.

2.6 Tukey Kramer Method

Tukey Kramer method is a post hoc analysis test used for multiple comparisons along with the ANOVA. It finds the significant difference between the means of all the possible comparisons. The mean of treatment group is compared with mean of each and every other treatment group.

$$\mu_i - \mu_j$$

where μ_i is the mean of the i^{th} treatment group.

Formula for Tukey Kramer Method is $(\mu_i - \mu_j)/(\text{Standard Error})$ [20]. This is compared with the studentized range distribution to check for the significant difference. Tukey Kramer analysis corrects for the TYPE I error. The confidence intervals obtained from tukey Kramer analysis give us the range (upper limits and lower limit) for the true mean to fall. If the both limits of confidence interval does not include zero, then the means are said to be significant.

CHAPTER 3

RESULTS

The parameters extracted from the CO_2 waveform are ETCO2 value, Exhaled CO_2 Concentration Sum (ECCS), Inspiration to Expiration Ratio, Peak to Peak Interval (P-P). In the study of simulated sleep apnea, the values of these metrics were compared for exhaled breaths following the breath hold maneuvers. The comparison was carried out for settings within the two protocols and postures, across the protocols and postures. As for the cardiac response measures, the parameters extracted from the ECG wave is Heart Rate (HR). These HR values during breath hold are compared with the values normal breathing and across protocols and postures. For the statistical analysis Mixed Linear Model (MLM) and ANOVA with tukey-kramer test are used.

3.1 Simulated Sleep Apnea Study

In this section, the analysis for the simulated sleep study is performed by comparing the post breath hold values with the baseline for the exhaled CO_2 features and breath hold values with the baseline for ECG. The below results show the analysis obtained from the Mixed Linear Model for all the parameters obtained.

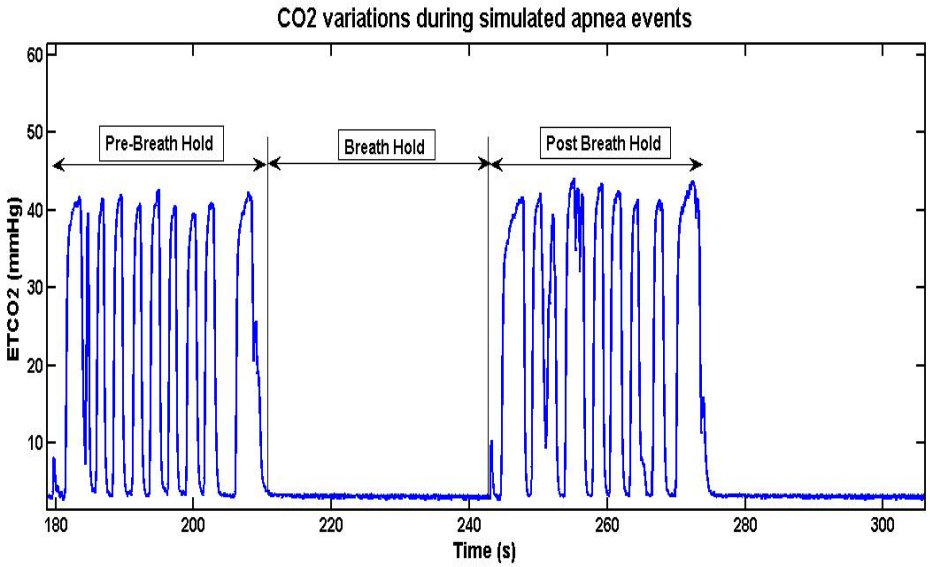

Figure 3.1 CO_2 variations during simulated apnea events

3.1.1 Baseline Comparisons

3.1.1.1 End-Tidal CO_2

The mixed linear approach for the $ETCO_2$ gave the following results. The below graphs (Figure 3.2 to 3.5) shows the graphical representation of comparisons of $ETCO_2$ between baseline and normal breathing.

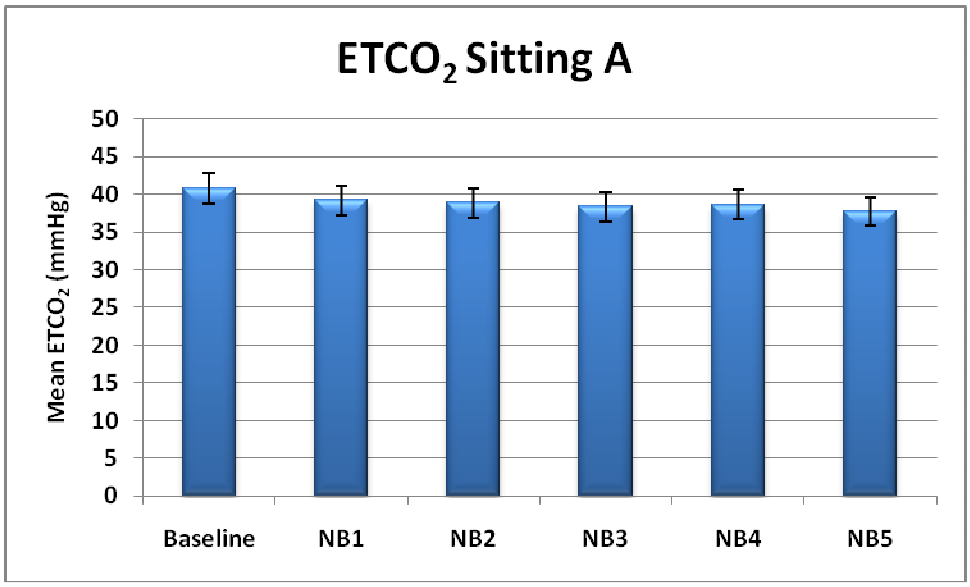

Figure 3.2 Comparisons of $ETCO_2$ during baseline and normal breathings for sitting A

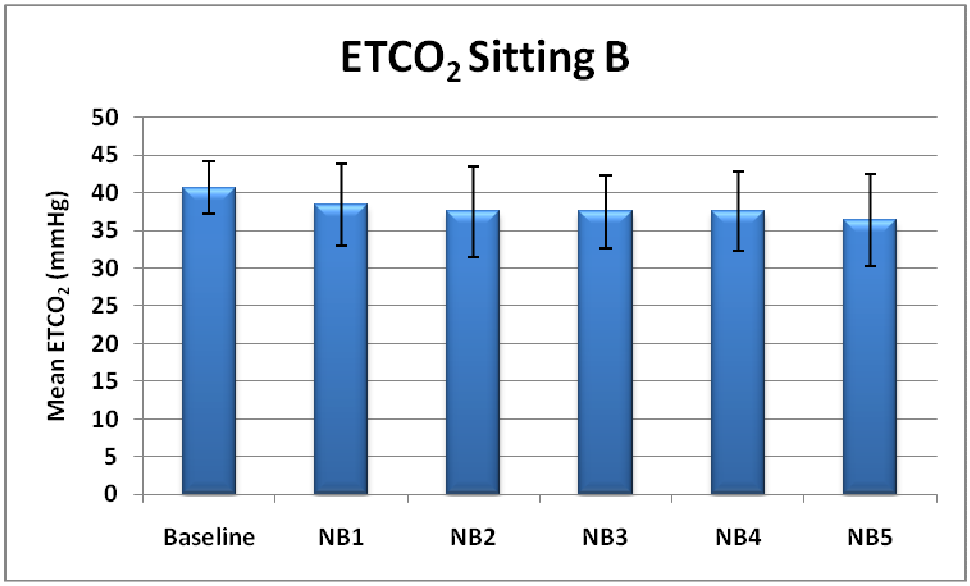

Figure 3.3 Comparisons of $ETCO_2$ during baseline and normal breathings for sitting B

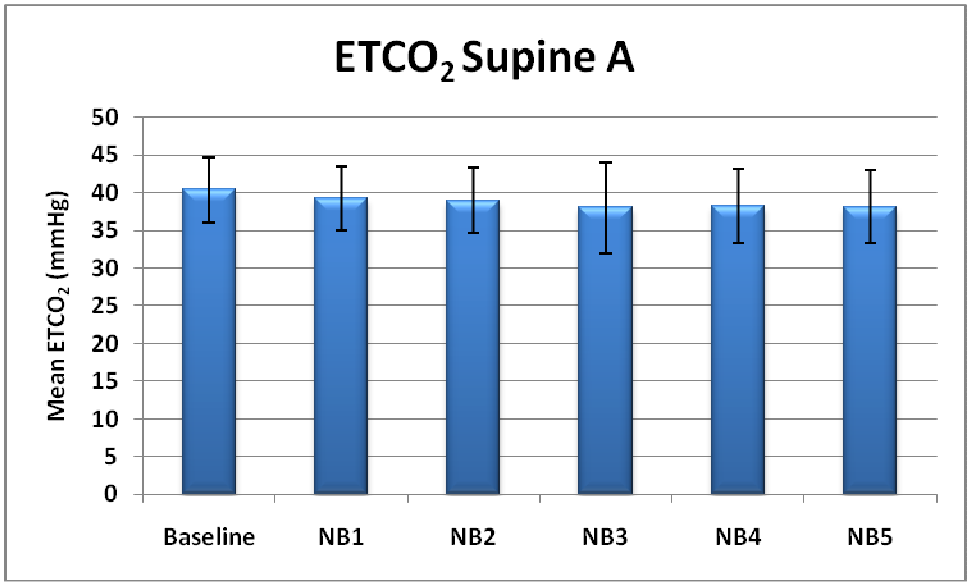

Figure 3.4 Comparisons of $ETCO_2$ during baseline and normal breathings for supine A

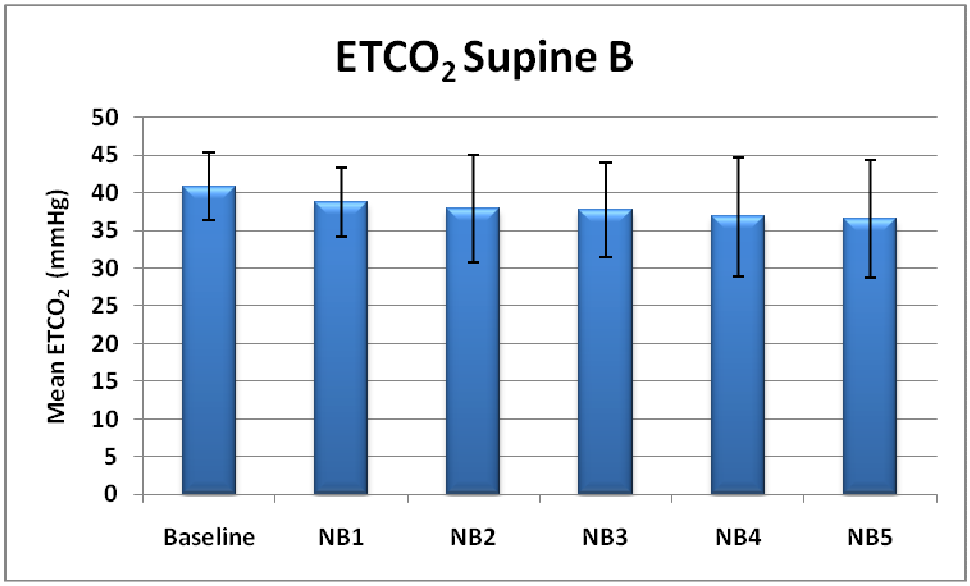

Figure 3.5 Comparisons of $ETCO_2$ during baseline and normal breathings for supine B

The below table shows the comparisons of normal breathing with the baseline using mixed linear model. The table contains the P-values for the comparisons.

Table 3.1 P-values of $ETCO_2$ from Mixed Linear Model (MLM) for Breath Hold Effect

$ETCO_2$	Baseline Vs NB2	Baseline Vs NB3	Baseline Vs NB4	Baseline Vs NB5	Baseline Vs NB6
Sitting A	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*
Sitting B	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*
Supine A	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*
Supine B	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*

3.1.1.2 Exhaled CO_2 concentration Sum

The Mixed Linear Approach (MLM) for ECCS gave the following results. The graphs below (Figure 3.6 to 3.9) show the comparisons of ECCS during baseline and normal breathings.

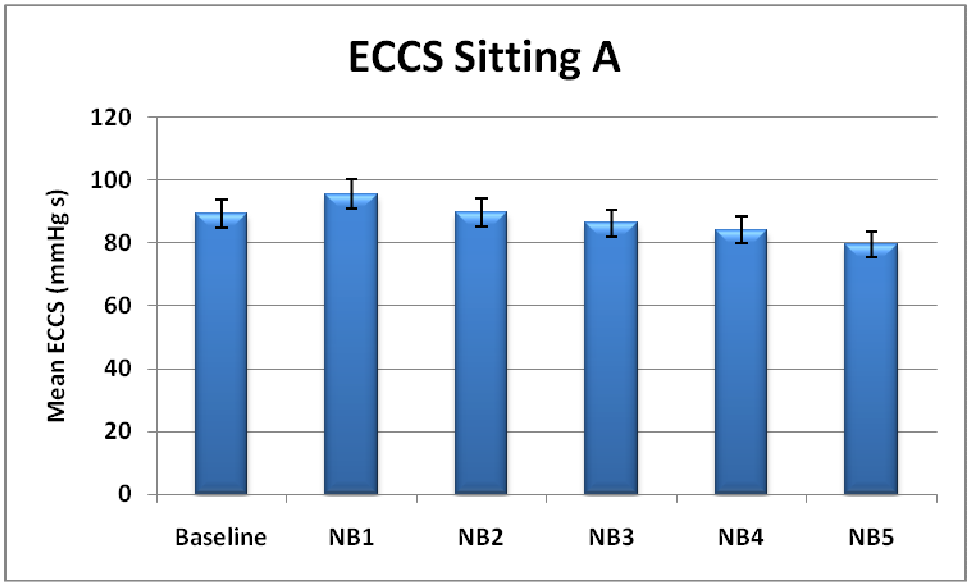

Figure 3.6 Comparisons of ECCS during baseline and normal breathings for sitting A

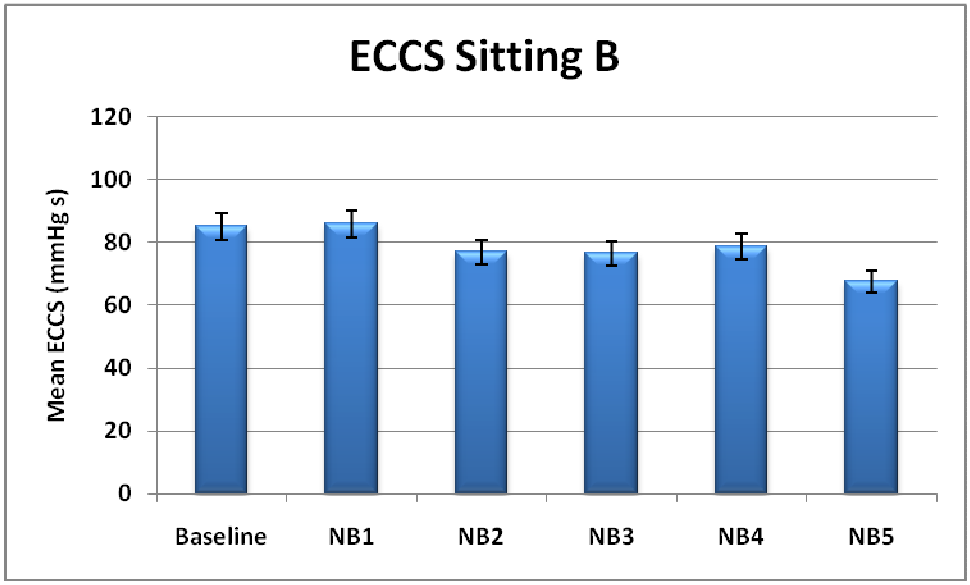

Figure 3.7 Comparisons of ECCS during baseline and normal breathings for sitting B

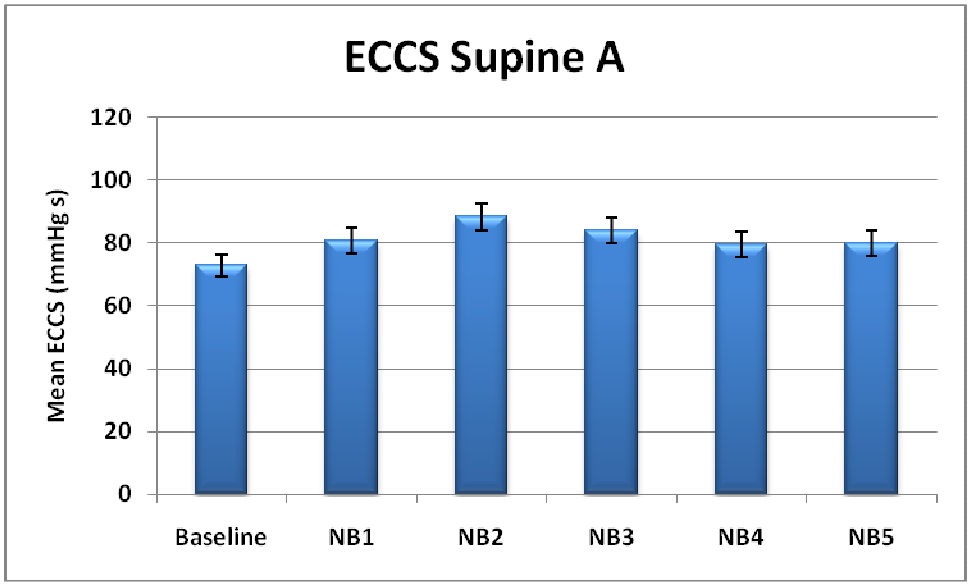

Figure 3.8 Comparisons of ECCS during baseline and normal breathings for supine A

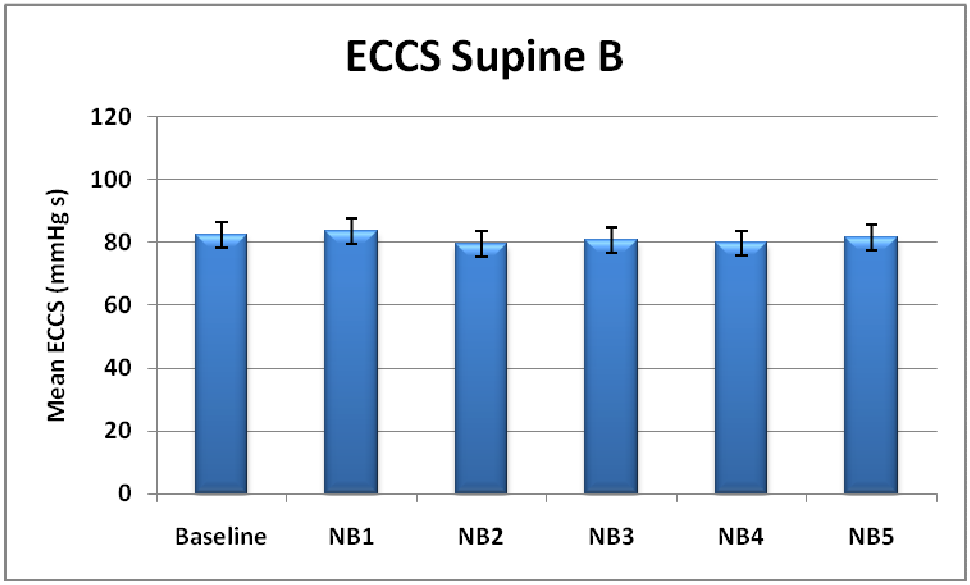

Figure 3.9 Comparisons of ECCS during baseline and normal breathings for supine B

The below table shows the comparisons of normal breathing with the baseline using mixed linear model. The table contains the P-values for the comparisons.

Table 3.2 P-values of ECCS from Mixed Linear Model (MLM) for Breath Hold Effect

ECCS	Baseline Vs NB2	Baseline Vs NB3	Baseline Vs NB4	Baseline Vs NB5	Baseline Vs NB6
Sitting A	0.3000	0.9693	0.4647	0.0463*	0.1910
Sitting B	0.6723	0.0145*	0.0500*	0.1120	0.0013*
Supine A	0.6128	0.0833	0.1558	0.8243	0.8393
Supine B	0.9266	0.3611	0.5036	0.5450	0.6791

3.1.1.3 Inspiration to Expiration Ratio

The Mixed Linear Approach (MLM) for IE gave the following results. The graphs below (Figure 3.10 to 3.13) shows the comparisons of IE ratio during baseline and normal breathings.

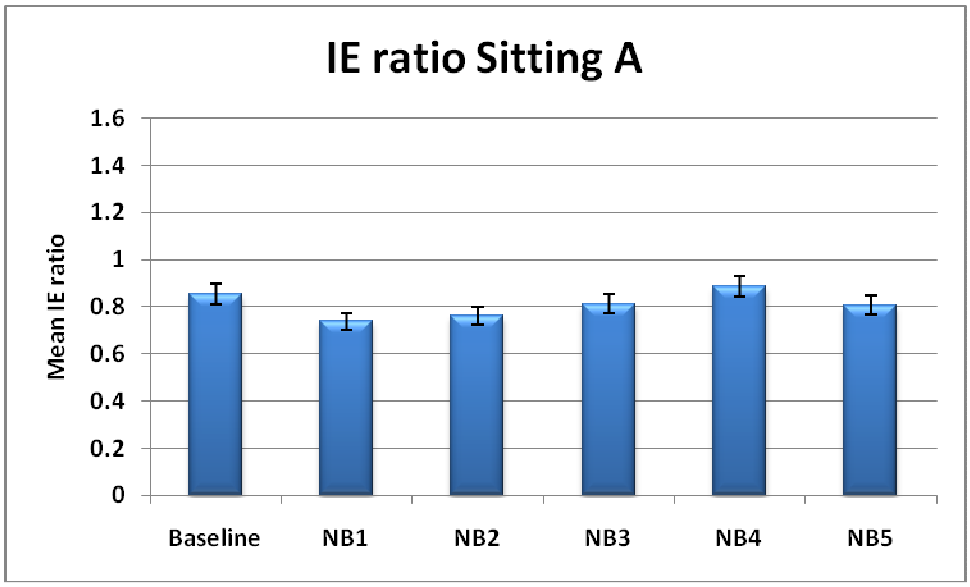

Figure 3.10 Comparisons of IE ratio during baseline and normal breathings for sitting A

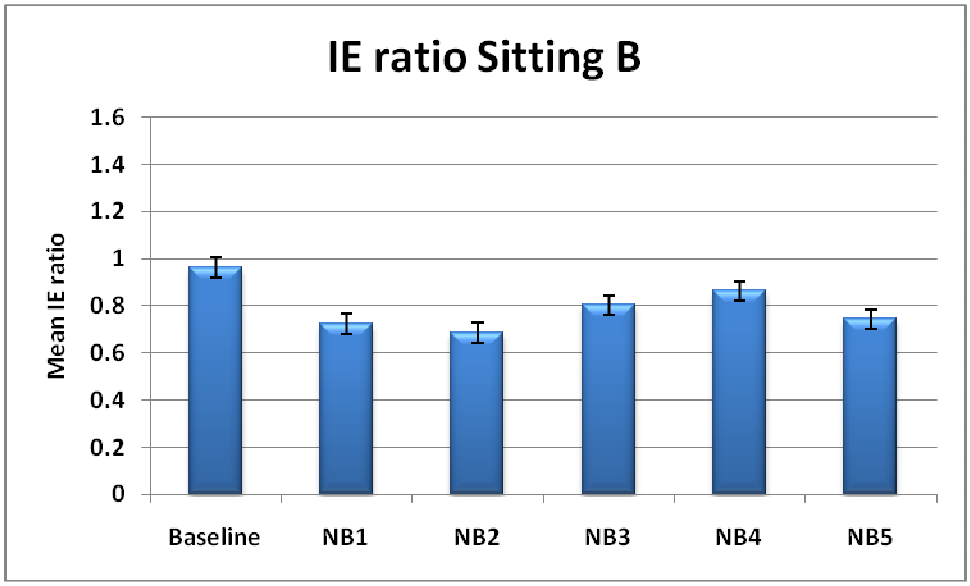

Figure 3.11 Comparisons of IE ratio during baseline and normal breathings for sitting B

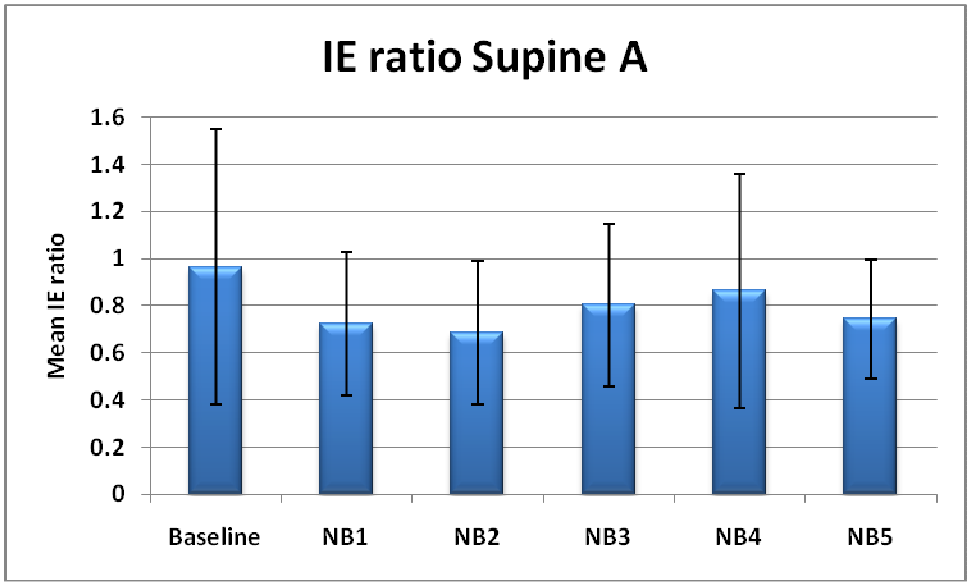

Figure 3.12 Comparisons of IE ratio during baseline and normal breathings for supine A

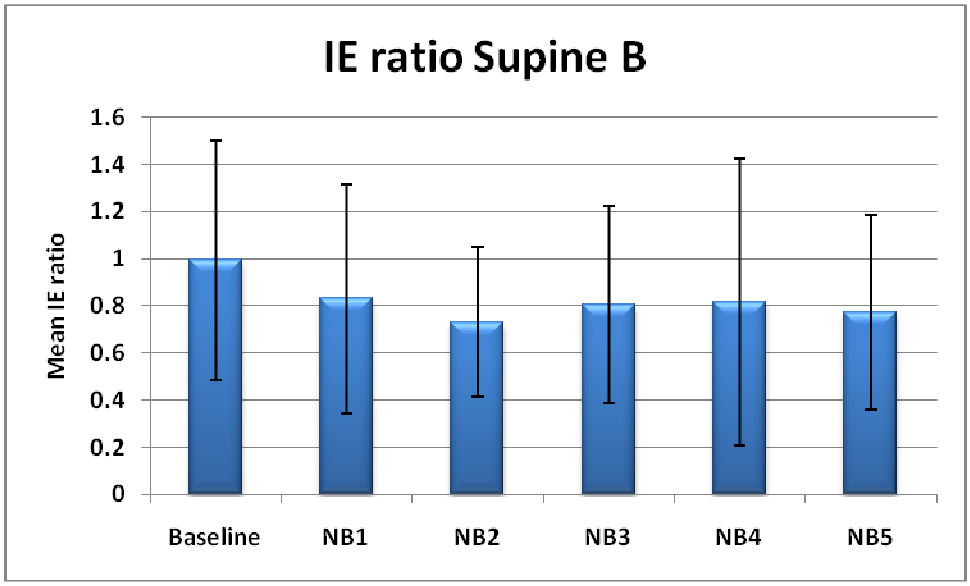

Figure 3.13 Comparisons of IE ratio during baseline and normal breathings for supine B

The below table shows the comparisons of normal breathing with the baseline using mixed linear model (MLM). The table contains P-value of the comparisons.

Table 3.3 P-values of IE ratio from Mixed Linear Model (MLM) for Breath Hold Effect

IE ratio	Baseline Vs NB2	Baseline Vs NB3	Baseline Vs NB4	Baseline Vs NB5	Baseline Vs NB6
Sitting A	0.2818	0.0384*	0.0105*	0.9574	0.4194
Sitting B	0.0012*	<0.001*	0.0280*	0.0947	0.0037*
Supine A	0.05*	0.0005*	0.0243*	0.0523	0.0023*
Supine B	0.0009*	0.0031*	0.2013	0.0040*	0.0032*

3.1.1.4 Peak-Peak Interval

The Mixed Linear Approach (MLM) for Peak-Peak Interval gave the following results. The graphs below (Figures 3.14 to 3.17) show the comparisons of the peak-peak interval during baseline to normal breathings.

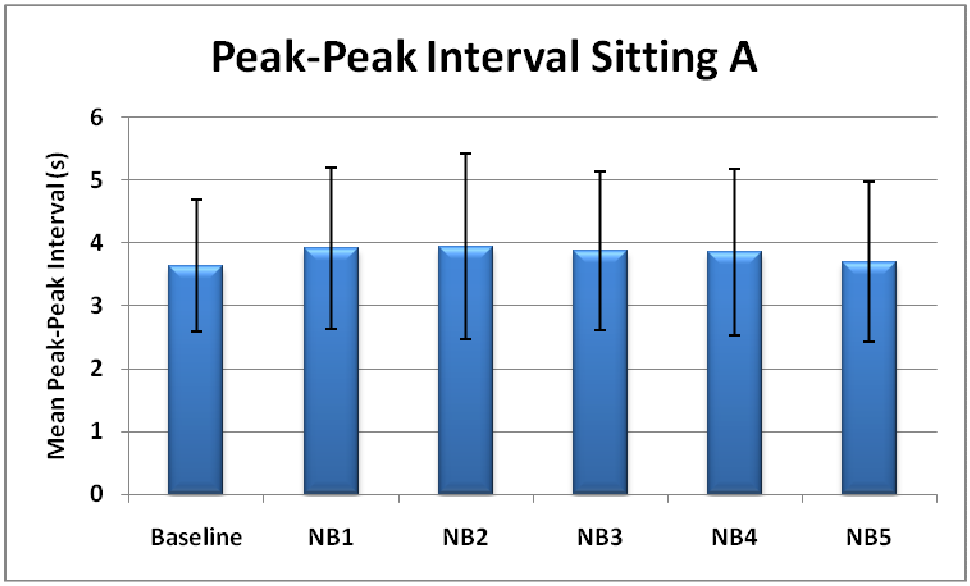

Figure 3.14 Comparisons of Peak-Peak Interval ratio during baseline and normal breathings for sitting A

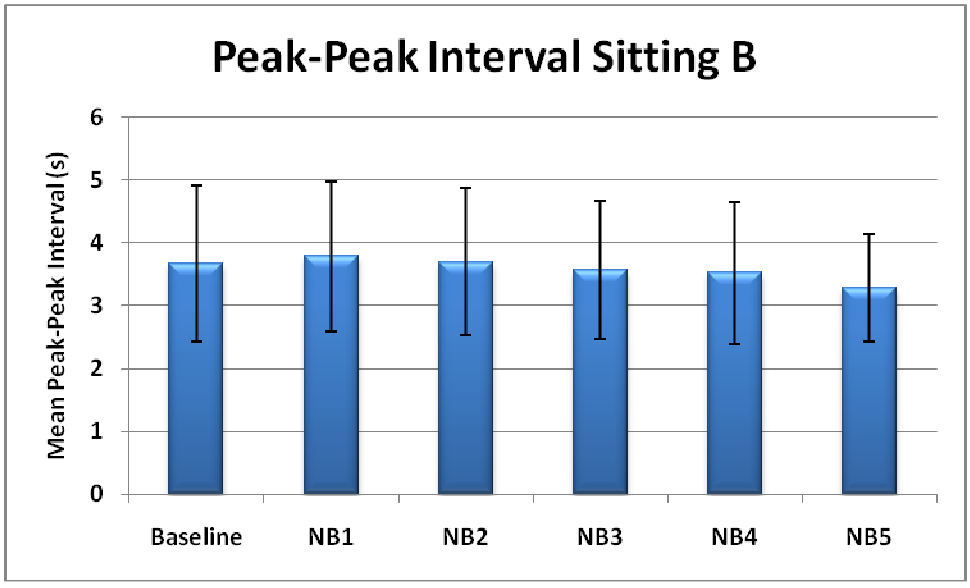

Figure 3.15 Comparisons of Peak-Peak Interval ratio during baseline and normal breathings for sitting B

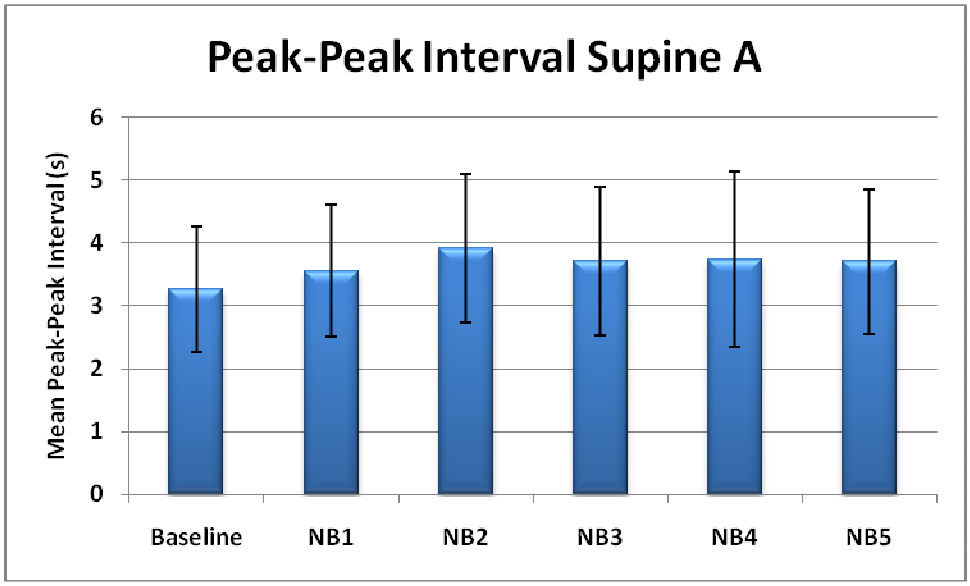

Figure 3.16 Comparisons of Peak-Peak Interval ratio during baseline and normal breathings for supine A

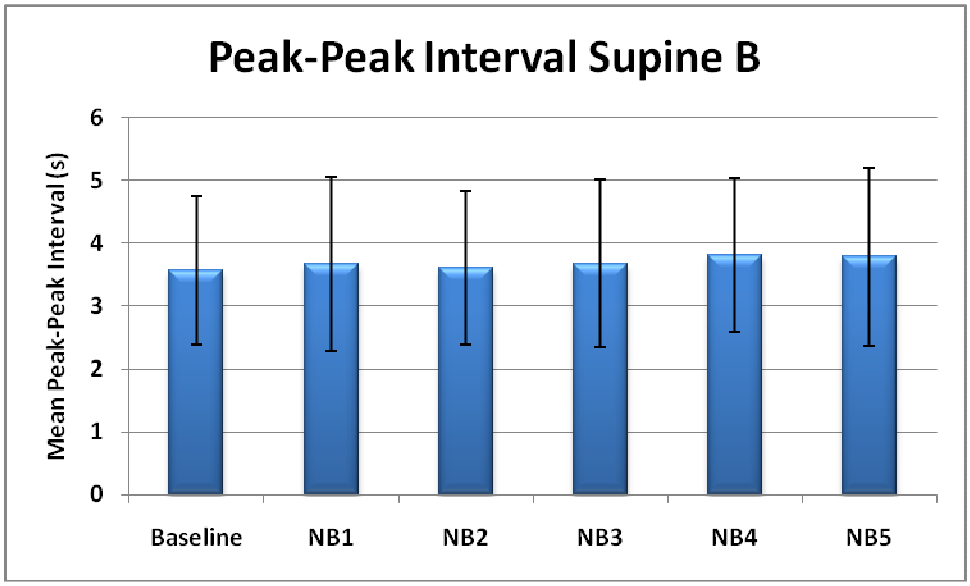

Figure 3.17 Comparisons of Peak-Peak Interval ratio during baseline and normal breathings for supine B

The below tables shows the comparisons between normal breathings and baseline, comparisons across postures and protocols using mixed linear model. The table contains P-values of the comparisons.

Table 3.4 P-values of Peak-Peak interval from Mixed Linear Model (MLM) for Breath Hold Effect

Peak-Peak Interval	Baseline Vs NB2	Baseline Vs NB3	Baseline Vs NB4	Baseline Vs NB5	Baseline Vs NB6
Sitting A	0.1077	0.0635	0.1704	0.4377	0.5387
Sitting B	0.7884	0.2810	0.1473	0.0991	0.0053*
Supine A	0.2142	0.0025*	0.0411*	0.6750	0.4840
Supine B	0.9116	0.8557	0.9136	0.5816	0.4216

3.1.1.5 Heart Rate

The Mixed Linear Approach (MLM) for HR gave the following results. The graphs below (Figure 3.18 to 3.21) shows the mean heart rate during baseline and the breath holds for different postures and protocols.

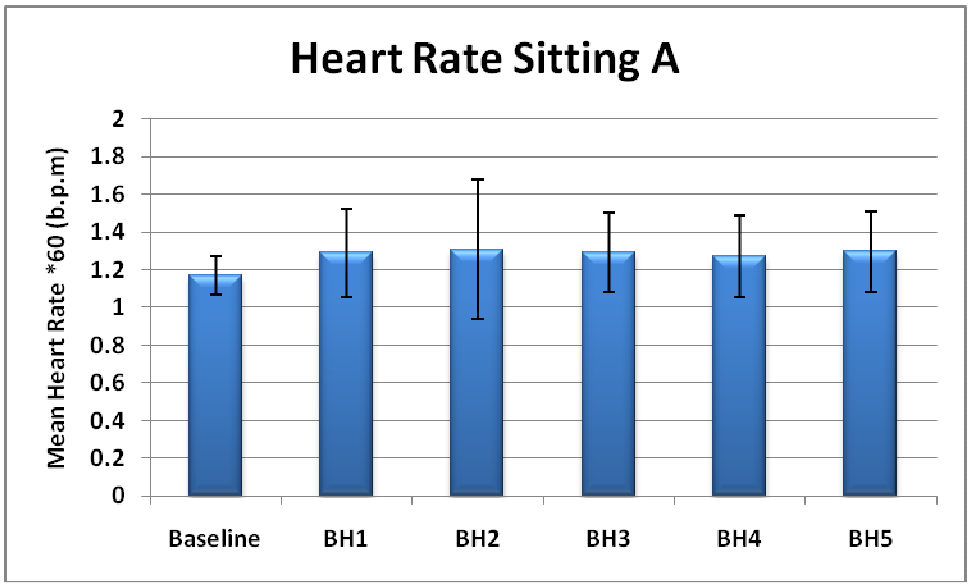

Figure 3.18 Comparisons of heart rate during baseline and breath holds for sitting A

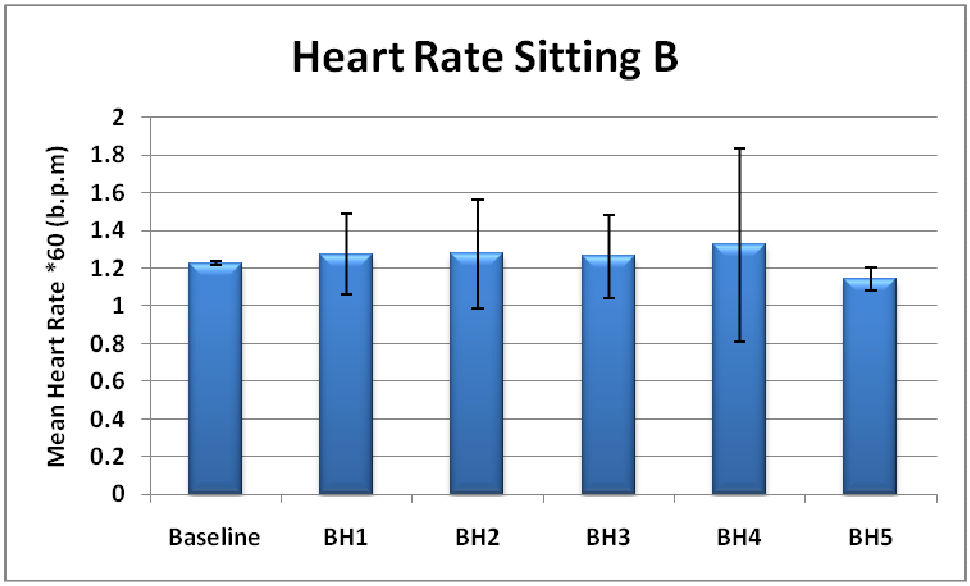

Figure 3.19 Comparisons of heart rate during baseline and breath holds for sitting B

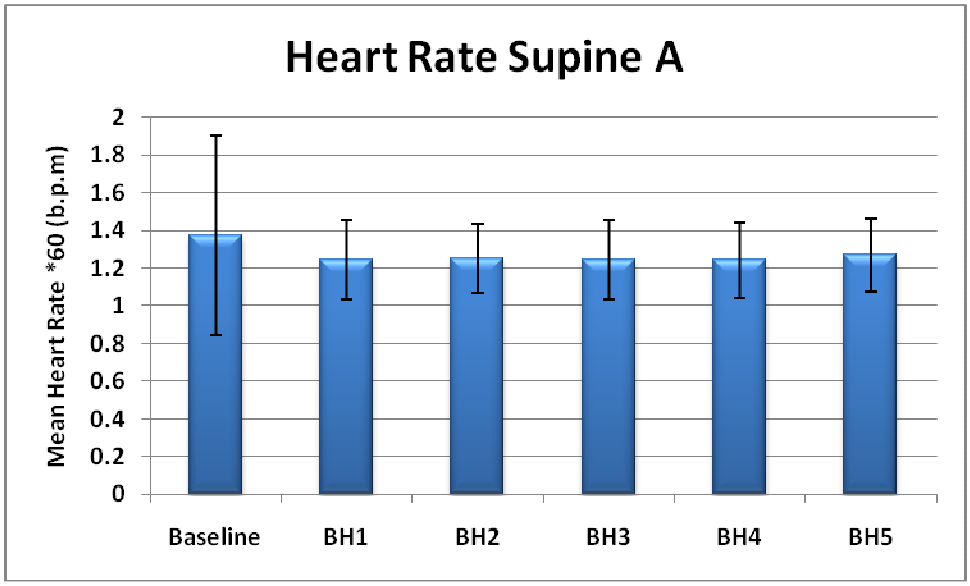

Figure 3.20 Comparisons of heart rate during baseline and breath holds for supine A

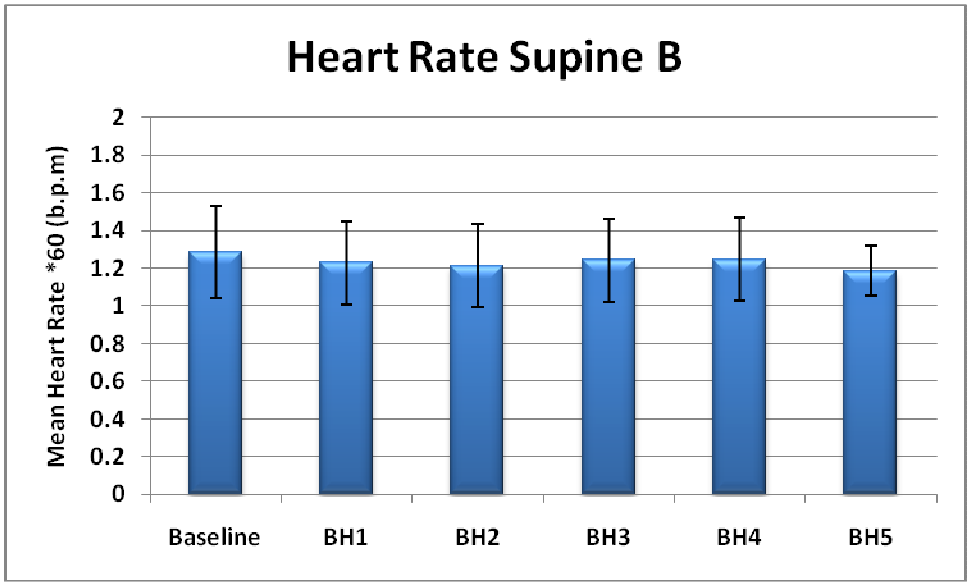

Figure 3.21 Comparisons of heart rate during baseline and breath holds for supine B

The below tables shows the comparisons between normal breathings and baseline, comparisons across postures and protocols using mixed linear model. The table contains P-values of the comparisons.

Table 3.5 P-values for heart rate from Mixed Linear Model (MLM) for Breath Hold Effect

Heart Rate	Baseline Vs BH1	Baseline Vs BH2	Baseline Vs BH3	Baseline Vs BH4	Baseline Vs BH5
Sitting A	0.0261*	0.0210*	0.08	0.0004*	0.048*
Sitting B	0.0025*	0.0234*	0.0021*	0.2479	0.0009*
Supine A	0.0935	0.0909	0.1082	0.0867	0.062
Supine B	0.0065*	0.0007*	0.023*	0.0277*	0.2664

3.1.2 Effect of posture and frequency of apnea

3.1.2.1 $ETCO_2$

The graphs below (Figure 3.22, 3.23) shows the mean $ETCO_2$ during sitting and supine positions, protocol A and B.

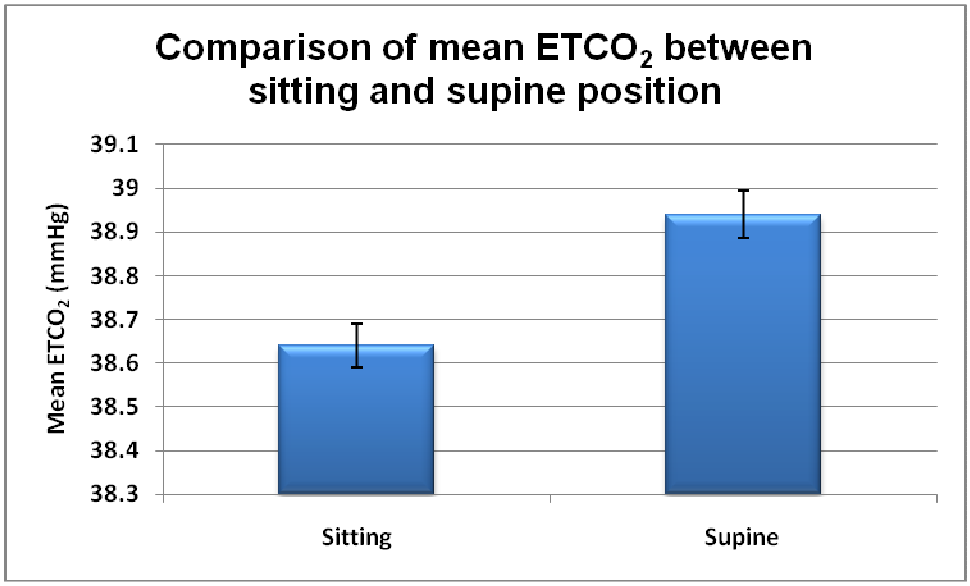

Figure 3.22 Comparisons of $ETCO_2$ during sitting and supine positions

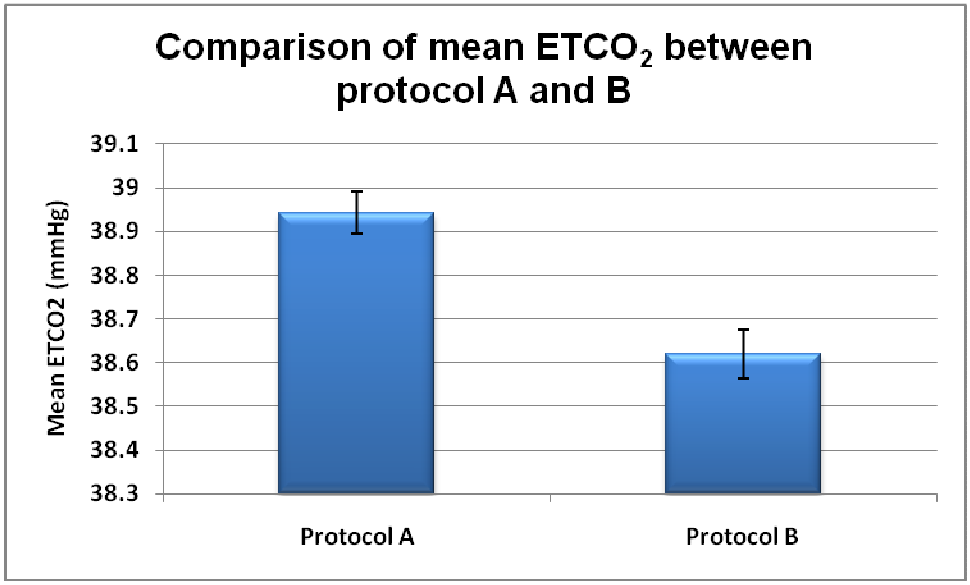

Figure 3.23 Comparisons of $ETCO_2$ during protocol A and protocol B

3.1.2.2 ECCS

The graphs below (Figure 3.24, 3.25) shows the mean ECCS during sitting and supine positions, protocol A and B.

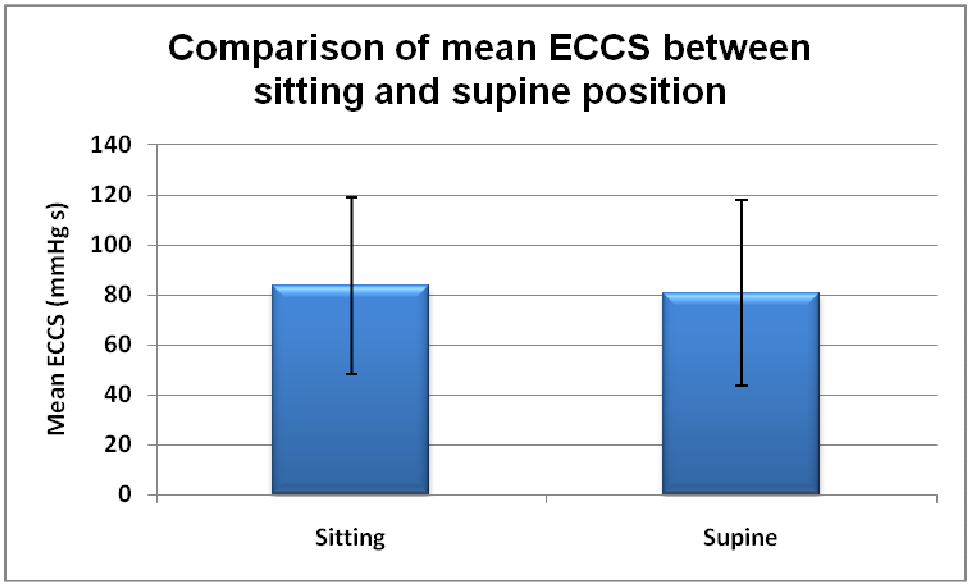

Figure 3.24 Comparisons of ECCS during sitting and supine positions

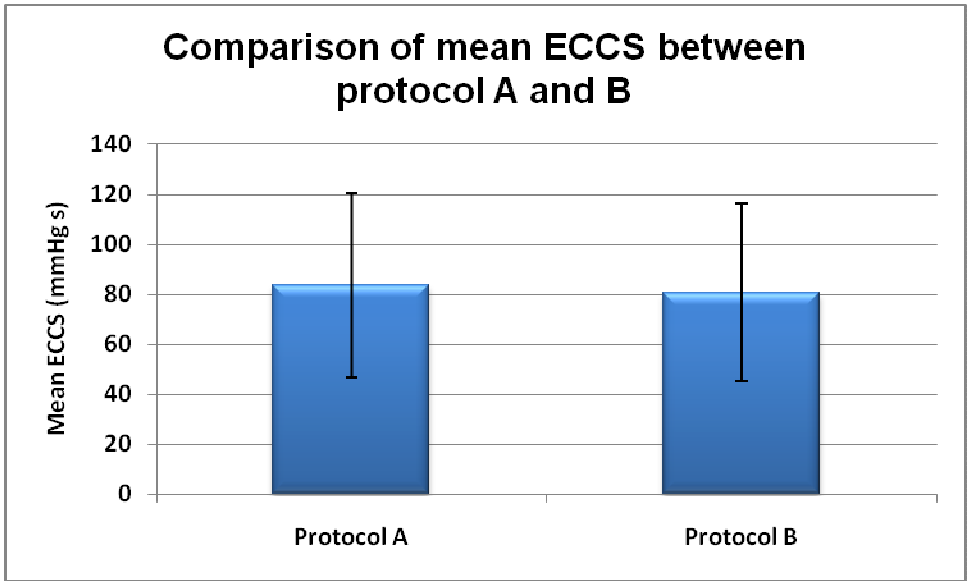

Figure 3.25 Comparisons of ECCS during protocol A and protocol B

The below table shows the comparisons across protocols and postures for the ECCS during baseline and normal breathings. It contains the P-values for the corresponding comparisons.

Table 3.6 Comparisons of ECCS across protocols and postures using Mixed Linear Model

	Sit A Vs Sit B	Sup A Vs Sup B	Sit A Vs Sup A	Sit B Vs Sup B
Baseline	0.7240	0.5034	0.2747	0.8712
NB1	0.1838	0.6960	0.0642	0.9837
NB2	0.1301	0.3361	0.8214	0.5020
NB3	0.2223	0.9017	0.7620	0.4840
NB4	0.4743	0.6638	0.5897	0.5495
NB5	0.7674	0.7060	0.7674	0.1216

3.1.2.3 Inspiration to Expiration Ratio

The Mixed Linear Approach (MLM) for IE gave the following results. The graphs show the comparisons across postures and protocols.

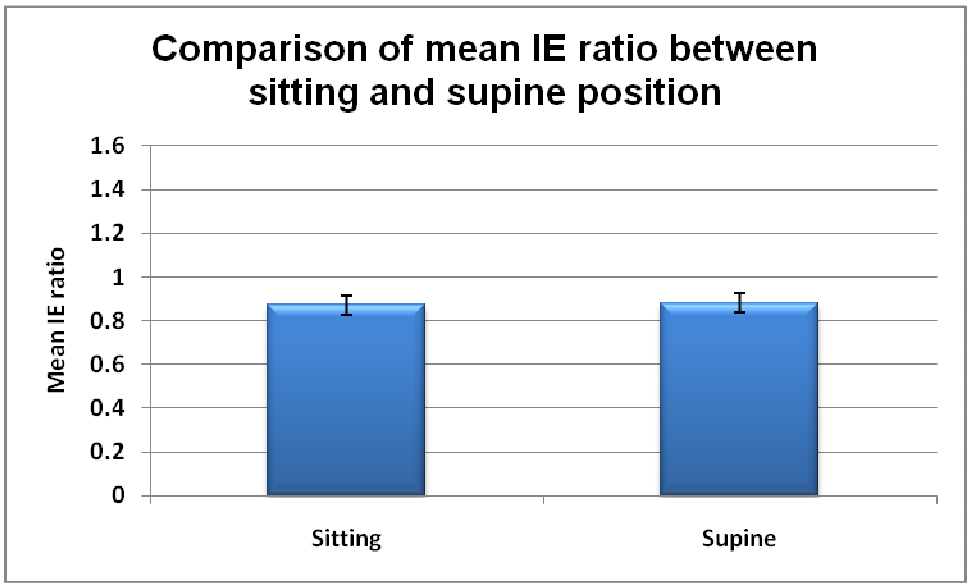

Figure 3.26 Comparisons of IE ratio during sitting and supine positions

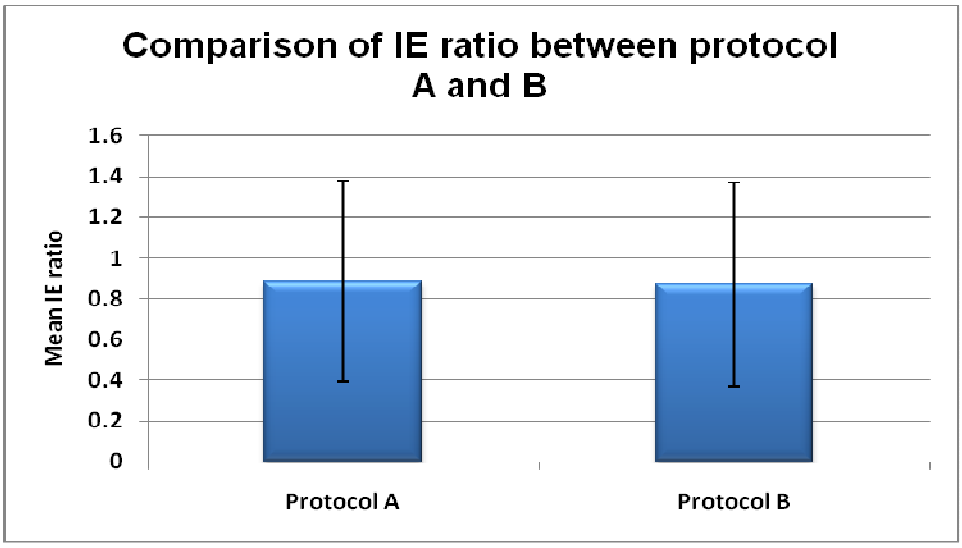

Figure 3.27 Comparisons of IE ratio during sitting and supine positions

Table 3.7 Comparisons of IE ratio across protocols and postures using Mixed Linear Model

	Sit A Vs Sit B	Sup A Vs Sup B	Sit A Vs Sup A	Sit B Vs Sup B
Baseline	0.1385	0.8566	0.1337	0.8638
NB1	0.7737	0.7011	0.6774	0.7224
NB2	0.5104	0.4711	0.8786	0.2148
NB3	0.9957	0.4728	0.8393	0.3025
NB4	0.9512	0.7333	0.6120	0.4919
NB5	0.1066	0.7776	0.1687	0.4388

3.1.2.4 Peak-Peak Interval

The Mixed Linear Approach (MLM) for Peak-Peak Interval gave the following results. The graphs below (Figure 3.28, 3.29) shows the mean peak-peak interval during sitting and supine positions, protocol A and B.

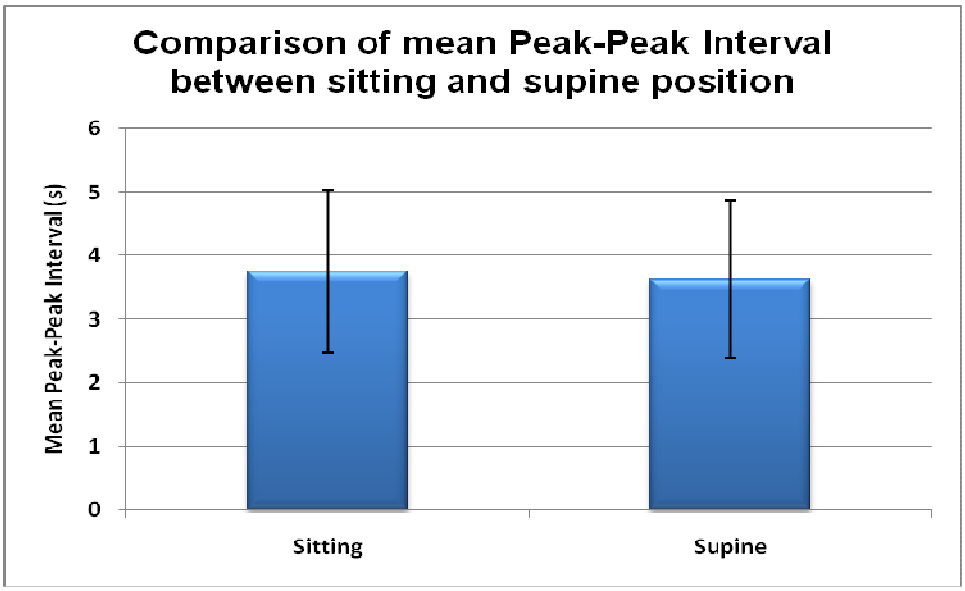

Figure 3.28 Comparisons of Peak-Peak interval during sitting and supine positions

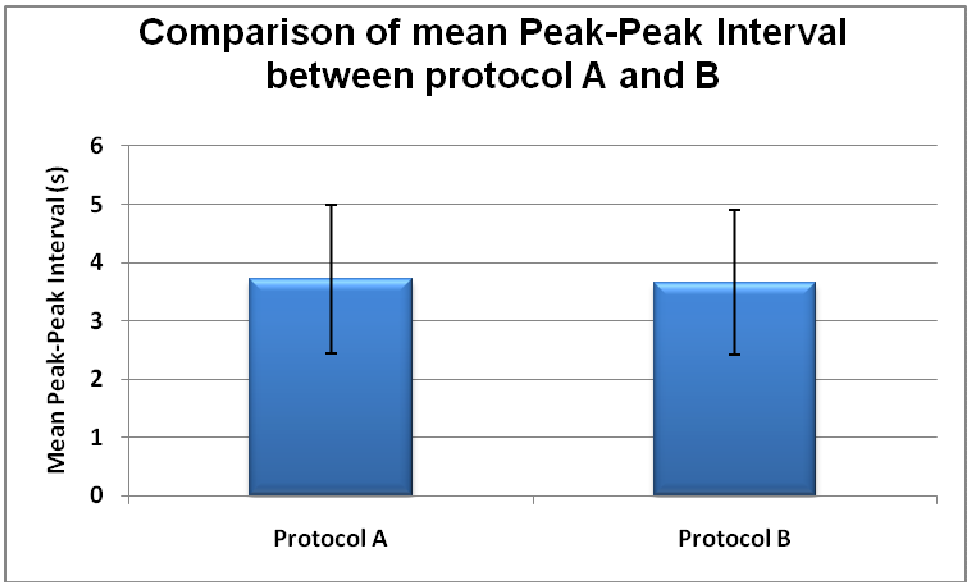

Figure 3.29 Comparisons of Peak-Peak interval during protocol A and protocol B

Table 3.8 Comparisons of Peak-Peak interval across protocols and postures using Mixed Linear Model

	Sit A Vs Sit B	Sup A Vs Sup B	Sit A Vs Sup A	Sit B Vs Sup B
Baseline	0.5340	0.3094	0.5008	0.7909
NB1	0.2505	0.6652	0.1023	0.6088
NB2	0.1921	0.3614	0.8967	0.6927
NB3	0.1549	0.8869	0.5464	0.4949
NB4	0.3369	0.3546	0.5124	0.2223
NB5	0.0236*	0.4164	0.5824	0.0223*

3.1.1.5 Heart Rate

The Mixed Linear Approach (MLM) for HR gave the following results. The graphs below (Figure 3.30 to 3.31) shows the mean heart rate during baseline and the breath holds for different postures and protocols.

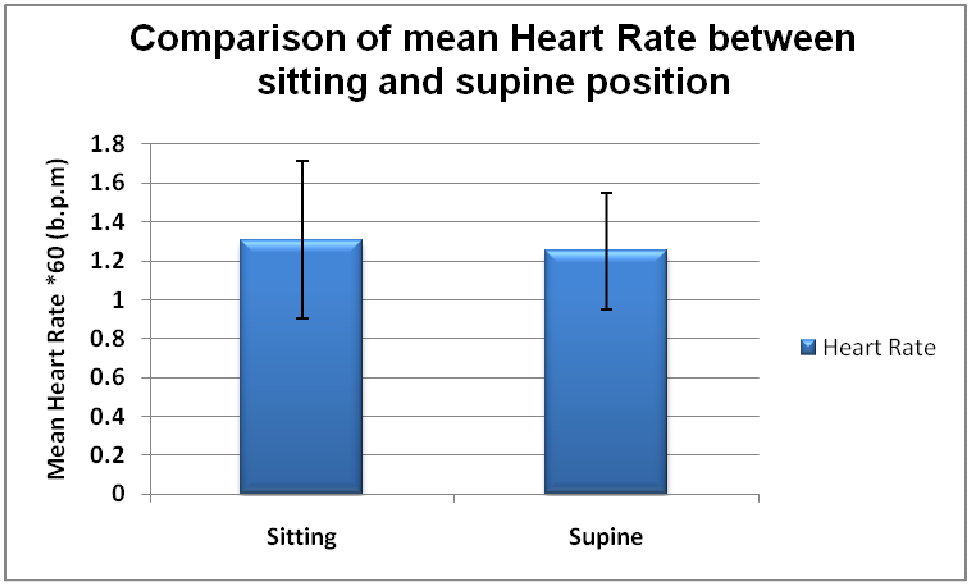

Figure 3.30 Comparisons of Heart Rate during sitting and supine positions

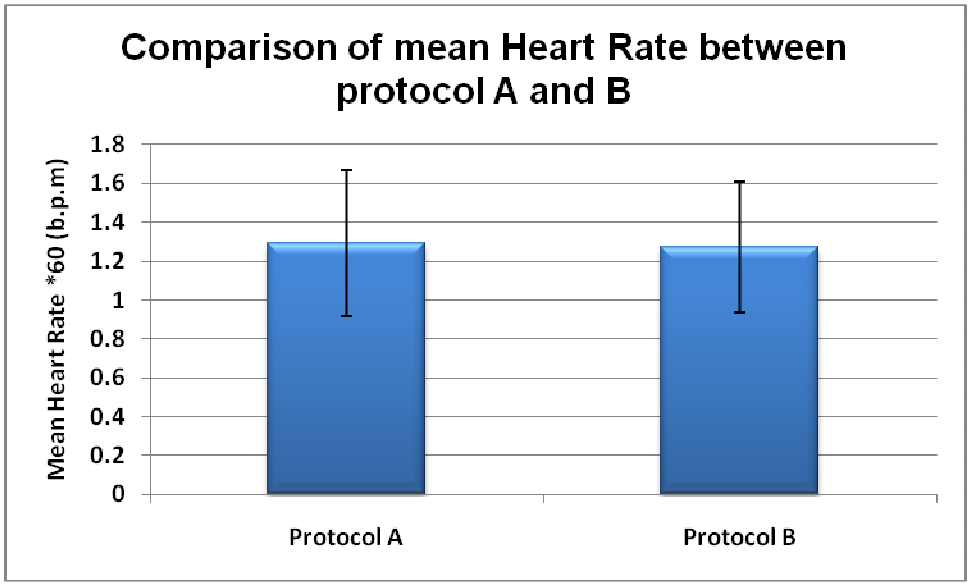

Figure 3.31 Comparisons of Heart Rate during protocol A and protocol B

Table 3.9 Comparisons of Heart rate across protocols and postures using Mixed Linear Model

	Sit A Vs Sit B	Sup A Vs Sup B	Sit A Vs Sup A	Sit B Vs Sup B
Baseline	0.5028	0.3170	0.5645	0.0724
NB1	0.8547	0.8661	0.7190	0.4239
NB2	0.8938	0.6189	0.7261	0.3178
NB3	0.9634	0.7896	0.7254	0.5180
NB4	0.4157	0.9398	0.8028	0.2938
NB5	0.8263	0.6740	0.5338	0.9666

3.1.3 Effect of posture and protocol on breath hold tolerance.

Duration of breath hold is a measure of breath hold tolerance. The below graphs (Figures 3.32 and 3.33) show the effect of posture and frequency of apnea on the breath hold tolerance.

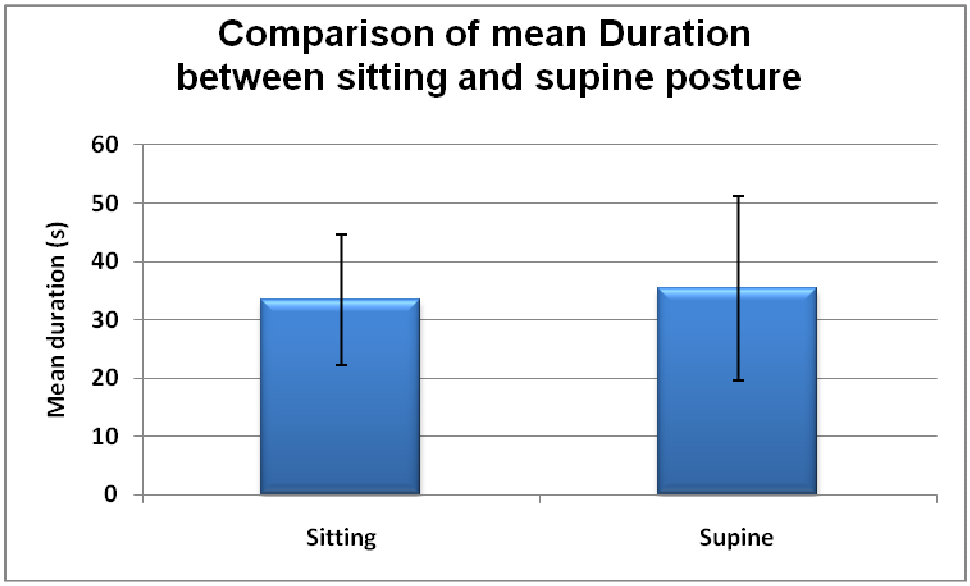

Figure 3.32 Comparisons of duration during sitting and supine positions

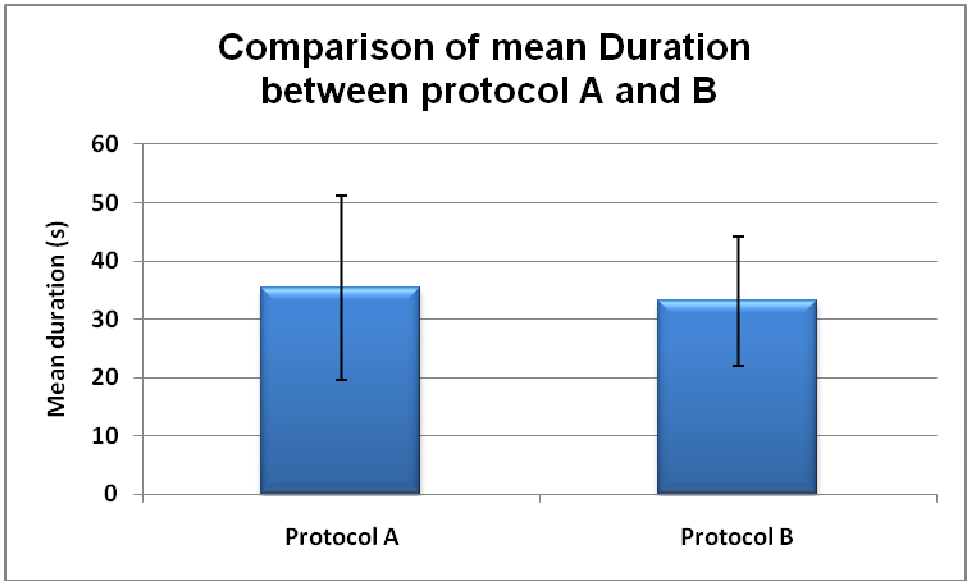

Figure 3.33 Comparisons of duration during protocol A and protocol B

Table 3.10 Comparisons of duration across protocols and postures using Mixed Linear Model

	Sit A Vs Sit B	Sup A Vs Sup B	Sit A Vs Sup A	Sit B Vs Sup 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

3.1.4 Gender effect on the features of CO2 and ECG

In the simulated study there were 9 males and 7 females. Each features extracted was compared based on the gender using Mixed Linear Model (MLM) which resulted in the following P-values.

Table 3.11 Analysis of gender effect using Mixed Linear Model

Features	P-value
$ETCO_2$	<0.0001*
ECCS	0.0005*
IE ratio	0.6824*
Peak-Peak Interval	0.0200*
Heart Rate (ECG)	0.6245*

3.2 Sleep Apnea Study

In this section, the analysis for the sleep study is performed by comparing the features between normal breathings, apnea events and hypopnea events for exhaled CO_2 features and heart rate. The graphs (Figures 3.34 to 3.38) shows the mean value of features during normal, apnea and hypopnea events.

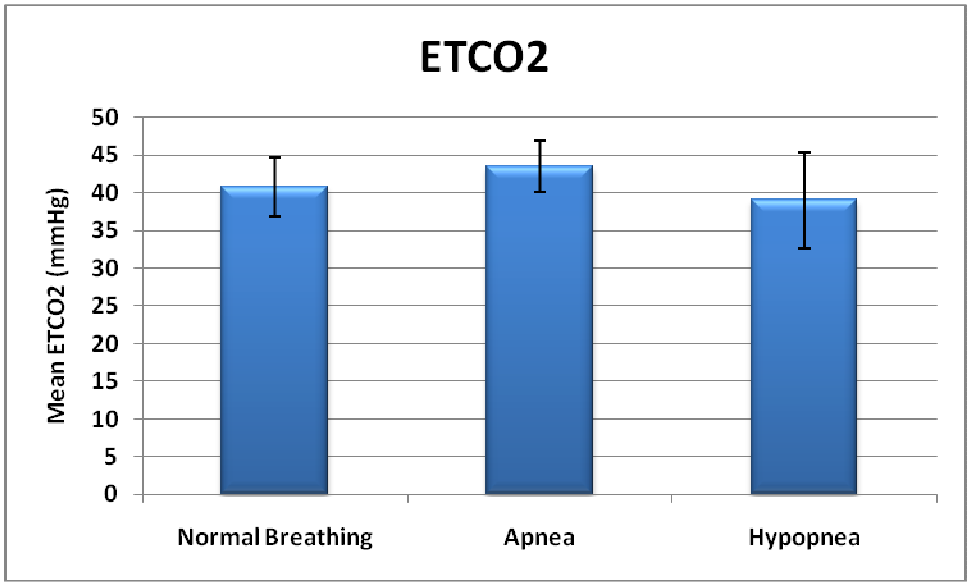

Figure 3.34 Comparison of mean $ETCO_2$ during normal breathing, apnea and hypopnea

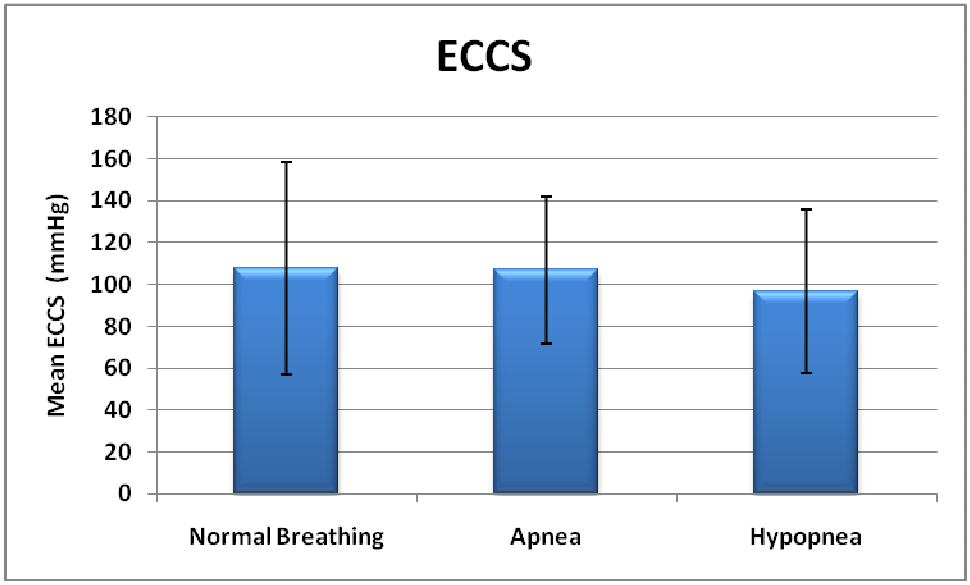

Figure 3.35 Comparison of mean ECCS during normal breathing, apnea and hypopnea

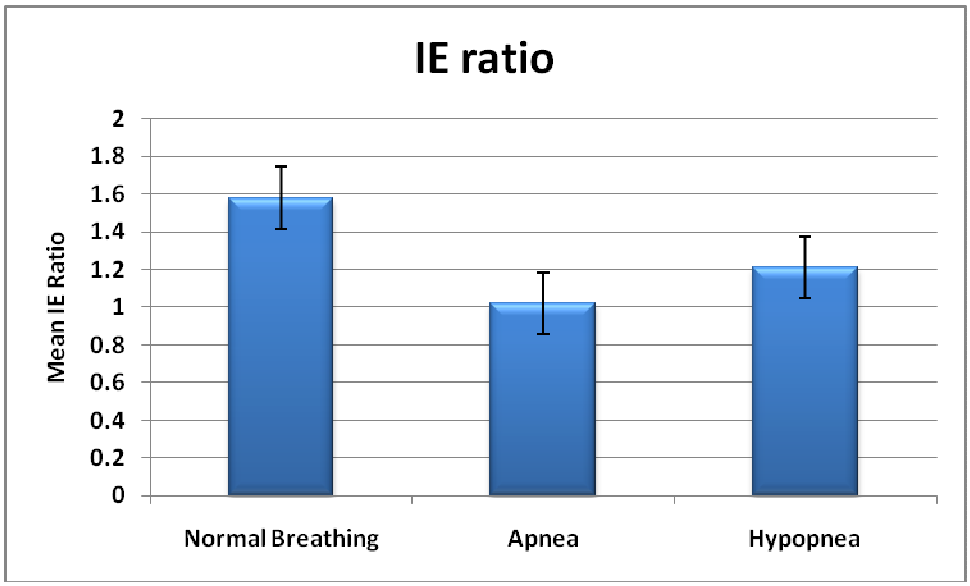

Figure 3.36 Comparison of mean IE ratio during normal breathing, apnea and hypopnea

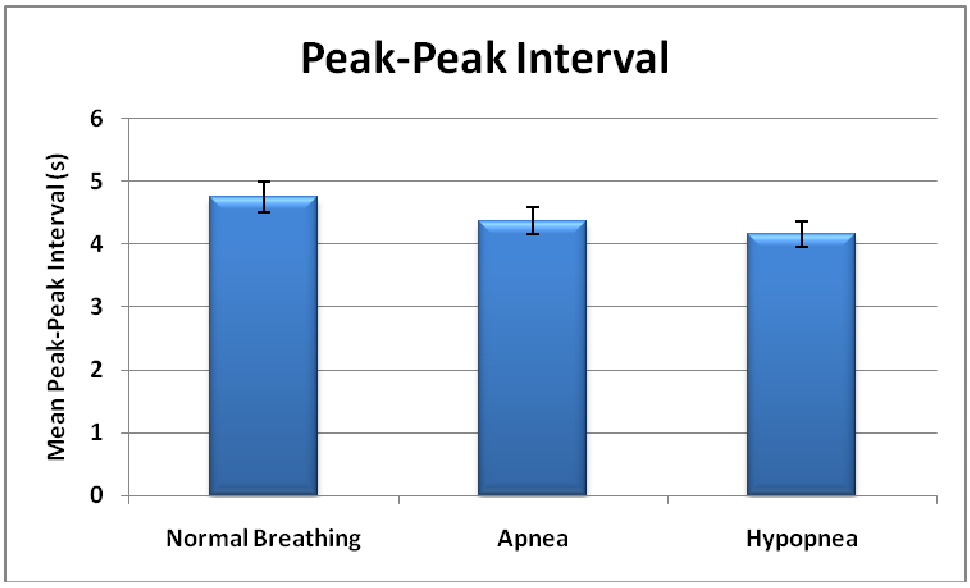

Figure 3.37 Comparison of mean Peak-Peak interval during normal breathing, apnea and hypopnea

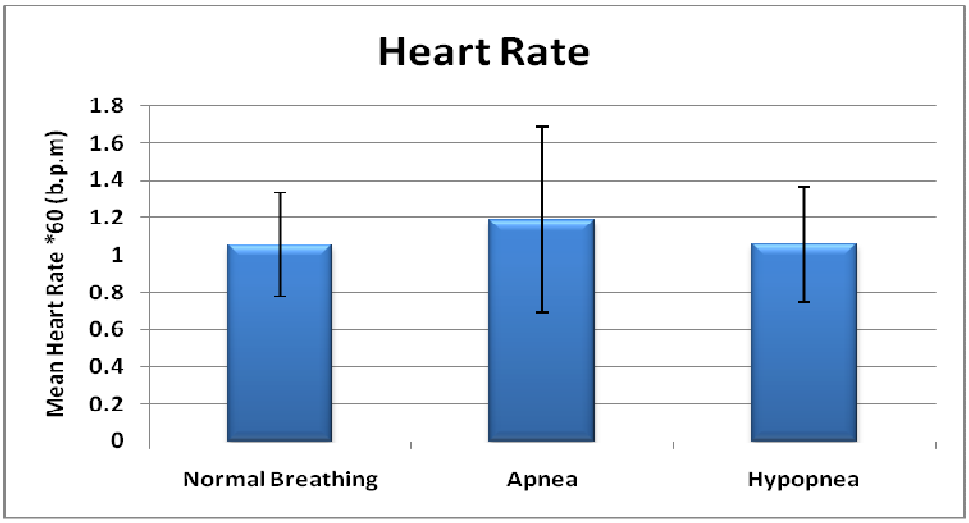

Figure 3.38 Comparison of mean Heart Rate during normal breathing, apnea and hypopnea

Table 3.12 ANOVA analysis for sleep study with TUKEY KRAMER METHOD

	States Comparisons	LSMEANS	TUKEY KRAMMER METHOD	
		P-values	95% Confidence Limits	
$ETCO_2$	Normal Breathing Vs Apnea	< 0.0001*	0.02068	0.033819
	Normal Breathing Vs Hypopnea	0.0015*	0.002395	0.015977
	Apnea Vs Hypopnea	< 0.0001*	0.029457	0.043416
ECCS	Normal Breathing Vs Apnea	0.756	-6.192	8.082
	Normal Breathing Vs Hypopnea	0.0005*	3.631	18.401
	Apnea Vs Hypopnea	0.0033*	2.033	18.108
IE ratio	Normal Breathing Vs Apnea	< 0.0001*	0.39909	0.74055
	Normal Breathing Vs Hypopnea	< 0.0001*	0.19787	0.5504
	Apnea Vs Hypopnea	0.0122*	-0.37871	-0.01266
Peak-Peak	Normal Breathing Vs Apnea	0.0169*	0.0071	0.7504
	Normal Breathing Vs Hypopnea	0.0004*	0.2019	0.9687
	Apnea Vs Hypopnea	0.2237	-0.1916	0.6047
Heart Rate	Normal Breathing Vs Apnea	< 0.0001*	-0.15906	-0.10271
	Normal Breathing Vs Hypopnea	0.8748	-0.03155	0.02758
	Apnea Vs Hypopnea	<0.0001*	0.10332	0.15447

CHAPTER 4

DISCUSSION AND CONCLUSION

This chapter discusses the results obtained from the simulated apnea as well the sleep study of apnea patients. The discussion includes the efficacy of all the features described in previous chapters in reflecting the physiological response to apnea. The effect of posture and frequency of apnea on these features are also examined. The effect of duration of breath hold in simulated apnea is also discussed.

4.1 Simulated Apnea Study

4.1.1 Baseline Comparisons

The baseline is compared with the normal breathings for all the CO_2 features and with breath holds for the features extracted from ECG. For these comparisons we used Mixed Linear Model because of repeated measurements and inter dependence of breath hold with normal breathings, protocols postures dependence.

The baseline comparisons for sitting A according to the tables 3.1 to 3.5, it indicates that p-values obtained from comparing baseline with normal breathing were significant for $ETCO_2$, heart rate and not significant for ECCS, IE ratio, peak-peak interval. The probable reason for this might be that during breath hold CO_2 builds up and results in significant change in the $ETCO_2$ values. The vagus nerve is activated during the apnea event which leads to significant decrease in the heart rate. There are long inter breath hold intervals in protocol A and low load on stomach and diaphragm during breathing in sitting posture because of which oxygen deprivation is low. If oxygen deprivation is more the subjects strives to take in air with long inspirations. But because of less oxygen deprivation during protocol A the IE ratio, Peak-

Peak Interval and ECCS which are dependent on the breathing durations are less sensitive towards the breath holds.

For sitting B, the p-values were significant for $ETCO_2$, ECCS, IE ratio, Heart Rate and not significant for peak-peak interval. The probable reason for this might be as follows. During breath hold CO_2 builds up and results in significant change in the $ETCO_2$ values. During the high frequency apneic events the accumulation of CO_2 is more and the breathing patterns change (long inspirations) because of which there is a significant change in the ECCS, IE ratio. For the heart rate the vagus nerve activation during breath hold leads to the change.

For Supine A, the p-values were significant for $ETCO_2$, IE ratio, Heart Rate and not significant for ECCS, Peak-Peak. CO_2 builds up during breath holds resulting in significant change in the $ETCO_2$ values. The vagus nerve activation during the apnea event leads to significant decrease in the heart rate. The probable reason for ECCS and Peak-Peak not to be significant might be because of the long recovery time which does not make the subjects tires compared to other protocol.

For Supine B, the p-values were significant for $ETCO_2$, IE ratio and Heart Rate. CO_2 build up and vagus nerve activation during breath holds results in significant change in the $ETCO_2$ and heart rate. The ratio of inspiration time to expiration time is significant because of change in breathing pattern (long inspirations). This change in breathing pattern might be due to load on stomach, diaphragm load, and short rest periods between breath holds thereby changing the IE ratio.

4.1.2 Effect of posture and frequency of apnea

The purpose of analyzing the posture effect is to check whether the gravity on the body has any effect on the features analyzed. During sitting position the gravity acts differently on different parts where as in supine position the gravity effect is fairly constant but has the effect of the load of diaphragm on the lungs which provides significant variations in the features extracted. The supine position closely depicts the actual sleep study.

To analyze the frequency of apnea effect, the protocol A is compared with protocol B using the Mixed Linear Model. From the tables 3.6 to 3.9 we can see that in this study there is no significant p-value for CO_2 features when comparison is made on corresponding normal breathings and corresponding breath holds across protocols and postures. The reason for this might be that CO_2 build up is more related to the degree of closure of the airway. The p-value for heart rate during posture comparisons is not significant implying that change in heart rate would have been same in sitting and supine. The probable reason might be that carotid sinus reflex is compensated by the autonomic regulation [21].

4.1.3 Effect of posture and protocol on breath hold tolerance.

The effect of posture and frequency of apnea on the breath hold tolerance is analyzed using the mixed linear model. From the table 3.11 we get the p-values for these comparisons as non-significant which implies that the breath hold tolerance does not get affected by the posture or the protocol. Breath hold tolerance is mainly dependent on lung capacity. The reason for breath hold tolerance to be insignificant might be that subjects (healthy) have larger lung capacities that do not change with the posture or protocol.

4.1.4 Gender effect on the features of CO_2 and ECG.

The features extracted from the CO_2 and ECG are analyzed based on the subjects gender. The table 3.11 shows that the p-values for $ETCO_2$, ECCS, Peak-Peak interval are significantly different from male to female. The probable reason might be due to the difference in the lung capacities being higher in men and less in women [22]. High lung capacities leads to greater breath hold tolerance which implies that there is more CO_2 accumulation. Thus $ETCO_2$ and ECCS are significant when compared across gender. The increase in CO2 accumulation leads to intense breathing patterns changing the time of respiratory cycle (Peak-Peak Interval). Thus, the peak-peak interval is significant.

4.2 Sleep Study

In the sleep study the features are compared across the normal breathing, apnea events and hypopnea events. For this analysis the ANOVA is used along with the tukey-krammer method as post-hoc analysis. The table 3.12 shows the p-value across different comparisons of normal breathing, apnea and hyponea. The $ETCO_2$ is significant when compared across normal breathing and apnea, normal breathing and hypopnea, apnea and hypopnea. In apnea there is complete obstruction of the airway which leads to hypercapnia. In hypercapnia, the CO_2 levels increase resulting in increase in $ETCO_2$. In hypopnea, there is partial obstruction of the airway and patient has shallow breathing. Due to partial obstruction in airway the oxygen deprivation is less. So, the CO_2 build up is less than compared to apnea. Even the partial obstruction has a little effect on the CO_2 levels leading to significant change in $ETCO_2$ during normal and hypopnea comparisons.

The ECCS was significant when compared across normal breathing and hypopnea, apnea and hypopnea.

The p-values for IE ratio indicate that it is significantly different. It indicated that due to apnea or hypopnea there is a change in the inspiration and expiration durations. The probable reason might be due to the load of the diaphragm and stomach during supine position making it difficult to breathe the air which leads to expiration time being more than the inspiration time.

The peak-peak interval is significant during comparison of normal breathings with apnea and normal breathings with hypopnea. The reason for this goes back to the same as discussed for the IE ratio above.

The heart rate when compared across normal breathing and apnea is significant due to the vagus nerve activation during apnea event. The comparison of apnea with hypopnea is also significant, Comparison of normal breathing with hypopnea is not significant. The

probable reason for this might be that the patients may have some cardiovascular problems or they might be in some medications process which leads to such results.

4.3 Conclusion

The above results and discussion reveals that $ETCO_2$, IE ratio and the Heart Rate are the features that change significantly both in simulated apnea study and sleep study. So, these features can be used to test the efficacy of the apnea treatment. The frequency of apnea, posture had no significant effect on the features. The duration of breath hold was also not significantly different from postures to protocols. The limitation of this study is that the subject population for the sleep study was less (5 subjects), younger population for simulated apnea study, subjects in simulated apnea study were awake rather than sleeping which is not the usual case in actual apnea.

APPENDIX A

CO2 ANALOG MODULE

The Analog Output Module has a DB15 connector pin. The pin configuration of the Analog Output Module is shown in the table 1.

Table 1: Pin Configuration

Signal	Pins	Specifications
CO_2 waveform	1 – CO_2, 2 – Reference	10 mV = 1 Torr
Respiratory rate	3 – CO_2, 4 – Reference	7 mV = 1 breath/min
$ETCO_2$	5 – CO_2, 6 – Reference	10 V = 1 Torr

APPENDIX B

ECG ANALOG MODULE

The ECG output Module had a phone jack 3.55mm to BNC female connector. The switch on the ECG module can be set to 1-16 which corresponds to the output channel from where analog output can be sent to the DAQ card for data acquisition. For this study channel 1 has been used as the analog output port.

APPENDIX C

SUBJECTS SELECTION

The subjects signed a consent form that was approved by the Institutional Review Board (IRB) of the University of Texas at Arlington. The subject demographics are shown below.

Table 2: Subject Demographics for simulated study

Subject	Age (mean ± σ) yrs	Height (mean ± σ) (cm)	Weight (mean ± σ) (kg)	BMI (mean ± σ) (kg/m^2)
9 M, 7 W	29 ± 4.89	165.88 ± 9.23	67.19 ± 19.31	24.07 ± 4.84
Men	30.11± 5.11	172 ± 6.86	77.78 ±17.99	26.14 ± 4.6 8
Women	27.57 4.54	158± 4.89	53.57± 10.78	21.4± 3.83

Table 3: Subject Demographics for sleep study

Subject	Age (mean ± σ) yrs	Height (mean ± σ) (cm)	Weight (mean ± σ) (kg)	BMI (mean ± σ) (kg/m^2)
4 M *, 1 W	53.6 ± 7.4	166.1± 6.6	93.00±23.60	33.66 ± 7.27

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BIOGRAPHICAL INFORMATION

Bashaboyina Aditya was born in a Hyderabad, India also known as the city of pearls in the year 1986. With his keen interest towards education, he has excelled in his studies ranking first from the Gokaraju and Rangaraju Institute of Engineering and Technology, Hyderabad, India, 2007. He was also good at cultural activities and leadership skills. His skills helped him to get a job in Infosys Technologies Limited, India, as a software engineer where he worked for 1 year. As he was interested to pursue his higher education, he joined for his Master's Degree in Bioengineering at University of Texas at Arlington, 2008. His interest towards medical equipment and bio-instrumentation led him opt for thesis in bioinstrumentation track. He is currently working on sleep apnea and planning to get a job in a reputed biomedical company to improve his skills.