AN INVESTIGATION OF THE COVARIATIONS BETWEEN VARIATIONS IN EXHALED CARBON DIOXIDE AND CEREBRAL BLOOD FLOW LEVELS DURING APNEA

by

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Abstract

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Sleep apnea is a breathing disorder characterized by repetitive reduction or cessation of breathing during sleep. It is estimated that that around 17% of adults suffer from mild to severe sleep disordered breathing.

The aim of this study was to investigate the level of correlation between variations in exhaled CO_2 and cerebral blood flow (CBF) during apnea. It is difficult to measure the CBF during sleep. This relationship was found in an effort to substitute the measurement of the changes in CBF with the changes in the CO_2. The relationship between these two physiological parameters was first studied in healthy subjects. Two protocols were devised to examine the effect of posture – sitting versus supine – and frequency of apnea on the relationship between the variations in the two parameters: protocol A and B. The time between the two breath holds for protocol A was 90 s and for protocol B was 30 s. The two protocols were considered to study the cumulative change in the physiological signals due to successive apneas have on the relationship between the exhaled CO_2 and CBF. End tidal CO_2 ($ETCO_2$) – peak of exhaled CO_2 after apnea – and change in $ETCO_2$ (Delta $ETCO_2$) – difference in post apneic $ETCO_2$ and the peak of exhaled CO_2 in the baseline – was measured from the capnogram. From the cerebral blood flow recording, 11 metrics were computed: slope, Del_1, PR_1, Del_2, PR_2, Del_3, PR_3, $oDel_2$, oPR_2, PRArea and Norm Area. Slope is defined as the slope of the trend of the

systolic points. Del_1 is the change in the systolic value with respect to the baseline. PR_1 is the percentage rise of the change defined by Del_1. Del_3 is the change in the systolic value from the normal breathing before the apnea. $oDel_2$ is the change in the systolic value from the minimum of first 4 systolic point in the apnea. PRArea is the percentage rise in area under the CBF wave. Norm Area is normalized area under the systolic points with respect to 35 seconds in the baseline. We quantified the correlation between the metrics derived from exhaled CO_2 and CBF using Kendall's Rank and Spearman's Rank order correlation methods. Spearman's method indicated that in the supine position under protocol A, Norm Area had a correlation coefficient of 0.66 with Delta $ETCO_2$ ($p=2x10^{-3}$). It also had the highest correlation with $ETCO_2$ correlation coefficient of 0.56($p=1.01x10^{-2}$). The same method also showed that in the supine position under protocol B, PR_1 had the highest correlation with $ETCO_2$ of -0.6 ($p=1.63x10^{-4}$) and Norm Area had a correlation coefficient of 0.67 with Delta $ETCO_2$ ($p=7.96x10^{-7}$). Between the protocols the means of Del_3 were statistically greater in protocol A (greater by (Δ)=7.21 cm/sec $p=2.78x10^{-2}$) in the supine position. Between the postures the means of the following metrics were statistically greater in the supine position in protocol A; Norm Area (Δ=0.33 $p=2.14\ x10^{-2}$); Del_3 (Δ=9.24 cm/sec $p=5.07\ x10^{-3}$); $oDel_2$ (Δ=9.3 cm/sec $p=4.5\ x10^{-3}$); slope (Δ=0.41 cm/sec^2 $p=4.23\ x10^{-4}$); Del_1 (Δ=10.7 cm/sec $p=2.38\ x10^{-3}$). The means of the following metrics were statistically greater in the supine position in protocol B; Norm Area (Δ=0.36 $p=1.6\ x10^{-2}$); Del_3 (Δ=6.06 cm/sec $p=3.85\ x10^{-2}$); $oDel_2$ (Δ=5.97 cm/sec $p=4.2\ x10^{-4}$). The means of Delta $ETCO_2$ were statistically greater in the sitting position (Δ=2.99 mmHg $p=3.29x10^{-2}$) in protocol A.

In the second part of this research, the relationship between exhaled CO2 and CBF in sleep apnea patients was investigated during sleep. In this study using both Kendall and Spearman's methods none of the CBF and CO_2 metric pairs, which had a

significant correlation had a correlation coefficient greater than 50%. From the results of this study we can conclude that the proposed CBF CO_2 metric pairs did not exhibit strong correlation to allow estimation of CBF via the changes in the exhaled CO_2.

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Chapter 1

Introduction

This chapter provides the background and significance for the study that was conduct for present thesis. It describes sleep disordered breathing, referred to as sleep apnea, methods of detecting it and current treatment options for it. A description of the effect on exhaled CO_2 levels and cerebral blood flow is given to. It put forward the main goal of this thesis.

1.1 Sleep Apnea

1.1.1. What is Sleep Apnea

Sleep apnea is a disorder which is characterized by repetitive reduction or cessation of breathing during sleep. This cessation leads to an increase in the ventilatory effort. This effort, if exceeds the 'ventilatory effort arousal threshold' results in the person waking up and resuming breathing [1]. It is estimated that around 17% of adults suffers from mild to severe sleep disordered breathing [2]. Symptoms of sleep apnea may include snoring excessive daytime sleepiness, difficulty concentrating, depression, irritability and learning and memory difficulty.

1.1.2. Types of sleep apnea

There are three types of sleep apnea: central, obstructive and mixed

Central sleep apnea (CSA) is the occurrence of apnea due to loss of ventilatory function [3]. It is the less common type of apnea and can occur due to cessation of signals from the brain to the respiratory diaphragm

Obstructive Sleep Apnea (OSA) is characterized by the collapse of the airway due to excessive muscle relaxation in the upper airway [4].Along with this the position of the tongue also plays an important role in OSA [5, 6]. This is regarded to be the most common form of sleep apnea.

Mixed Sleep Apnea is characterized by the occurrence of both CSA and OSA together. This is also called as Complex Sleep Apnea [1]. Since the prevalence of OSA is far greater than other two types of sleep apnea, the focus of this study presented here is primarily on OSA.

1.1.3. Effect on health due to Sleep Apnea

Sleep Apnea is associated with sleep fragmentation and excessive sleepiness during daytime. Loss in the efficiency of the cognitive skills has also been known to arise due to this condition. Coronary dysfunctions like hypertension, coronary heart diseases, atherosclerosis, and stroke have also been linked to sleep apnea [7]. Accidents that occur due to drowsiness during the daytime could form a huge risk. Type 2 diabetes is more prevalent with people with sleep apnea, however it is not clear if this relationship is causal [8].

1.1.4. Detection and Treatment of Sleep Apnea

Sleep apnea is detected using polysomnography. It involves recording and analyzing multiple physiological data when the subject is sleeping. Some of the physiological signals that are measured during detection and treatment of sleep apnea include electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), electrocardiogram (ECG\EKG), airflow, blood pressure and blood oxygen level (SaO_2) [9]. The polysomnography data is analyzed by a certified sleep technician to determine whether sleep apnea is detected.

OSA is a disease that requires long term management. The most common treatment of obstructive sleep apnea is the use of continuous positive airway pressure (CPAP) machine [10]. This involves using a compressor to generate and apply pressurized air to the airway to keep the airway from collapsing. This is, by far, the preferred method of management of the disease. Alternate therapies are offered if the

patient so prefers [10]. Factors like the severity of the apnea, the patient's anatomy and risk factors are considered before assigning an alternative therapy. These include medical and surgical option, oral appliances and behavioral therapy. Medical and surgical options are available for the treatment of sleep apnea. Custom made oral appliances can be prescribed to hold the mandible in an advanced and the tongue in a forward position in an effort to manage OSA. This is prescribed to patients with mild to moderate apnea. Behavioral strategies can also be used to manage sleep apnea. This involves behavioral treatment to motivate weight loss and reduce the patient's body mass index (BMI). Positional therapy, another part of behavioral therapy, involves conditioning the patient to sleep in a non-supine position. This method can be used in patients with low AHI in non-supine position than supine position.

1.2 Change in Exhaled CO_2 levels due to Sleep Apnea

There is a loss of proper ventilatory function during sleep apnea. This results in instabilities in the homeostasis in the blood [11]. This causes a change in the exhaled CO_2 levels in the breath. A study conducted by Barton C.W. *et al* [12] showed that end tidal CO_2 ($ETCO_2$) correlates positively and well with arterial CO_2 in hospital patients. These patients had arterial blood gas determination as a part of their evaluation. Maximum $ETCO_2$ was recorded at the same time as arterial blood gas sampling. The study provides evidence that $ETCO_2$ measurement can be used as an indication of CO_2 levels in the blood. Moreover a capnography handbook written by Carefusion [13] states that the arterial CO_2 is greater than the end tidal CO_2 by 2-5 mm of Hg. The method by which the changes in exhaled CO_2 affect the changes in cerebral blood flow is mentioned in section 1.4.

1.3 Change in Cerebral Blood Flow due to Sleep Apnea

Cessation of breathing during apnea results in lack of resupply of oxygen to the blood. Cerebral autoregulation tries to overcome the lack of oxygen by increasing the flow of blood to the brain [14]. This increase in blood flow reduces after the end of the apnea. Studies have shown that cerebrovascular control is impaired in people suffering with OSA [15]. Multiple apnea episodes can have a long term impact like decreased cerebral blood flow during sleep and wakefulness compared to subjects without OSA. Blood gasses and pH changes along with stimulations of vasoactive central neurons could influence the changes in cerebral blood flow during OSA [15]. The section below states the method by which the changes in cerebral blood flow is affected by the changes in exhaled CO_2.

1.4 CO_2 influence on Cerebral Blood Flow

Cerebrovascular resistance is influenced by the CO_2 level in the blood [15]. Hypercapnia causes a vasodilation at the arterioles and precapillary sphincters. This effect is reversed in hypocapnia, which causes a vasoconstriction. The actual mechanism by which CO_2 affects cerebrovascular resistance is not fully understood. Some studies suggest that the elevation in CO_2 and the change in the pH activate the K^+ channels in the vascular smooth muscle [16]. Among the classes of K^+ channels Adenosine triphosphate (ATP) sensitive K^+ and voltage sensitive K^+ channels are activated by the change in pH. This suggests their involvement in the vasodilation which in turn increases the cerebral blood flow. Sympathetic nerve activity was assumed to have a limited influence on this relationship. This activity increases with hypertension but not with hypotension. A study has shown that sympathetic nerve activity attenuates the changes in CBF due to the changes in CO_2 levels [17]. However this influence did not have a major effect on the above mentioned changes during normal conditions. This suggests

that there is a limited influence of sympathetic nerve change due to CO_2 affecting cerebral blood flow [18, 19].

1.5 Previous Studies

A study conducted by Battisti-Charbonney, et al [15] looked at the correlation between percentage rise of mean cerebral artery velocity (MCAv) and end tidal CO_2 ($ETCO_2$). Duffin's rebreathing method [20] was utilized for this study. This method involved inducing hyperventilation followed by Read's rebreathing method. They induced hyperventilation to reduce the $ETCO_2$ so as to produce maximum vasoconstriction. After this, they used Read's rebreathing method [21] to increase $ETCO_2$ and cerebral blood flow. Read's rebreathing method involved breathing in air mixture containing 7% CO_2. Percentage rise in MCAv was calculated using recorded values during hyperventilation and breath-by-breath values. This was done for Hyperoxic (P_{ETO2}= 150 mmHg) and Hypoxic (P_{ETO2}= 50 mmHg) conditions. They found that within individual subjects the relationship between $ETCO_2$ and MCAv was nonlinear, sigmoidal and positive until a threshold TMCAv. This threshold was found manually by examining the data for each subject separately. This threshold during hyperoxic conditions was at 51.7±2.8 mmHg when recording was done from the right side and was at 51.6±2.8 mmHg when the recording was done from the left side. During hypoxic conditions this threshold was at 45.4±2.4 mmHg when recording was done from the right side and was at 47.4±6.9 mmHg when the recording was done from the left side. After this point $ETCO_2$ and MCAv has a linear and positive relationship.

A study conducted by Klingelhofer et al [22] computed what they termed as CO_2 reactivity and compared its values during sleep apnea in various sleep stages (Awake, Sleep Stage 1, Sleep stage 2 and REM). CO_2 reactivity was calculated by taking the ratio between the percentage increase in mean cerebral flow velocity (MFV)(cm/s) and the

difference in the $ETCO_2$ (mmHg)values before and after the apnea. They found that the CO_2 reactivity values were significantly different during the different sleep stages. Another study conducted by M. Cigada et al [23] aimed to evaluate a standardized method to find cerebral CO_2 vasoreactivity. In the study the subject was asked to lie in a supine position and inhaled a gas of 50% O_2 5% CO_2 and N_2 and 50% O_2 and N_2 alternating between the two mixtures to control the CO_2 inhalation from 0% to 5%. Correlation between change in $ETCO_2$ and percentage change in mean blood velocity (Vm) and between change in $ETCO_2$ and pulsatility index (PI), which was calculated as PI = (Vsystolic-Vdiastolic)/Vmean, was found using linear regression. They concluded that CO_2 is a can be used to change cerebral perfusion.

A study conducted by Markwalder T.M. et al [24] looked at the relation between CO_2 and the change in velocity in the middle cerebral artery in normal subjects. They considered 3 age groups, Group 1 consisted of subjects with ages between 5-15 years, Group 2 between 16-40 years and Group 3 between 41-73 years. The study procedure had multiple steps. In step 1 subjects were asked to breathe room air until a steady state of normocapnia (36-40 mmHg) was reached. In step 2, they were asked to hyperventilate until they reached a mild hypocapnic (28-33 mmHg) state and then a low hypocapnia (17-23 mmHg) state. In step 3, they were asked to inhale air mixture containing 7% CO_2 and then 5% CO_2. Velocity in the middle cerebral artery (Vmca) was recorded at each stage over a period of 3-5 minutes after the P_{CO2} reached a steady state. Relationship between percentage change in Vmca and $ETCO_2$ was found. When $ETCO_2$ was 40 mmHg the corresponding Vmca was considered as 100%. This relation was found by finding the best curve fit for the plots of $ETCO_2$ and Vmca. This was nonlinear and positive. Moreover they found that the cerebrovascular reactivity to P_{CO2} did not differ between subjects in different age groups. This reactivity was defined as $(dVmca/Vmca)/dP_{CO2}$. A

study conducted by Markus H.S. et al [25] justified using breath holding method to correlate the changes in CO_2 and cerebral blood flow. Subjects breathed in room air, and then they were asked to hyperventilate. The subjects were then asked to hold their breath after a rest of four minutes to remove the effects of hyperventilation. After a rest of two minutes the subjects were asked to hold their breath. Then they were asked to inhale air containing 5% CO_2 then they increased the CO_2 mixture by 1% until no more increase in mean middle cerebral velocity (Vmca) was seen due to CO_2. They inhaled each mixture of gas for two minutes and at the end of this CO_2 and Vmca were recorded. They looked at the changes in Vmca this was calculated over a period of 4 seconds and displayed on the TCD display. They compared the breath holding method to the inhaled CO_2 method. It was concluded that breath holding techniques offers a more convenient method to evaluate CO_2 reactivity. A study conducted by Tancredi. F.B. et al [26] looked at the different methods to evaluate the cerebral vascular reactivity. They measured CBF by using a functional magnetic resonance imaging (fMRI). They quantified the CBF by arterial spin labeling (ASL). Four methods were studied; prospective control (PC); breath holding (BH); fixed inspired (FI) and hyperventilation (HV). In PC the subjects were asked to breathe through a rebreathing apparatus. This apparatus would increase the $ETCO_2$ by 7mmHg from the baseline. This was done twice with a rest period of 2 minutes 20 seconds each. For BH the subjects were asked to hold their breath 12 times for 20 seconds. Between each breath hold the subjects were asked to perform paced breathing for 30 seconds. To assist with this they were asked to breath by following a metronome tone which was calibrated at 16 breaths per minute. In FI the subjects were asked to breathe in an air mixture of 5% CO_2. This was done twice with 2 minutes 20 seconds interval between them. In HV the subjects were asked to perform six breath holds of 20 seconds with a single breath between them. This was repeated after an interval of 2

minutes 20 seconds where the subject would breathe by following a metronome tone for 24 breaths per minute. They correlated CBF with $ETCO_2$ by fitting a sigmoidal curve. They found that PC had the most linear estimate of cerebrovascular reactivity. They also suggested that the same level of linearity could be achieved by FI and BH by reducing the breathing rate.

From the studies mentioned above it is found that changes in CO_2 can influence changes in cerebral blood flow. Moreover study conducted by Klingelhofer et al [20] shows that the established relationship differs with the sleep stage therefore warranting a better way of finding a relationship between the two.

1.6 Research Goal

Previous studies have established that the values of CO_2 after an apnea event and the cerebral blood flow (CBF) during the apnea are different from their normal breathing waveform. These changes indicate physiological changes that occur in the body due to sleep apnea. However it is difficult to measure the CBF during sleep. The objective of this study is to investigate the possibility that the changes in CO_2 may be used to estimate the changes in CBF. The goal is to explore the possibility of quantifying the changes in CBF via measurement of the changes in CO_2 levels. To do so, the following hypothesis is formulated:

'There is a statistically significant high correlation between the CO_2 and the CBF during sleep apnea that would allow one to estimate the changes in CBF from the changes in exhaled CO_2 due to obstructive sleep apnea.'

1.7 Thesis Organization

Chapter 2 deals with Capnogard and TCD devices describing their components and principle of operation. The chapter covers the instrumentation used and the protocols implemented for the study as well as subject demographics and the data acquisition

system. Further, the algorithms used for signal processing, parameter extraction and analysis are also covered in Chapter 2. Results from the experimental studies and statistical analysis of the metrics are presented in Chapter 3. In the same chapter, the results of exploring the relationship between metrics derived from exhaled CO_2 and CBF are also presented. Chapter 4 presents the discussion of the results followed by the conclusions. Limitations to the study are also discussed in Chapter 4.

Chapter 2

Materials and Methods

This chapter describes the experimental setup for both simulated sleep apnea and nocturnal sleep apnea studies. Further, it details the subject selection, the protocols involved as well as the algorithms and the metrics used to quantify the exhaled carbon dioxide (CO_2) concentration and cerebral blood flow velocity (CBFV). It also covers the equipment involved in the study, highlighting their principle of operation along with a brief description of their major parts.

2.1 Capnostat (Capnography)

There is a balance of O_2 and CO_2 maintained in the body due to breathing. Normal respiration is paramount to maintaining this balance. During apnea and hypopnea this balance is disturbed due to interruption in normal breathing pattern. Capnostat is a device that measures the partial pressure of CO_2 in the exhaled breath. The device displays the output in mmHg. This device was used to measure the CO_2 patterns before, during and after apnea events.

2.1.1. Principle of Operation

Capnography uses infra-red (IR) light technique to calculate the CO_2 levels in the exhaled flow. Exhaled flow is sampled and collected in a chamber through a cannula. IR light is first filtered and then passed through the collected exhaled gases. Light at 4.26 µm wavelength is absorbed by CO_2 causing the transmitted light to attenuate in proportion to the concentration of CO_2 in the exhaled gases. The intensity of the IR light is compared with the intensity of a reference light which has not been shone through CO_2. This comparison yields the concentration of CO_2 present in the exhaled air [27]. The capnostat gives both instantaneous and average readings, including a waveform of varying CO_2 concentration with respect to time. This is referred to as a capnogram. In our

study, we use the waveform (i.e. capnogram) to analyze the effect apnea and hypopnea on the CO_2 production.

2.1.2. Monitor Description

Capnogard monitor consists of a nasal cannula and tubing, a detector and the monitor (Model 1265, Novametrix Medical Systems INC. CT, USA).

The sample of the exhaled gas used for measuring the CO_2 partial pressure captured using a nasal cannula. This device is made of tubing with two prongs with open ends in the middle and tubing at either ends of it. These two prongs are inserted into the nostrils. They are made with a soft pliable material so as to be flexible and to be universally used. After the cannula collects the exhaled air, it passes through a tube called as the sampling tube. The function of this tube is to transport the gas from the cannula to the detector. A typical oronasal cannula is shown in Figure 2-1

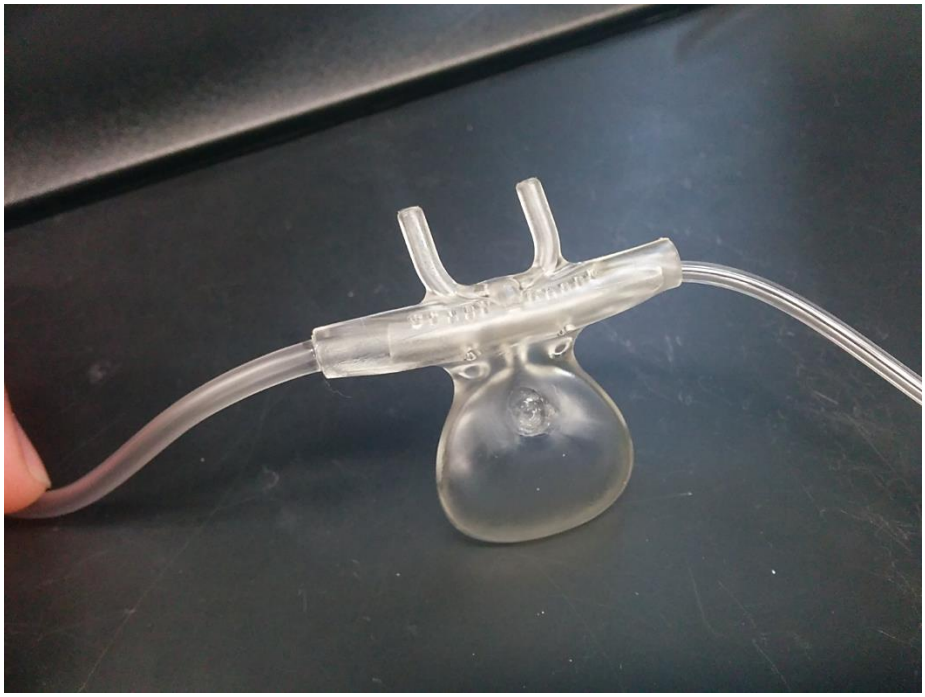

Figure 2-1 Oronasal Cannula

The detector is 'U' shaped with a detachable sample cell in the middle. This sample cell is connected to the sampling tube at one end and a tube that connects to the monitor at the other. The cell has two transparent windows on either side. On one arm of the 'U' shaped detector infrared light is generated at 4.26 μm [27]. This light passes through the sample cell to the other arm of the detector which has a sensor which detects this light and records it. This light, when passed through the sample cell which contains the exhaled air, is attenuated due to the CO_2 present in the air. This recorded light is then compared with the un-attenuated light to calculate the CO_2 levels. There are two cells attached on the wire of the sensor; the 'Zero cell' and the 'Reference cell'; which help in the calibration of the monitor. Figure 2-2 shows the capnostat sensor.

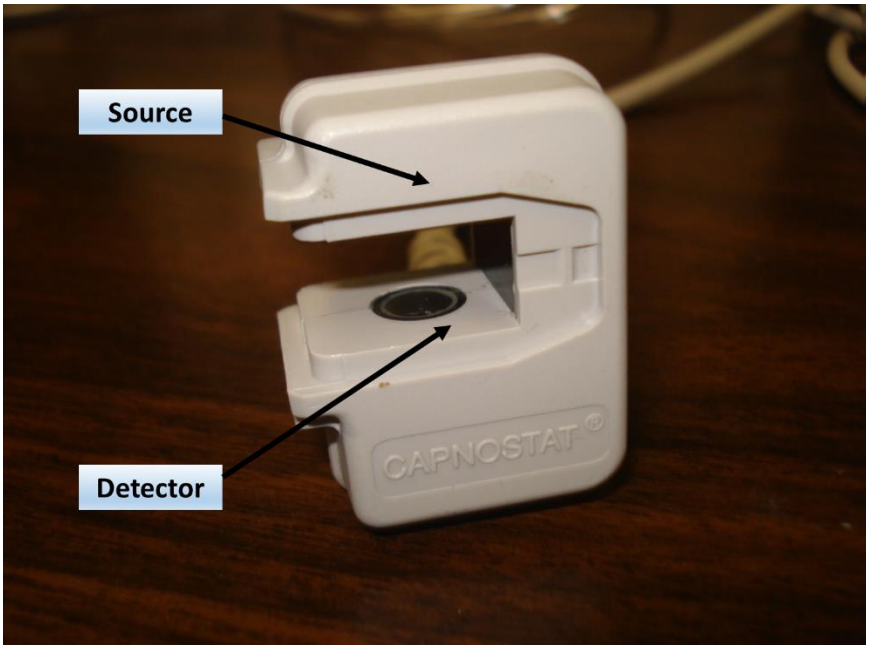

Figure 2-2 Capnostat Sensor *[28]*

The Capnogard monitor (Model 1265, Novametrix Medical Systems INC. CT, USA) contains all the electronics and circuitry involved in the collection and detection of CO_2 levels. The output from the detector and the sample cell is attached at two ports on

the front face of the monitor. It contains a pump that drives the exhaled air from the cannula to the sample cell. This is done using the tube connecting the monitor and the sample cell. The monitor also acts as the front end to the device. It contains a screen and a few buttons that acts as the user interface. The user would use the buttons to navigate through the multiple settings and stages of the device. The device has an option to transfer the data to another device via analog cables attached at the back of the monitor. The monitor is shown in Figure 2-3.

Figure 2-3 Capnogard monitor *[26]*

2.1.3. Calibration

The device is calibrated using the calibration option in the user interface. The program first asks the user to place the zero cell in place of the sample cell in the detector. The zero cell is a cell which is devoid of any CO_2 molecules. It then asks the user to place the reference cell in the detector. The reference cell contains a known amount of CO_2. The device then takes a few seconds to calibrate for each cell. During this time no air should pass through the cannula. The zero and the reference cell is shown in Figure 2-4.

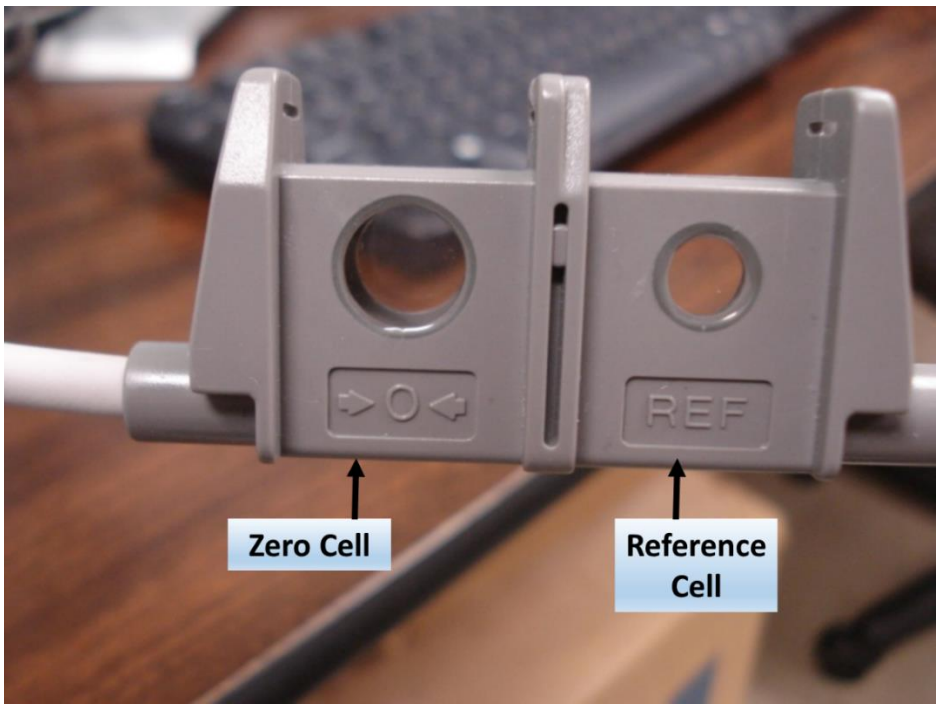

Figure 2-4 Calibration Set Up *[28]*

2.2 Transcranial Doppler

Blood flow to the brain or cerebral blood flow (CBF) is a highly regulated and important physiological mechanism. During an apnea to meet brain's metabolic demands the CBFV increases. To measure this change, a device known as Transcrainal Doppler was used.

2.2.1. Principle of Operation for Transcrainal Doppler

Transcrainal Doppler (TCD) works on the principle of the Doppler Effect. This effect states that there is a change in the frequency of sound from a moving object as it moves towards or away from the observer. This is also known as Doppler shift. TCD records the flow of blood in the middle cerebral artery (MCA). It is one of the major arteries that supply blood to the brain. Broca's area, Wernicke's area, basal ganglia, internal capsule and most of the lateral surface of the hemisphere are perfused by MCA. TCD sensor is placed at the temple which provides the shortest distance to the MCA. An ultrasound transducer transmits sound waves at 2MHz on the MCA [29]. This sound travels through the tissue until it reaches the MCA. Here it hits the red blood corpuscles (RBCs) which are in motion. Based on the Doppler principles, the reflected wave will have a shift in frequency. This wave is picked up by the transducer. The shift in the frequency depends majorly upon the velocity of the RBCs in the blood. Due to this fact the velocity of the blood in the MCA can be recorded. Moreover studies have shown that the diameter of MCA does not change significantly during fluctuations in CO_2, blood pressure and autoregulation hence we can assume that CBFV is a good estimate of CBF[30, 31]. The velocity is given by the following equation [29]:

$$v = \frac{c}{2\cos\theta} \times \frac{f}{f_o}$$

Where;

v= blood flow velocity (cm/sec)

c= speed of sound (average of 1, 540 m/sec in human tissue)

f= Doppler shift frequency (kHz)

f_o= Original transmitted frequency (2MHz)

θ= angle of insonation

This is recorded continuously and the output is a waveform is the velocity with respect to time. This waveform peaks at the systolic phase of the cardiac cycle and is at its minimum during the diastolic phase.

2.2.2. Parts Description

There are three main parts to the TCD; the ultrasound probe, the Doppler box and the software front end.

The ultrasound probe contains a piezoelectric crystal [32]. This crystal has 3 axes; electrical axis, mechanical axis and optical axis [33]. Of these the electrical and mechanical axis is utilized in ultrasound production and detection. Piezoelectric crystal has a special property of changing one axis when a change is applied on the other, i.e. if a potential difference is applied to the electrical axis there is a slight change in the size of the crystal at its mechanical axis. Similarly when a mechanical force is applied at the mechanical axis a potential difference is generated at the electrical axis. When the size of the crystal changes, due to the potential difference applied at its electrical axis, it forces the air around the crystal to compress. When this potential difference is removed the crystal reverts back to its original size causing the air to rarefy. This creates a sound wave. At high frequencies it creates an ultrasound wave. When the reflected wave reaches the transducer, it interacts with the mechanical axis creating a potential difference, which is recorded and read as amplitude with respect to time.

The Doppler box (Compumedics DWL, Germany) contains the electronics needed to drive the ultrasound probe. This box is controlled by proprietary software. In the front it has connections to which the ultrasound probes are connected. This device can interface with four probes simultaneously. The front also contains a switch which turns the device. The rear panel consists of a power connector, an analog input, an analog output and an Ethernet port. Using this port, the box is connected to a PC on which the proprietary software QL runs. The Doppler box is shown in Figure 2-5.

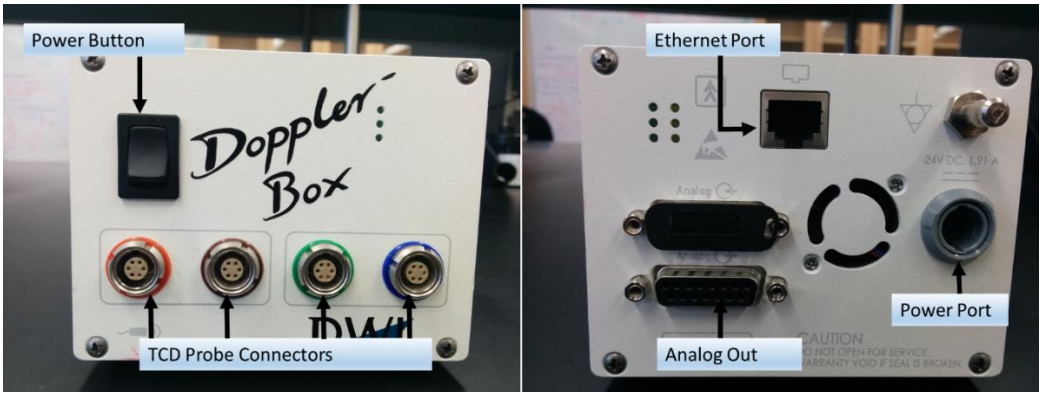

Figure 2-5 Doppler Box *[34]*

The Doppler box comes with software called as QL. This software runs on a Windows PC. It controls the box which in turn drives the ultrasound probe. This software acts as a front end. It has controls which allow the user to change the depth and the gain of the ultrasound. It also displays the TCD data continuously. Along with this the software also displays the one dimensional ultrasound data in continues time colored B-Mode image. This helps to find the MCA. It also has space to select the sample volume, the power limit and the filter level.

2.2.3. Instrumentation Hook Up

The ultrasound probe is placed on the temple of the subject after adding a dab of ultrasound gel on it. Next the probe is moved around both laterally and angularly to find

the best location to pick up the MCA signal. The gain and the depth of the ultrasound probe are adjusted to pick up the best possible signal. After this a mold is made from dental extrude to fix the probe in its right angle. During the making of this mold certain lines are marked on the subject, which would indicate the spatial position of the mold. These lines were made with a marker which wipes away with water. An elastic band was tied around the subjects head to hold the mold in place. This band was adjusted to meet the subjects comfort and to get the proper signal.

2.3 Experimental Design and Data Collection

This section explains the experimental design and the methods employed for data collection for both simulated sleep apnea and nocturnal sleep apnea study.

2.3.1. Simulated Sleep Apnea Study

To simulate the apnea condition, a breath holding method was employed. The process of holding one's breath creates the cessation of breathing which is characteristic to sleep apnea. This is done to induce the physiological response of the body to apnea. This experiment was done across two protocols and two postures.

Two experimental protocols; Protocol A and Protocol B; were implemented to study the effect of simulated sleep apnea on the cerebral blood flow velocity and exhaled carbon dioxide. The two protocols differed only in the duration between successive breath hold. Both protocols were performed under two separate postures; sitting and supine. This was done to study the effect of apnea under varying condition of posture and type of apnea episodes. The order of testing between the two protocols and positions were randomized. However the two postures tests associated with the selected protocol were conducted before starting the second protocol.

In both protocols the subject was asked to breathe room air for 60 seconds to establish a base line. After which they were asked to hold their breath for as long as they

can. To prevent accidental breathing through the nose a nose clip was placed on their nose. The subject would indicate when they could no longer hold their breath. At this point the nose clip was removed and the subject started breathing normally. In protocol A, the normal breathing continued for 90 seconds, after which the subject was asked again to hold their breath. Five such breath holds were performed in this protocol. After the final breath hold 60 seconds of data was collected. The timing diagram of protocol A is shown below. Protocol A was conducted to emulate the conditions in which the successive apneas have enough time in between for the physiological changes to return to its baseline levels. Figure 2-6 gives a diagrammatic representation of protocol A. The rising edge indicates the start of the breath hold and the falling edge indicates the stop of the breath hold.

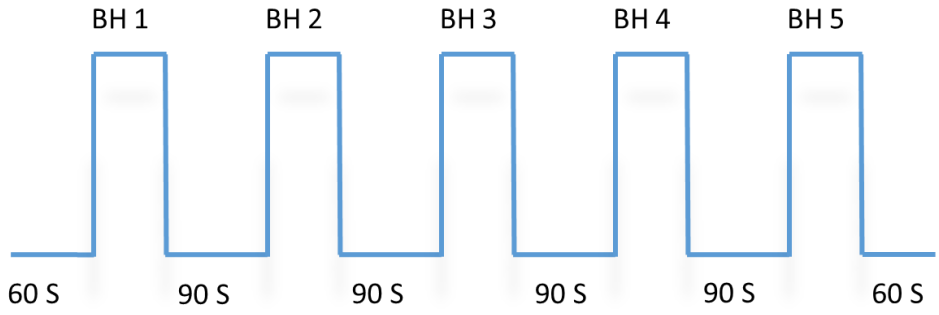

Figure 2-6 Timing Diagram Protocol A

Protocol B was similar to protocol A, the difference being the duration between two successive breath holds was 30 seconds. This protocol was done to emulate the condition in which the duration between two apneas is short. This was done to investigate the possibility that the physiological changes could be the accumulation of successive apneas if the time between the apneas is not enough for the changes to return to the baseline. The timing diagram for protocol B is given below. Figure 2-7 gives a

diagrammatic representation of protocol B. The rising edge indicates the start of the breath hold and the falling edge indicates the stop of the breath hold.

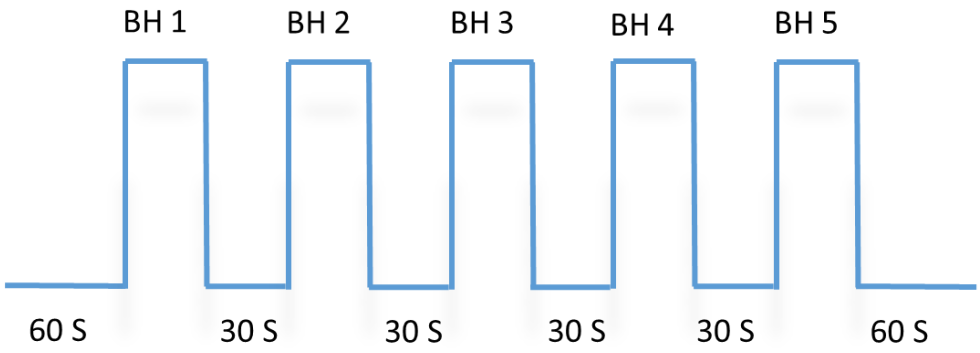

Figure 2-7 Timing Diagram Protocol B

The above mentioned protocols were performed on two postural conditions; sitting and supine. This was done to investigate the possibility of different positions affecting the physiological changes due to sleep apnea. As mentioned earlier the order in which the siting and supine conditions were performed was randomized.

For the sitting position the subject was asked to sit on a chair and perform the test. Sensors were placed on the subject before the start of the test. After this the subject was asked to perform the protocols. Further for different protocols this position will be referenced as SiA and SiB which identifies protocol A and protocol B in the sitting position respectively. Figure 2-8 illustrates the setup for the sitting position.

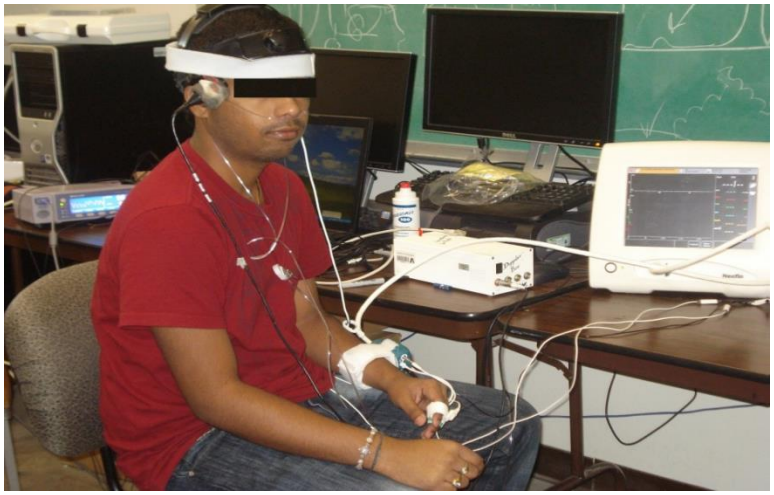

Figure 2-8 Subject with instrumentation attached in a Sitting Position *[28]*

For the supine position the subject was asked to lie down on an inflatable mattress while the sensors were attached to the subject. The subject was then asked to perform the protocols. Further for different protocols this position will be referenced as SuA and SuB which identifies protocol A and protocol B in the supine position respectively. Figure 2-9 illustrates the setup for the supine position.

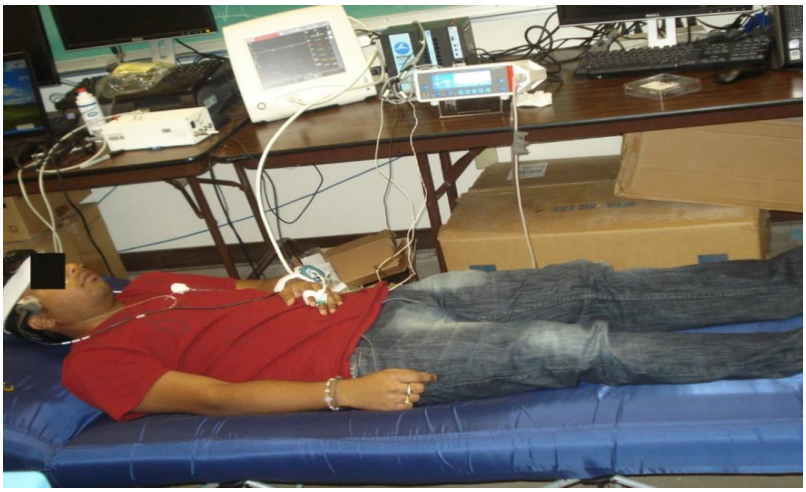

Figure 2-9 Subject with instrumentation attached in a Supine Position *[28]*

2.3.2. Nocturnal Sleep study

An 8 hour nocturnal polysomnography was performed on subjects who had previously been diagnosed as having sleep apnea. This was done in an accredited sleep lab Sleep Consultants Inc (Fort Worth, TX) under the supervision of the lab personals. Parameters recorded during this test were CBFV, capnography, blood pressure, blood oxygen saturation (SaO_2), electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), nasal pressure, chest and abdominal movement, leg movements, snoring and a video monitoring of the subject. Some of the signals were recorded using our equipment and the others were recorded using the sleep lab's equipment. The data were synchronized between these two setups. A sleep lab technician scored the test which was then used as an area of interest for analysis. Figure 2-10 illustrates the setup for the nocturnal sleep study.

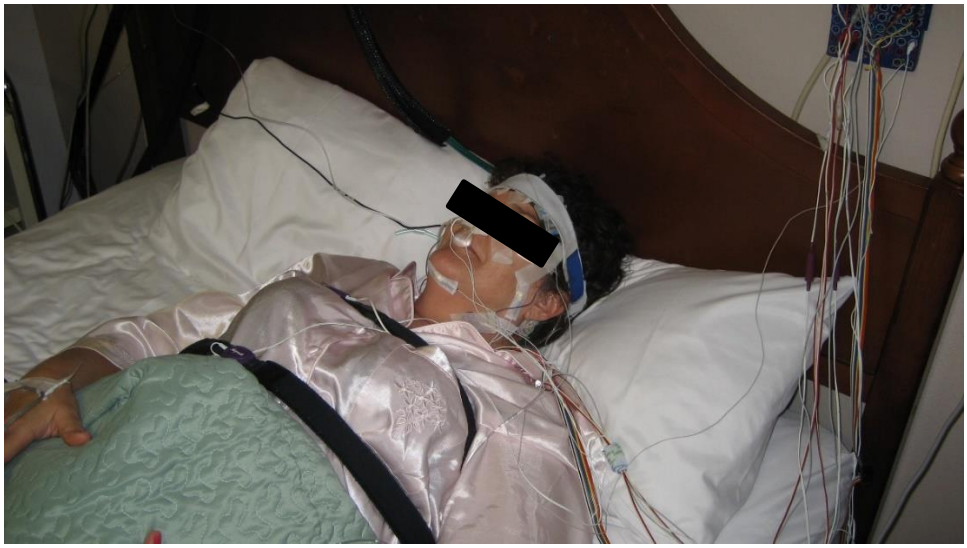

Figure 2-10 Subject with instrumentation attached in the nocturnal Sleep Study

2.3.3. Subject Demographics

There were two study groups of subjects considered. The first group had 26 volunteer subjects, without any known apnea, cardiac or respiratory disorder, who underwent stimulated apnea study with the above mentioned protocols. The second group consisted of 10 patients 4 of which were previously diagnosed with sleep apnea and 6 were suspected to have sleep apnea. These patients went through an 8 hour polysomnography. Table 2-1 and 2-2 tabulates the subject demographics for the simulated sleep apnea study and nocturnal sleep apnea study

Among the subjects who took part in the simulated apnea study data from some subjects in each protocol had to be omitted since their capnogram indicated a breathing pattern during the breath hold. In the sitting position from protocol A 8 subjects and 7 subjects from protocol B had to be omitted. In the supine position 13 subjects from protocol A and 10 subjects from protocol B had to be omitted.

Table 2-1 Subject Demographics Simulated apnea Study

Study Group	Number of Subjects	Age (mean±σ)	BMI (mean±σ) (kg/m^2)
Simulated apnea Study	15 M, 11 F	27 ± 5	22.9 ± 4.1

Table 2-2 Subject Demographics Nocturnal Sleep Study

Study Group	Number of Subjects	Age (mean±σ)	BMI (mean±σ) (kg/m^2)	AHI (mean±σ)
Nocturnal Sleep Study	9 M, 1 F	50 ± 7	31.5 ± 4.7	63 ± 20

2.3.4. Data Acquisition System

The output from the CO_2 monitor was connected with a data acquisition (DAQ) card which was in turn connected to a computer. For this study DAQ 6024 E (National Instruments Austin, TX) was used. This had a 200 kS/s sampling rate, 16 analog inputs with a 12 bit resolution. It has two 12 bit analog output lines, 8 digital I/O lines, and two 24 bit counters. The output from the Analog output ports of the measuring devices is given to the DAQ via a printed circuit board called CB-68 LP. This board contains 64 pins connector blocks. A customized program was designed on LABVIEW (National Instruments, Austin, TX) to display and store all the physiological waveforms that were collected. The collected data was sampled at 1 kS/s.

2.4 Data Analysis

The following section describes the steps taken to analyze the collected data for both exhaled CO_2 and CBF.

2.4.1. Simulated Apnea

Signals from capnograph and TCD were sampled at 1 kS/s sampling rate. This was stored for post processing. A trigger signal was also recorded indicating the breath hold. This signal has two levels 0 V and 5 V, this was recorded using pushbuttons. When the signal goes from 0 V to 5V this indicates start of breath hold and when it goes from 5 V to 0 V it indicates end of breath hold. This signal was used to separate and analyze signals from each breath hold individually. To analyze the signals MATLAB (Mathworks, Massachusetts, USA) was utilized.

2.4.1.1. Exhaled CO_2 Data Processing

The exhaled CO_2 waveform received from the capnogard contains high frequency noise which is added due to instrumentation and environmental noise. To remove this noise a moving average filter was applied. This filter is optimal for time

domain signal. Moving average filter averages the signal over a particular window. This is done for each point. To filter the exhaled CO_2 waveform the window chosen was 20 samples. This means that each point in the filtered signal was obtained by averaging 20 sample points.

2.4.1.1.1. Feature extraction

The main feature extracted from the CO_2 signal is the End tidal CO_2 ($ETCO_2$). The $ETCO_2$ is the point on the capnogram which corresponds to the end of the exhalation in the respiratory cycle. Ideally it lies at the fall of the plateau region of the capnogram (Figure 2-11). It is also the maximum point of one respiratory cycle of the capnogram. To find the $ETCO_2$, the individual respiratory cycle was first needed to be distinguished. To achieve this three levels were added to the capnogram; top, middle and bottom [35].

$$\mathrm{M} = \mathrm{mean}(\mathrm{CO}_{2\mathrm{baseline}})$$

$$\mathrm{T} = \mathrm{M} + \frac{\mathrm{Max}(\mathrm{CO}_{2\mathrm{baseline}}) - \mathrm{Min}(\mathrm{CO}_{2\mathrm{baseline}})}{6}$$

$$\mathrm{B} = \mathrm{M} - \frac{\mathrm{Max}(\mathrm{CO}_{2\mathrm{baseline}}) - \mathrm{Min}(\mathrm{CO}_{2\mathrm{baseline}})}{6}$$

Where;

M= Middle Level

T= Top Level

B= Bottom Level

$\mathrm{Max}(\mathrm{CO}_{2\mathrm{baseline}})$= Maximum of the CO_2 value during baseline

$\mathrm{Min}(\mathrm{CO}_{2\mathrm{baseline}})$= Minimum of the CO_2 value during baseline

When the capnogram cuts the top level if it goes from bottom to top it is classified as the start of the cycle, and when it crosses from the top to bottom it was the end of the cycle. By this method the artifacts in the exhaled CO_2 waveforms were eliminated.

To find the $ETCO_2$, starting from the end of the cycle, going backwards, the slope of the capnogram was calculated. When the slope of the line was greater than -0.0125 (mmHg/sec) i.e. when the plateau region starts, $ETCO_2$ point was recorded. Along with this, as a means of error checking the point also had to be within five percent of the maximum CO_2 value of the cycle. Another metric that was extracted from capnogram is the change in the $ETCO_2$ with respect to the baseline. This was denoted as Delta $ETCO_2$. Figure 2-11 represents the method by which the features were extracted.

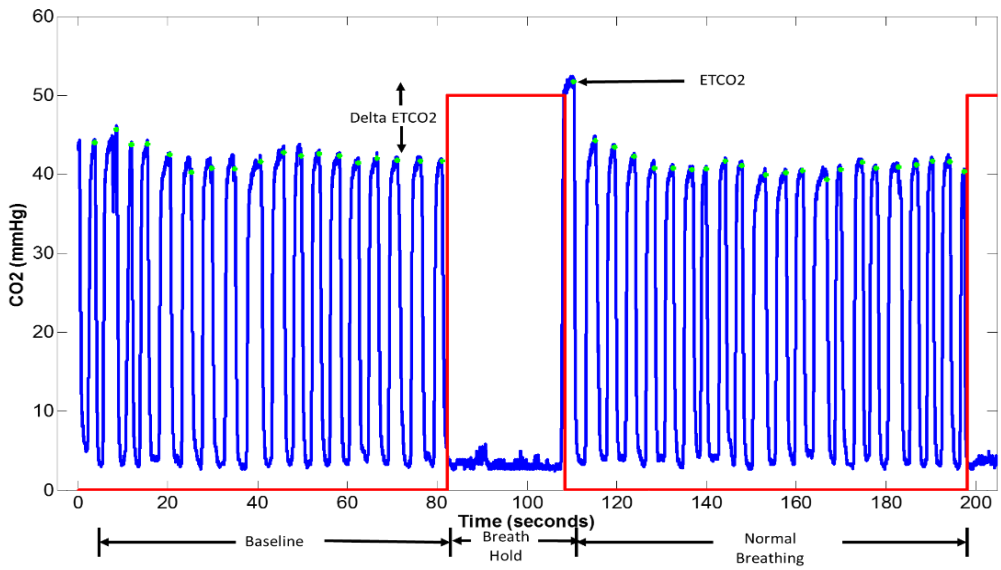

Figure 2-11 CO_2 Features Extracted

2.4.1.2. CBFV Data Processing

The rise in the TCD is observed during the breath hold. This rise continues for a few seconds after the breath hold. So the area of interest for the TCD calculations starts from the start of the breath hold and ends at a few seconds after the breath hold where the systolic value is at its maximum. Before processing the data the TCD signal was first filtered using a zero phase, equiripple low pass filter with pass band frequency as 5Hz and stop band frequency as 15Hz.

2.4.1.2.1. Peak detection

The very first step to find the CBF was to find the systolic and the diastolic flow velocities. In TCD these are represented by the peak and the valley respectively. To achieve this, an algorithm was designed. This algorithm goes through each point of the smoothed TCD waveform. It records the max point when the waveform falls below a certain value; delta, which by trial and error was found to be 0.15. Similarly to find the minimum point the waveform had to rise with the same delta.

There were two failsafe put in place. First the time between two peaks should be greater than 0.5 seconds. Second the time between the systolic and the diastolic point should be greater than 0.3 seconds. These were calculated from the cardiac cycle.

2.4.1.2.2. Feature Extraction

It is established that during breath hold the CBF increases. To find the increase three methods were employed; slope, delta change and percentage rise. To find the trend (slope), the systolic points in the area of interest were considered. A linear regression line spaced with time was fitted to these points. This line represented the trend. Slope of this line indicated the direction of the trend. The change in the CBF was measured using two parameters delta and percentage rise. Multiple methods were used to measure this. The first method considered was to calculate this change with respect to the baseline systolic value denoted as 'Del_1' and 'PR_1'. The second method was to calculate with the first systolic point during the apnea denoted as 'Del_2' and 'PR_2'. The third method calculated the change with respect to the systolic points just before the apnea. These were denoted by 'Del_3' and 'PR_3'. The fourth method of calculated the change with respect to the minimum of the first four systolic points at the start of the apnea. These were denoted by '$oDel_2$' and 'oPR_2'.

The percentage rise of the area under the curve at the maximum point was also considered. To minimize error three curves at the end of the apnea was used to find the percentage rise and the maximum was recorded. The final metric considered was the area under the systolic points. For this metric the systolic points were interpolated using spline interpolation. The area under this curve was found. This metric indicated the trend that the TCD followed as well as the time for which the CBF rose. To group this metric across all subjects, this metric was divided by the area under the systolic points for 35 seconds in the baseline. Figures 2-12 to 2-16 represents the methods by which the features were extracted. For ease of recognition the Table 2-3 shows the metric and its explanation.

Table 2-3 List of CBFV metrics with their description

Metric	Explanation
Slope	Slope of the trend calculated from regressing a linear line on the systolic points
Del_1	Change in the maximum systolic value at the end of the apnea from the mean systolic value of the baseline
PR_1	Percentage rise considering Del_1
Del_2	Change in the maximum systolic value at the end of the apnea from the first systolic value at the beginning of the apnea
PR_2	Percentage rise considering Del_2
Del_3	Change in the maximum systolic value at the end of the apnea from the mean systolic value before the apnea
PR_3	Percentage rise considering Del_3

Table 2-3: *Continued*

$oDel_2$	Change in the maximum systolic value at the end of the apnea from minimum of the first four systolic value at the beginning of the apnea
oPR_2	Percentage rise considering $oDel_2$
PRArea	Percent rise in area under the curve at the maximum point with respect to baseline
Norm Area	Normalized area under the interpolated systolic points with respect to the points for 35 seconds in the baseline.

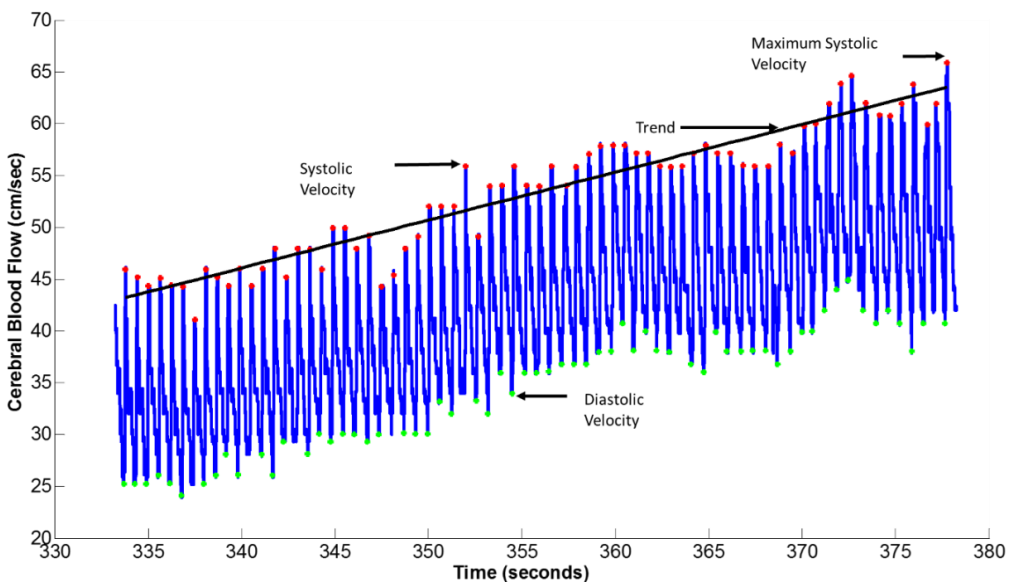

Figure 2-12 CBFV Features Extracted

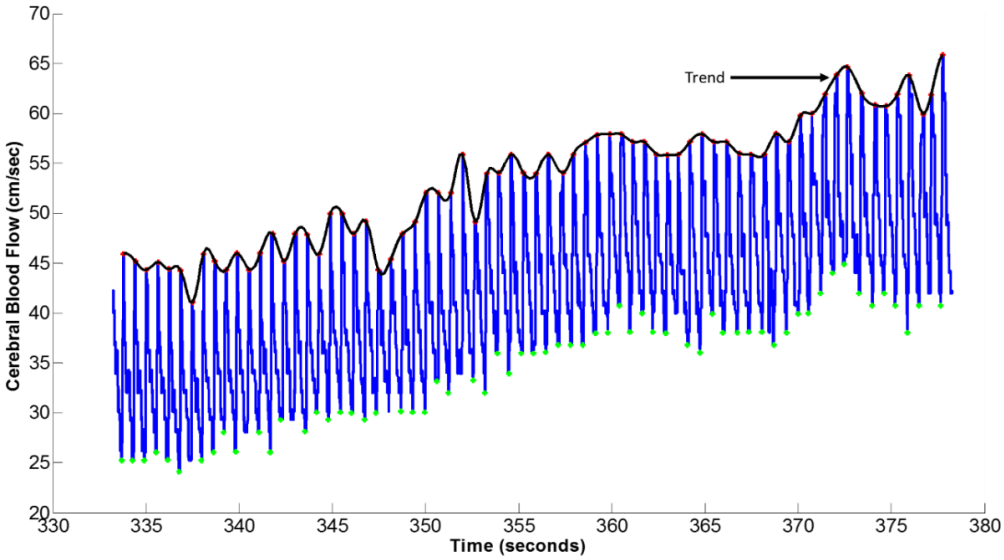

Figure 2-13 Feature Extraction: Area under Systolic points

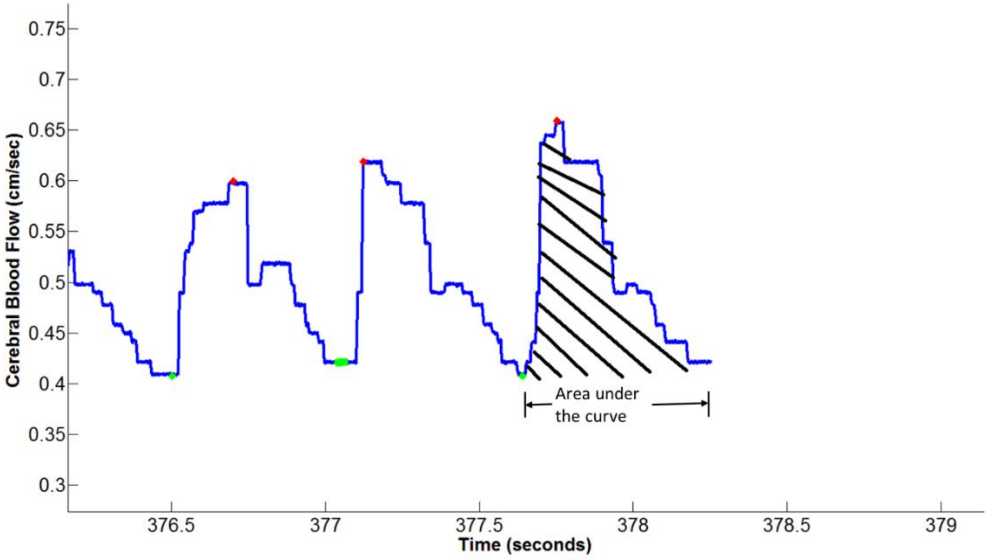

Figure 2-14 Feature Extraction: Area Under the Curve

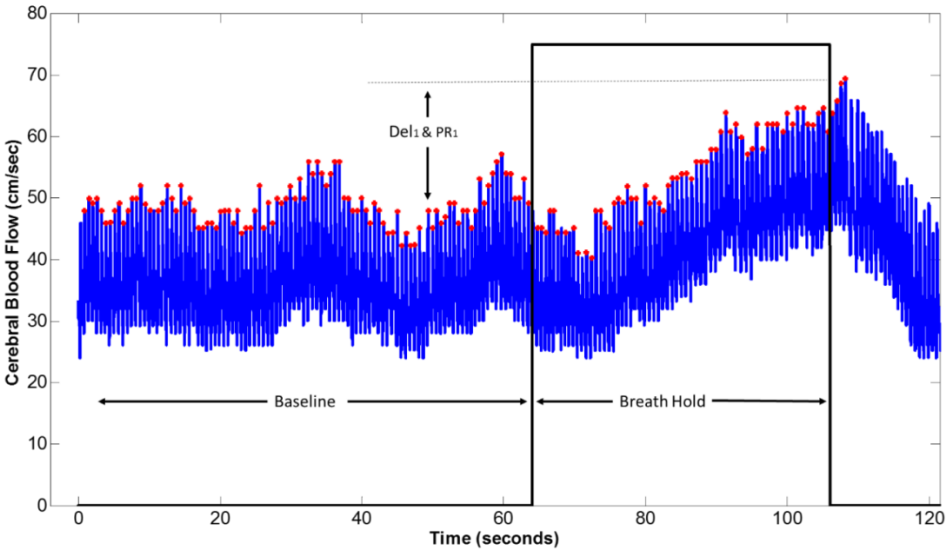

Figure 2-15 Feature Extraction Del_1 and Pr_1

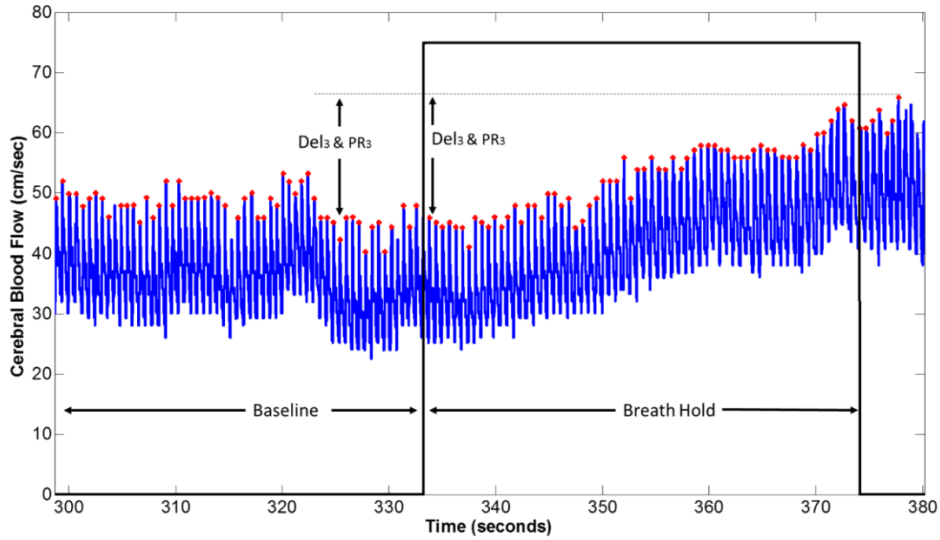

Figure 2-16 Feature Extraction Del_2, PR_2, Del_3 and PR_3

2.4.2. Nocturnal Sleep Study

The nocturnal sleep study lasts for 8 hours. During this time there may be multiple apneas spaced over time. To prepare this data a clipping program was designed. This program called upon a GUI with the capability of displaying four signals graphically.

One of the signals displayed was the apnea scoring signal obtained by the sleep lab technician. This signal was used to identify the apnea events. Once identified, the program allowed the user to select the start and the end of the region of interest by clicking on any graph with the data pointer tool and clicking a button that looks like the data pointer button. This area or clip could be saved by using the 'save clip' button. This clip was saved as a file with '.mat' extension.

One of the main distinctions between nocturnal sleep study data and simulated apnea study data is that in the simulated apnea study the 60 seconds before the first breath hold was considered as the baseline. In the nocturnal sleep study the baseline was taken as a part of the data before the first apnea event. The method for processing exhaled CO_2 and CBFV data remain the same. Figure 2-17 and 2-18 illustrates the capnogram and the CBFV signal during baseline.

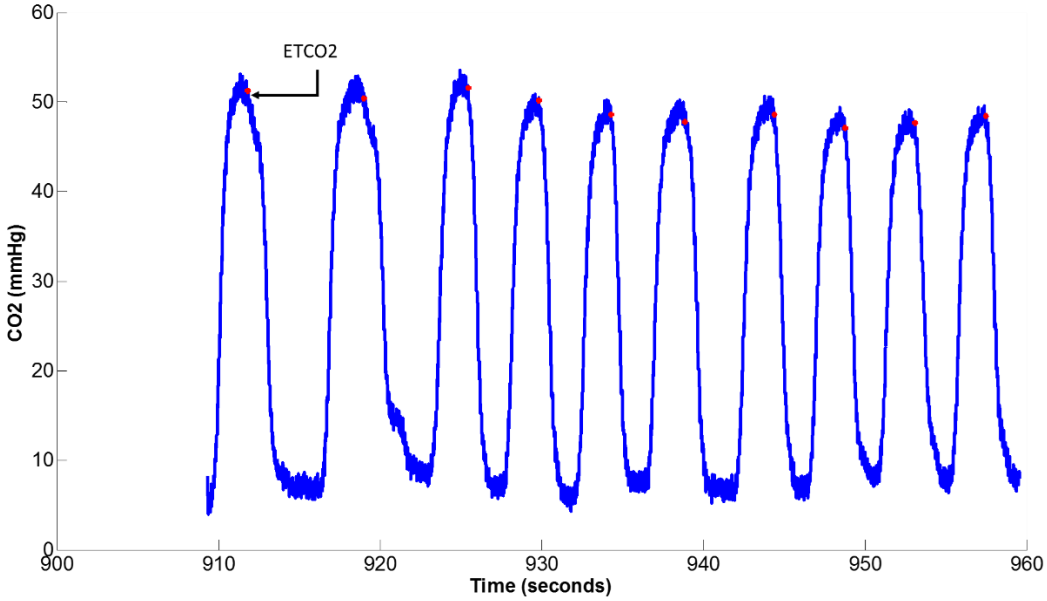

Figure 2-17 Capnogram signal for Baseline in nocturnal sleep apnea

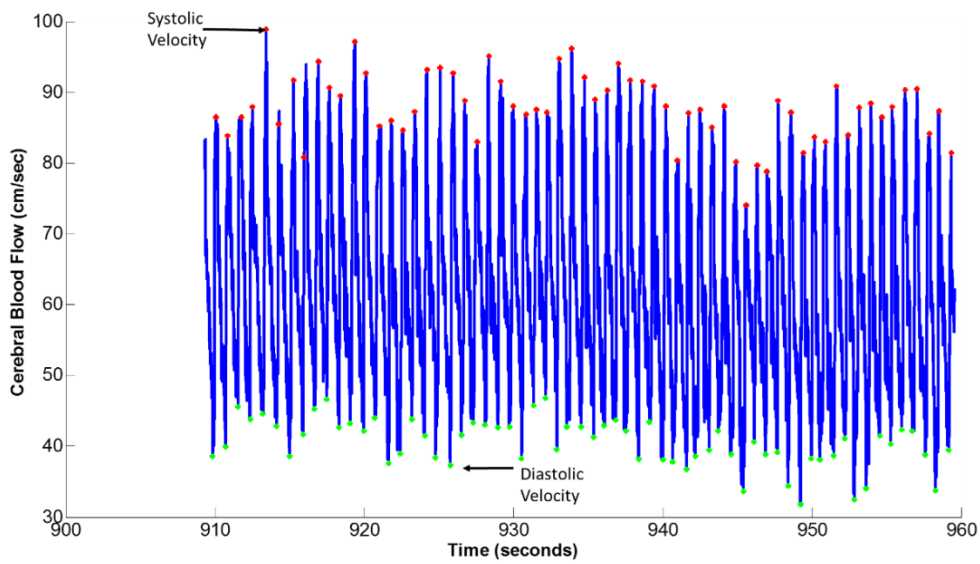

Figure 2-18 CBFV signal for Baseline in nocturnal sleep apnea

2.4.3. Statistical Analysis

The objective of the study was to find a relationship between the exhaled CO_2 and the CBF during sleep apnea. To find this a statistical method called as Correlation was used. There are three methods to perform this analysis; Kendall's tau, Spearman's rho and Pearson's product-moment.

2.4.3.1. Kendall's Rank Correlation

Kendall's Tau is a nonparametric rank based correlation (Appendix H). It ranks the values in both variables. In the second variable the concordant pairs and the discordant pairs are found. A value is said to be concordant if the rank in both the variable is the same when compared with another value. The discordant pair is the exact opposite to the concordant pair. For example consider x and y to be the two variable, then for the values in position 1 when compared with position 2 will be concordant if $x_1>x_2$ and $y_1>y_2$. It will be considered discordant if $x_1<x_2$ and $y_1>y_2$. This is found for each value in the second variable. After this the tau (τ) is found by the following formulae [36]:

$$\tau = \frac{\Sigma C - \Sigma \mathrm{D}}{\Sigma \mathrm{C} + \Sigma \mathrm{D}}$$

Where

C= Concordant Pairs

D=Discordant Pairs

Tau ranges from -1 to 1 where -1 indicates strong negative correlation and 1 indicates strong positive correlation. If tau is 0 it indicates no correlation.

2.4.3.2. Spearman's Rank-Order Correlation

Spearman's rho is also a nonparametric rank based correlation. In this test the variables are ranked. This test utilizes the difference in the ranks between the two variables at the same position. This is governed by the following formulae [36]:

$$\rho = 1 - \frac{6\Sigma {\mathrm{d_i}}^2}{\mathrm{n}(\mathrm{n}^2 - 1)}$$

Where

d_i= difference between the ranks

n= number of variables

Like the tau, rho (ρ) also ranges from -1 to 1 where -1 indicates a strong negative correlation and 1 a strong positive correlation. If rho is 0 it indicates no correlation.

2.4.3.3. Pearson's Product-Moment

Pearson's product-moment measures linear correlation between two variables. This correlation is calculated by the following formulae:

$$\mathrm{r} = \frac{\Sigma(\mathrm{x_i} - \bar{\mathrm{x}})(\mathrm{y_i} - \bar{\mathrm{y}})}{\sqrt{(\mathrm{x_i} - \bar{\mathrm{x}})^2}\sqrt{(\mathrm{y_i} - \bar{\mathrm{y}})^2}}$$

Where

x_i= i^{th} value of x

y_i= i^{th} value of y

$\bar{x}$ = mean of x

$\bar{y}$= mean of y

r varies from -1 to 1. -1 indicates strong negative correlation and 1 indicates strong positive correlation. If r is 0 it indicates no correlation.

Despite its popular uses, the Pearson's product moment correlation should be applied only if certain assumptions are satisfied. One major assumption is that both variables considered for calculation of r must be normally distributed [36]. A Kolmogorov-Smirnov test was performed to check the distribution of the metrics proposed as part of this study. This is shown in Appendix H. The results indicated that none of the metrics followed a Gaussian distribution, hence this method was not considered for the analysis. However, due to prevalence of its use, values of r for the metrics were calculated and are reported in the appendix A.

2.4.3.4. Analysis of Variance (ANOVA) and Multiple Comparison

Analysis was done to find the statistical difference of the metrics between the apnea frequencies and positions as well as between the nocturnal sleep study and simulated apnea study data. To achieve this a one way ANOVA [37] was performed. Along with this a Tukey Kramer analysis which a multiple comparison analysis was done to compare all possible pairs of means. This is done to compensate type I error. The equation for Tukey Kramer is given below [38].

$$\mathrm{Q} = \overline{T_{max}} - \overline{T_{min}}/\mathrm{S}\sqrt{\mathrm{n}}$$

Where

$\overline{T_{max}}$= maximum

$\overline{T_{min}}$ = Minimum mean

n= Number of observations

This is then compared with a studentized range distribution to find significance. The output of this is given as a confidence limit which specifies the estimated intervals for the mean. For a statistical test to be significant the confidence interval must not overlap 0.

The following chapter presents the results from the correlation analysis conducted between the exhaled CO_2 and CBFV metrics. Along with this it also presents the results of the ANOVA test conducted on the exhaled CO_2 and the CBFV metrics for both simulated sleep apnea study and nocturnal sleep apnea study.

Chapter 3

Results

This chapter presents the correlation coefficients from all the CBFV metrics considered. Moreover it also presents the comparison among the metrics that have the highest correlation coefficient under different apnea frequencies. A comparison was also done among the metrics that have the highest correlation coefficient between the simulated apnea study and the nocturnal sleep apnea study.

3.1 Simulated Sleep Apnea Study Results

The CBFV metrics that were extracted from the recorded TCD waveform were examined for their correlation with $ETCO_2$ and Delta $ETCO_2$. For this correlation both Kendall's Tau and Spearman's Rho were considered. In the simulated apnea study, the correlation for each of the protocol and posture was taken into account. The data from the simulated apnea study was analyzed by dividing the subjects into two parts. These were denoted as 'Group 1' and 'Group 2'. The difference in the methodologies between the two groups was that the subjects in Group 2 were asked not to inhale before the start of the breath hold. A one way ANOVA was performed on the data from the simulated apnea study considering all protocols as an individual effect. A two way ANOVA was also performed on this data considering the apnea frequencies and postures as individual effects. The results from this study was similar to the ones obtained from one way ANOVA. The results are presented in Appendix I.

Figure 3-1 and 3-2 shows the change in the exhaled CO_2 and the TCD signal due to breath hold in the simulated sleep apnea study with the rising edge of the red line indicating the start of the breath hold and the falling edge as the end of the breath hold. Figure 3-3 shows the filtered TCD signal the characteristics of this filter is mentioned in subsection 2.4.1.2.

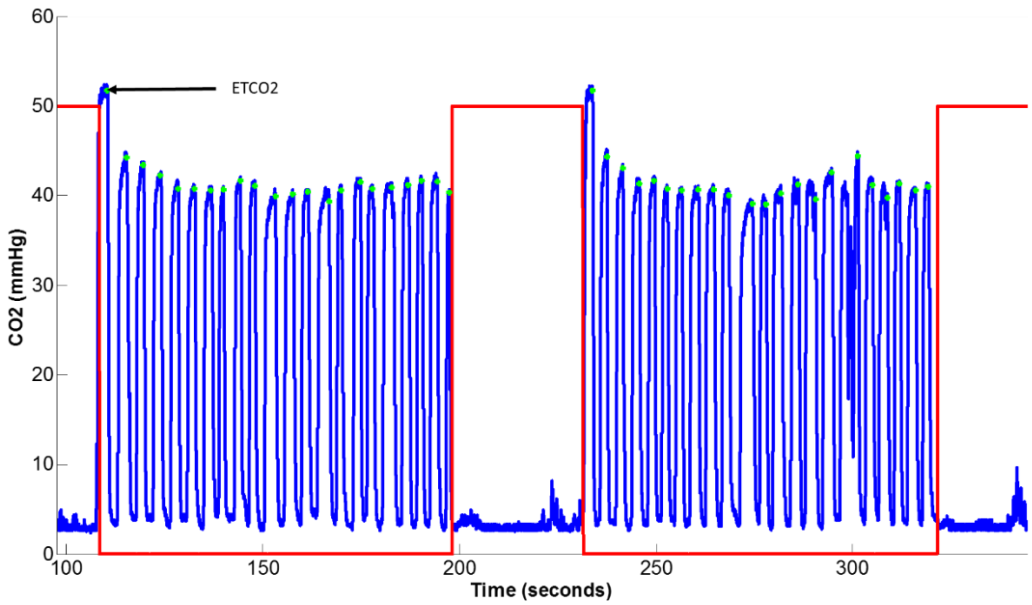

Figure 3-1 Capnogram for Simulated Apnea Study

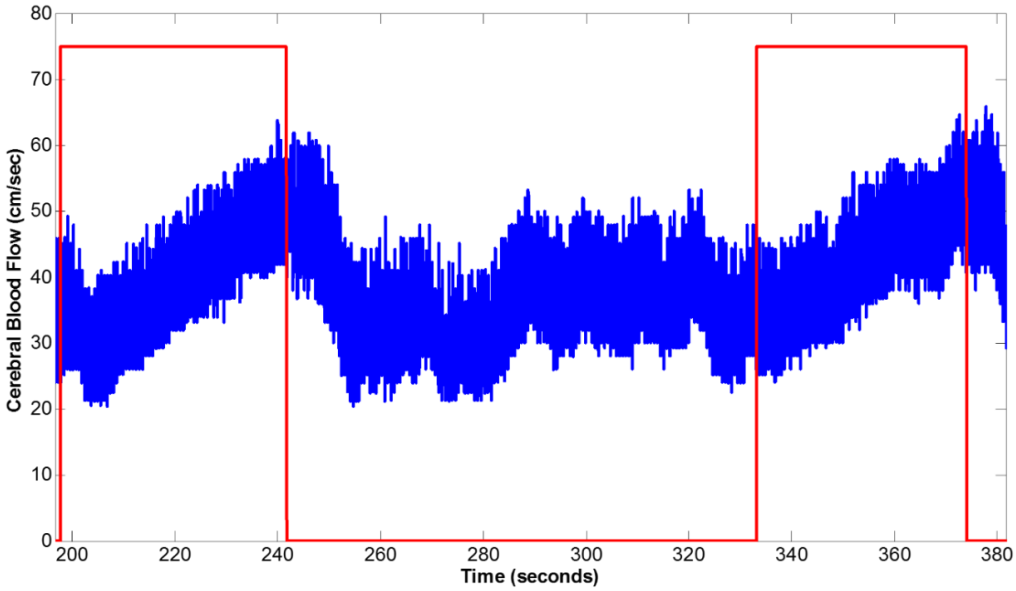

Figure 3-2 TCD for Simulated Apnea Study

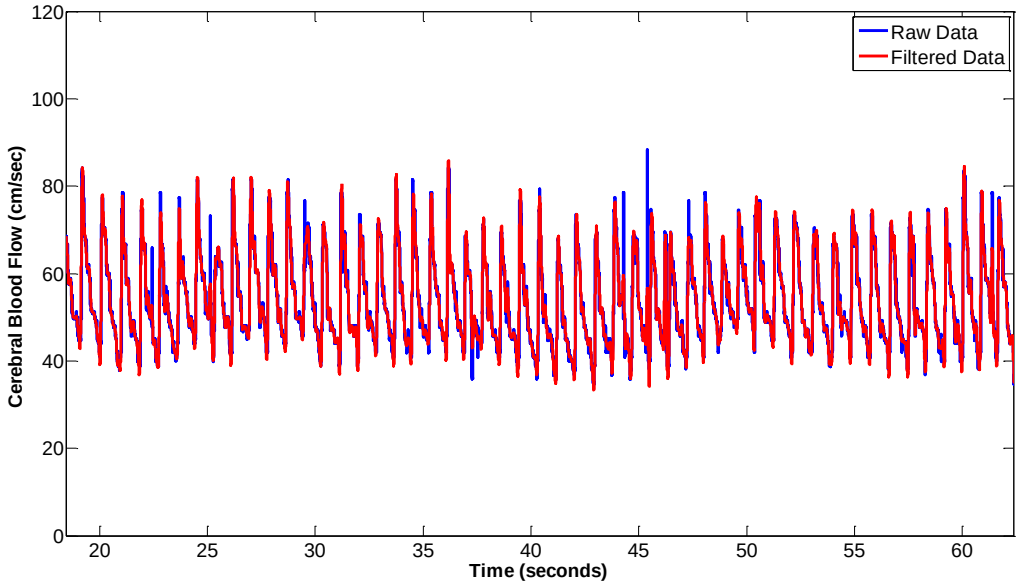

Figure 3-3 Filtered TCD for Simulated Apnea Study

3.1.1. Comparison Metrics Means between Apnea Frequencies and Positions

Analysis was done with exhaled CO_2 as well as CBFV metrics between apnea frequencies and positions. This was done to find out if a metric was statistically different in different apnea frequencies. To achieve this an ANOVA test was performed. After this a Tukey-Kramer test was performed which gives a statistical comparison between all possible groups. Some groupings were not used for further analysis since they differed in both apnea frequencies and positions. This analysis was done by separating the data into the separate subject groups as mentioned before. Table 3-1 and Table 3-2 present the findings from the ANOVA for exhaled CO_2 and the CBFV metrics respectively. The definition of the metrics shown in table 3-1 and 3-2 are discussed in chapter 2 section 2.4.1.1.1. and 2.4.1.2.2. respectively. The p value marked with an asterisk indicates significance of < 0.05.The results from the ANOVA test are presented in appendix D

Table 3-1 Results from ANOVA for the means of the metrics of exhaled CO_2 across all apnea frequencies and positions

ANOVA CO_2		
Metric	p	
	Group 1	Group2
$ETCO_2$	7.95×10^{-1}	5.40×10^{-2}
Delta $ETCO_2$	7.01×10^{-1}	3.77×10^{-2}*

Table 3-2 Results from ANOVA for the means of the metrics of CBFV across all apnea frequencies and positions

ANOVA CBFV		
Metric	p	
	Group 1	Group2
Slope	8.39×10^{-1}	1.83×10^{-4}*
Del_1	5.43×10^{-1}	2.41×10^{-3}*
PR_1	1.75×10^{-1}	3.98×10^{-1}
Del_2	6.32×10^{-1}	1.33×10^{-2}*
Pr_2	1.36×10^{-1}	5.96×10^{-1}
Del_3	3.27×10^{-1}	8.04×10^{-5}*
Pr_3	7.76×10^{-2}	1.32×10^{-2}*
$oDel_2$	8.38×10^{-1}	5.97×10^{-4}*
oPR_2	3.67×10^{-1}	9.29×10^{-2}
PRArea	5.30×10^{-1}	5.12×10^{-2}
Norm Area	8.81×10^{-4}*	1.22×10^{-1}

3.1.1.1. Comparison of Metrics Means Changes Due to Frequency of Apnea

This section focuses on the difference between the two apnea frequencies. Tukey Kramer was focused for comparison between them. This test revealed that between the two apnea frequencies exhaled CO_2 metrics did not differ in the considered metric pairs.

3.1.1.1.1. Comparison of Exhaled CO_2 Metrics Means

Table 3-3 shows the Tukey Kramer analysis for the means of the metrics derived from exhaled CO_2 between the two apnea frequencies. Since this section focuses on the difference between the two apnea frequencies the table only shows the Tukey Kramer results for comparison between them. The p value marked with an asterisk indicates significance of < 0.05. SiA, SiB, SuA and SuB are short hand representation explained in subsection 2.3.1.

3.1.1.1.2. Comparison of Cerebral Blood Flow Velocity Metrics

Table 3-3 shows the Tukey Kramer analysis for the means of the metrics derived from CBFV between the two apnea frequencies. This table shows the Tukey Kramer results for comparison between the two apnea frequencies. The p value marked with an asterisk indicates significance of < 0.05. SiA, SiB, SuA and SuB are short hand representation explained in subsection 2.3.1.

Table 3-3 Results from Tukey Kramer for comparing the means of metrics derived from CBFV metrics for the two apnea frequencies

CBFV

Table 3-3: *Continued*

Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	p
Group 2	Del_3	SuA V/S SuB	0.55	13.88	2.78×10^{-2}*

3.1.1.2. Comparison of Metrics Means Changes Due to Posture

The section below focuses on the Tukey-Kramer analysis on the means of the metrics of exhaled CO_2 and CBFV which has a significant p value in the ANOVA analysis grouped according to the apnea frequencies.

3.1.1.2.1. Comparison of Exhaled CO_2 Metrics Means

Table 3-4 shows the Tukey Kramer analysis for the means of the metrics derived from exhaled CO_2 between the positions. Since this section focuses on the difference between the two positions the table only shows the Tukey Kramer results for comparison between them. The p value marked with an asterisk indicates significance of < 0.05.

Table 3-4 Results from Tukey Kramer for comparing the means of the metric derived from exhaled CO_2 for the two positions

CO_2					
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	p

Table 3-4: *Continued*

Group 2	Delta $ETCO_2$	SiA V/S SuA	0.17	5.82	3.29×10^{-2}*

3.1.1.2.2. Comparison of Cerebral Blood Flow Velocity Metrics

Table 3-5 shows the Tukey Kramer analysis for the means of the metrics derived from CBFV between the positions. This table shows the Tukey Kramer results for comparison between the two positions. The p value marked with an asterisk indicates significance of < 0.05.

Table 3-5 Results from Tukey Kramer for comparing the means of the metrics derived from CBFV metrics for the two positions

CBFV					
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	p
Group 1	Norm Area	SiA V/S SuA	-0.63	-0.034	2.14×10^{-2}*
		SiB V/S SuB	-0.68	-0.049	1.60×10^{-2}*
Group 2	Slope	SiA V/S SuA	-0.69	-0.15	4.23×10^{-4}*
	Del_1	SiA V/S SuA	-18.57	-2.91	2.38×10^{-3}*
	Del_3	SiA V/S SuA	-16.39	-2.08	5.07×10^{-3}*
		SiB V/S SuB	-11.91	-0.22	3.85×10^{-2}*
	$oDel_2$	SiA V/S SuA	-22.89	-0.81	2.97×10^{-2}*
		SiB V/S SuB	-11.7999	-0.14709	4.20×10^{-2}*

Figures 3-4 to 3-7 represents the mean comparisons for the CBFV metrics.

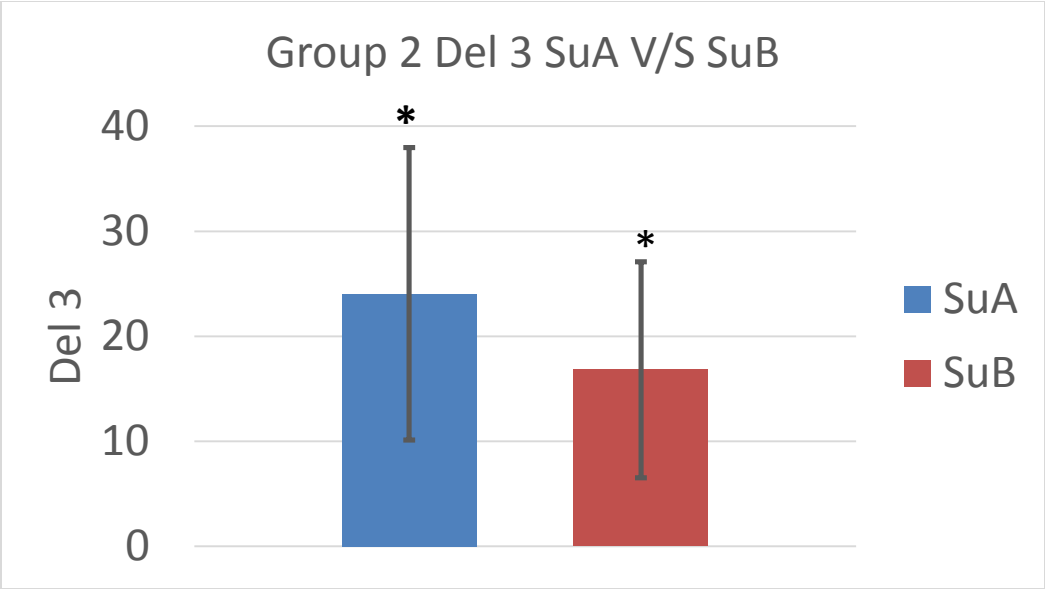

Figure 3-4 Mean Comparison between SuA and SuB for Del_3

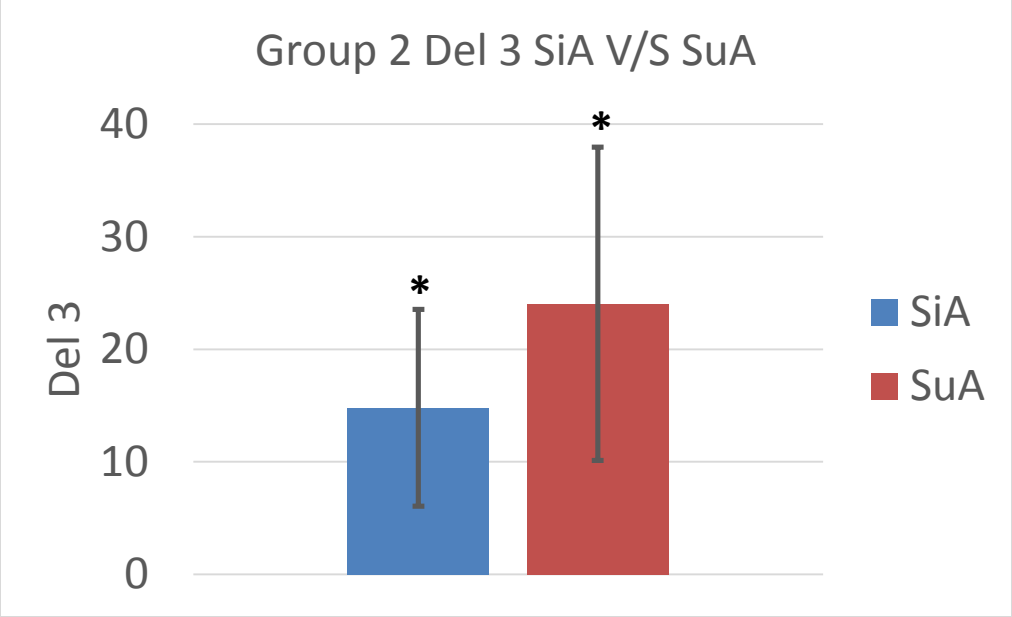

Figure 3-5 Mean Comparison between SiA and SuA for Del_3

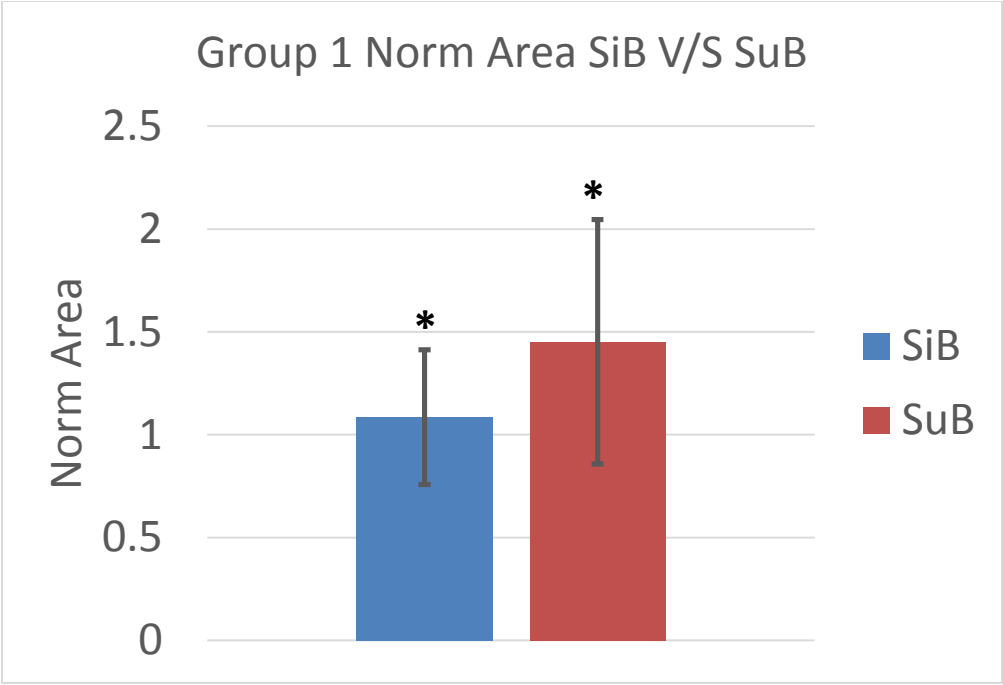

Figure 3-6 Mean Comparison between SiB and SuB for Norm Area

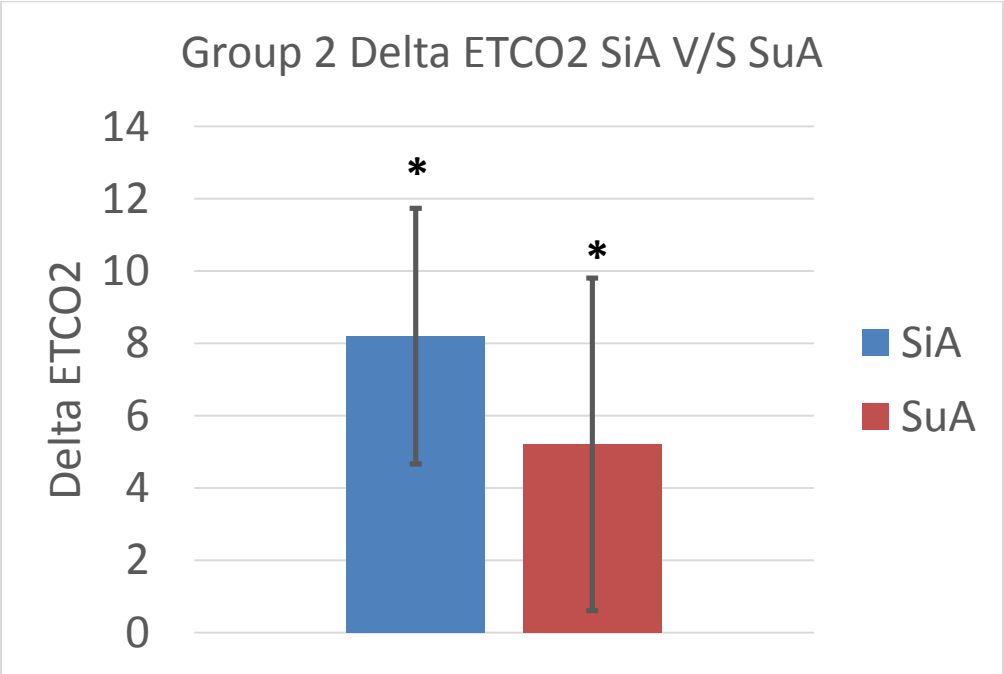

Figure 3-7 Mean Comparison between SiA and SuA for Delta $ETCO_2$

3.1.2. Correlation Study Results for Protocol A

This section focuses on the correlation between the exhaled CO_2 and the CBFV metrics under protocol A.

3.1.2.1. Correlation between CBFV metrics and Delta $ETCO_2$ for Protocol A

3.1.2.1.1. Correlation between CBFV metrics and Delta $ETCO_2$ for Protocol A for Group 1

Examining the correlation of Delta $ETCO_2$ with all CBFV metrics used in protocol A in the sitting position Kendall's method indicated that none of the CBFV metrics under the sitting position gave a significant correlation. Similarly, using the Spearman's method none of the CBFV metrics gave a significant correlation.

Studying correlation of Delta $ETCO_2$ with all CBFV metrics in the supine position, Kendall's method indicated that all metrics except PR_2, oPR_2 and PRArea are non-significant. The highest correlation was with PRArea -0.32 ($p= 1.78x10^{-3}$*) which was less than 50%. Spearman's Rho also indicated that all metrics except PR_2, oPR_2 and PRArea are non-significant. Among the significant metrics correlation for PRArea -0.517 ($p= 3.4x10^{-4}$*) was greater than 50% and the highest.

3.1.2.1.2. Correlation between CBFV metrics and Delta $ETCO_2$ for Protocol A for Group 2

Examining the correlation of Delta $ETCO_2$ with all CBFV metrics in protocol A in the sitting position using Kendall's method indicated that all metrics except PRArea were not significant. The correlation coefficient with PRArea was -0.27 ($p=3.4x10^{-2}$*) which was less than 50%. Spearman's method indicated that all metrics except PRArea were not significant. The correlation coefficient with PRArea was -0.363 ($p=4.92x10^{-2}$*) which was less than 50%.

Studying correlation of Delta $ETCO_2$ with all CBFV metrics in the supine position, Kendall's method indicated that Del_1, PR_1, Del_3, PR_3, $oDel_2$ and Norm Area had a significant correlation with Delta $ETCO_2$. The highest correlation was with Del_1 0.41 (p= $1.11x10^{-2}$*) which was less than 50%. Spearman's Rho also indicated that Del_1, PR_1, Del_3, PR_3, $oDel_2$ and Norm Area had a significant correlation with Delta $ETCO_2$. Among the significant metrics correlation for Norm Area 0.66 (p= $2x10^{-3}$*) was greater than 50% and the highest.

3.1.2.2. Correlation between CBFV Metrics and $ETCO_2$ for Protocol A

3.1.2.2.1. Correlation between CBFV metrics and $ETCO_2$ for Protocol A for Group 1

The correlation of $ETCO_2$ with all CBFV metrics in protocol A in the sitting position using Kendall's method indicated that under the sitting position none of the CBFV metrics gave a significant correlation. Spearman's Rho also indicated that none of the CBFV metrics gave a significant correlation.

Determining the correlation of $ETCO_2$ with all CBFV metrics in the supine position, Kendall's method indicated that all metrics except PR_2 and oPR_2 are not significant. The correlation with both PR_2 and oPR_2 was -0.21(p=$4.04x10^{-2}$*) which was less than 50%. Spearman's Rho indicated that all metrics except oPR_2 are not significant. The correlation with oPR_2 was -0.3(p=$4.05x10^{-2}$*) which was less than 50%.

3.1.2.2.2. Correlation between CBFV metrics and $ETCO_2$ for Protocol A for Group 2

The correlation of $ETCO_2$ with all CBFV metrics in protocol A in the sitting position using Kendall's method indicated that all metrics except Del_3 and PRArea are not significant. Among them the highest correlation was found with PRArea -0.31(p=$1.43x10^{-2}$*) which was less than 50%. Spearman's Rho also indicated that all metrics except Del_3

and PRArea are not significant. Among them the highest correlation was found with PRArea -0.43($p=1.77x10^{-2}$*) which was less than 50%.

Determining the correlation of $ETCO_2$ with all CBFV metrics in the supine position, Kendall's method indicated that none of the CBFV metrics gave a significant correlation. Spearman's Rho indicated that all metrics except Norm Area are not significant. The correlation with Norm Area was 0.56($p=1.01x10^{-2}$*) which was greater than 50%.

Table 3-6 lists the metric pairs with correlation coefficient greater than 50% in protocol A. The full results for the correlation are presented in the appendix B

Table 3-6 List of metric pairs in Protocol A with correlation coefficient greater than 50%

		Protocol A				
Group	CO_2 Metric	CBFV Metric	Position	Method	p	Correlation Coefficient
Group 1	Del $ETCO_2$	PRArea	SuA	Spearman	$3.40 x10^{-4}$*	-0.517
Group 2	Del $ETCO_2$	Del_1	SuA	Spearman	$1.51 x10^{-2}$*	0.54
		PR_1	SuA	Spearman	$1.26 x10^{-2}$*	0.55
		$oDel_2$	SuA	Spearman	$2.01 x10^{-2}$*	0.52
		Norm Area	SuA	Spearman	$2.00 x10^{-3}$*	0.66
	$ETCO_2$	Norm Area	SuA	Spearman	$1.01 x10^{-2}$*	0.56

3.1.3. Correlation Study Results for Protocol B

This section focuses on the correlation between the exhaled CO_2 and the CBFV metrics under protocol B

3.1.3.1. Correlation between CBFV Metrics and Delta $ETCO_2$ for Protocol B

3.1.3.1.1. Correlation between CBFV metrics and Delta $ETCO_2$ for Protocol B for Group 1

Examining the correlation of Delta $ETCO_2$ with all CBFV metrics in protocol B in the sitting position using Kendall's method indicated that all metrics except PR_2 and oPR_2 are not significant. The correlation with oPR_2 was the highest -0.187($p=2.85x10^{-2}$*) which was less than 50%. Spearman's Rho also indicated that all metrics except PR_2 and oPR_2 are not significant. Among them the highest correlation was found with PR_2 -0.28($p=2.4x10^{-2}$*) which was less than 50%.

Studying the correlation of Delta $ETCO_2$ with all CBFV metrics in the supine position Kendall's tau indicated that none of the metrics had a significant correlation. Spearman's Rho indicates that all metrics except PR_2 are not significant. The correlation with PR_2 was -0.33($p=4.93x10^{-2}$*) which was less than 50%.

3.1.3.1.2. Correlation between CBFV metrics and Delta $ETCO_2$ for Protocol B for Group 2

Examining the correlation of Delta $ETCO_2$ with all CBFV metrics in protocol B in the sitting position using Kendall's method indicated that none of the CBFV metrics had a significant correlation. Spearman's Rho also indicated that none of the CBFV metrics had a significant correlation.

Studying the correlation of Delta $ETCO_2$ with all CBFV metrics in the supine position Kendall's tau indicated that all metrics except Norm Area are not significant. The correlation coefficient for Norm Area was 0.48($p=1.25x10^{-6}$*) which was slightly less than 50%. Spearman's Rho also indicates that all metrics except Norm Area are not significant. The correlation with Norm Area was 0.67($p=7.96x10^{-7}$*) which was greater than 50%.

3.1.3.2. Correlation between CBFV Metrics and $ETCO_2$ for Protocol B

3.1.3.2.1. Correlation between CBFV metrics and $ETCO_2$ for Protocol B for Group 1

The correlation of $ETCO_2$ with all CBFV metrics in protocol B in the sitting position with Kendall's method indicated that none of the CBFV metrics had a significant correlation. Spearman's Rho also indicated that none of the CBFV metrics had a significant correlation.

The correlation of $ETCO_2$ with all CBFV metrics in the supine position with Kendall's method indicates that PR_1, PR_2, PR_3, oPR_2 and PRArea had a significant correlation. Among the significant metrics none of them had a correlation greater than 50%.The highest correlation was with PR_1 -0.39 (p= $7.57x10^{-4}$*). Spearman's Rho indicates that PR_1, PR_2, PR_3, oPR_2 and PRArea had a significant correlation. Among the significant metrics PR_1, PR_2, PR_3 and oPR_2 had a correlation greater than 50%. The highest correlation is with PR_1 -0.6 (p= $1.63x10^{-4}$*).

3.1.3.2.2. Correlation between CBFV metrics and $ETCO_2$ for Protocol B for Group 2

The correlation of $ETCO_2$ with all CBFV metrics in protocol in the sitting position B with Kendall's method indicated that all the metrics except Norm Area had a significant correlation. Correlation coefficient with Norm Area was 0.26 (p= $4.12x10^{-2}$*) which was less than 50%. Spearman's Rho also indicated that all the metrics except Norm Area had a significant correlation. Correlation coefficient with Norm Area was 0.36 (p= $4.72x10^{-2}$*) which was less than 50%.

The correlation of $ETCO_2$ with all CBFV metrics in the supine position Kendall's tau indicates that all the metrics except Norm Area had a significant correlation. Correlation coefficient with Norm Area was 0.33 (p= $1.25x10^{-3}$*) which was less than

50%. Spearman's Rho also indicated that all the metrics except Norm Area had a significant correlation. Correlation coefficient with Norm Area was 0.49 (p= 7.39×10^{-4}*) which was less than 50%.

Table 3-7 lists the metric pairs with correlation coefficient greater than 50% in protocol B. The result for the correlation are presented in the appendix B

Table 3-7 List of metric pairs in Protocol B with correlation greater than 50%

		Protocol B				
Group	CO_2 Metric	CBFV Metric	Position	Method	p	Correlation Coefficient
Group 1	$ETCO_2$	PR_1	SuB	Spearman	1.63×10^{-4}	-0.6
		PR_2	SuB	Spearman	1.58×10^{-3}	-0.520
		PR_3	SuB	Spearman	8.98×10^{-4}	-0.543
		oPR_2	SuB	Spearman	6.98×10^{-4}	-0.553
Group 2	Del $ETCO_2$	Norm Area	SuB	Spearman	7.96×10^{-7}	0.67

Figures 3-8 to 3-10 represent a strong correlation between CO_2 and CBFV metrics and Figure 3-11 represent a weak correlation between CO_2 and CBFV metrics.

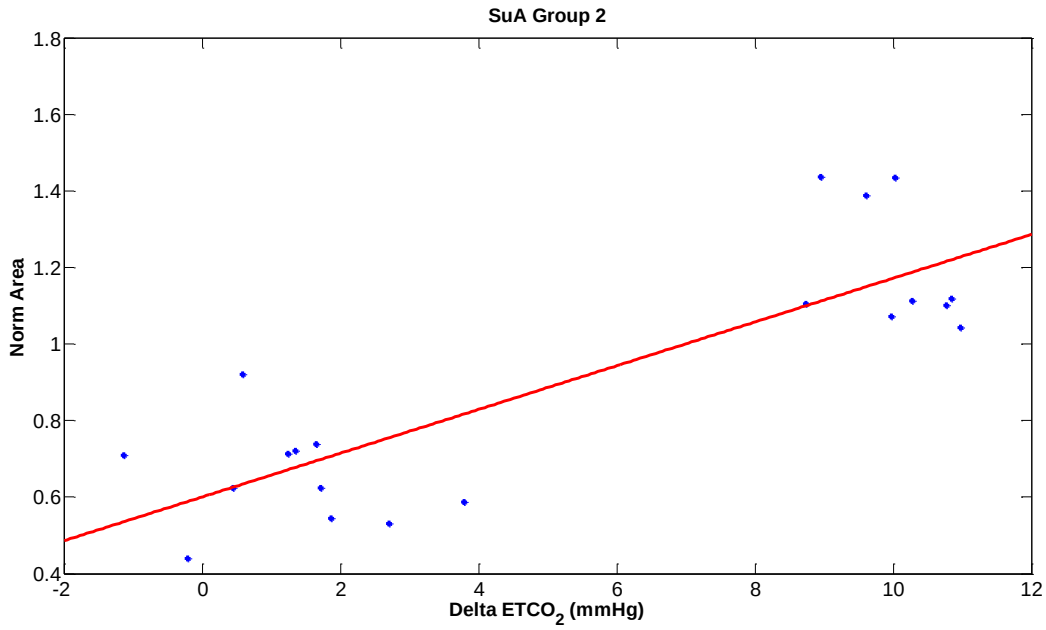

Figure 3-8 Correlation between Delta $ETCO_2$ and Norm Area for Group 2

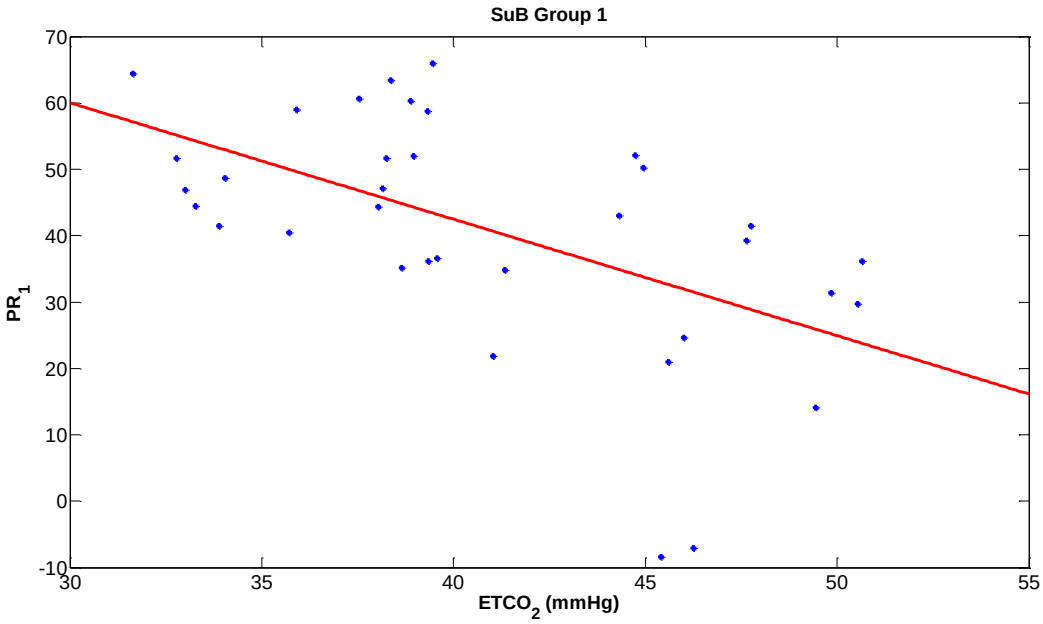

Figure 3-9 Correlation between $ETCO_2$ and PR_1 for Group 1

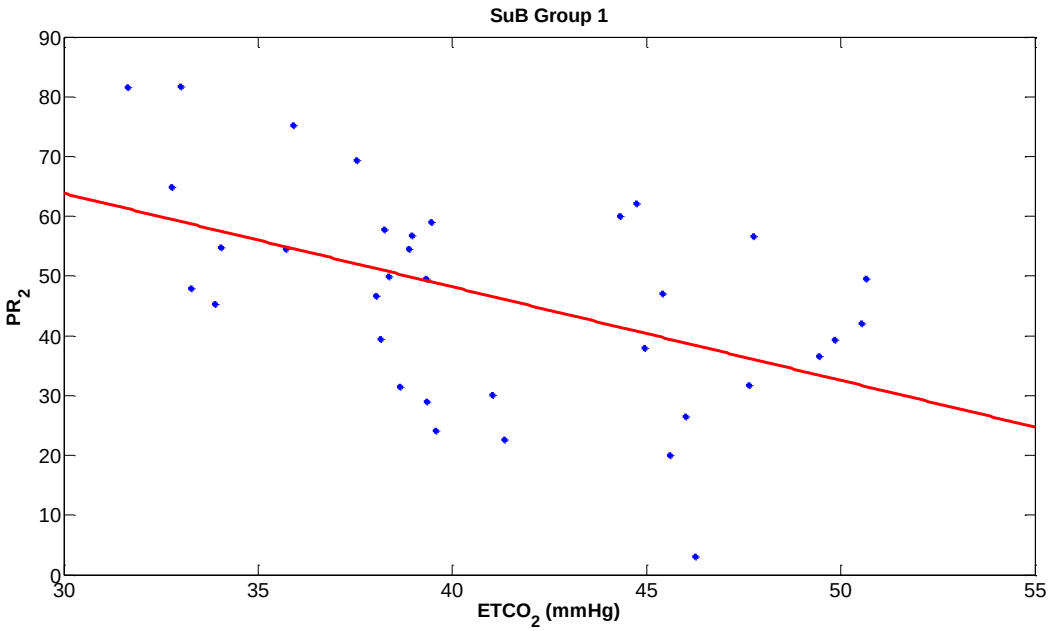

Figure 3-10 Correlation between $ETCO_2$ and PR_2 for Group 1

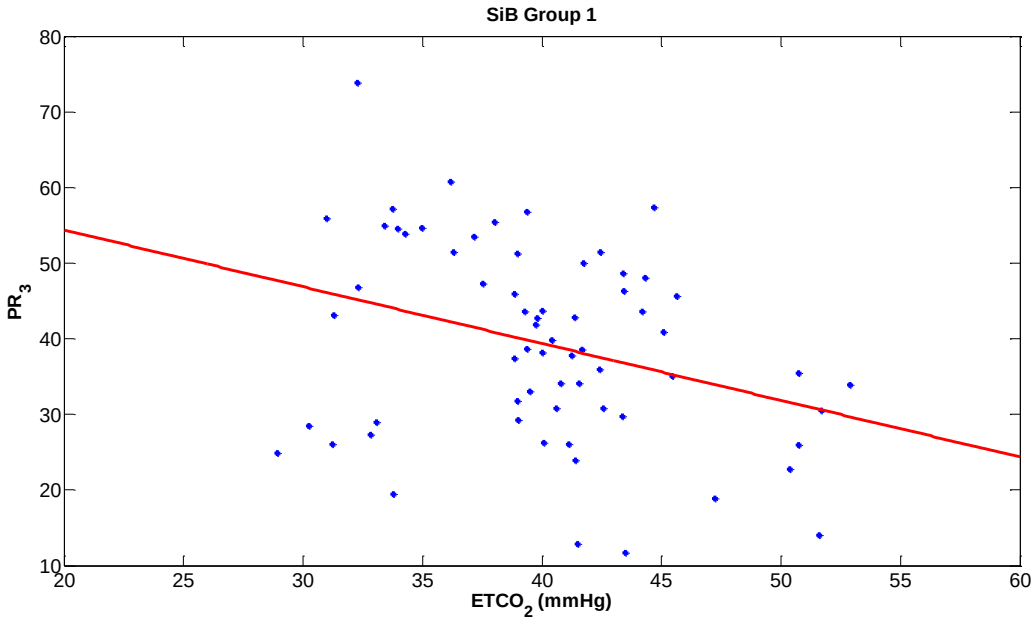

Figure 3-11 Correlation between $ETCO_2$ and PR_3 for Group 1

3.2 Nocturnal Sleep Study Results

There were 10 subjects considered who took part in nocturnal sleep study. From the nocturnal polysomnography a total of 131 apnea events were selected. Like the

simulated apnea study the metrics considered from exhaled CO_2 were Delta $ETCO_2$ and $ETCO_2$. Correlation coefficients of these parameters with the CBFV parameters were computed. Figure 3-12 and 3-13 shows the change in the exhaled CO_2 and the TCD signal due to apnea in nocturnal sleep apnea study.

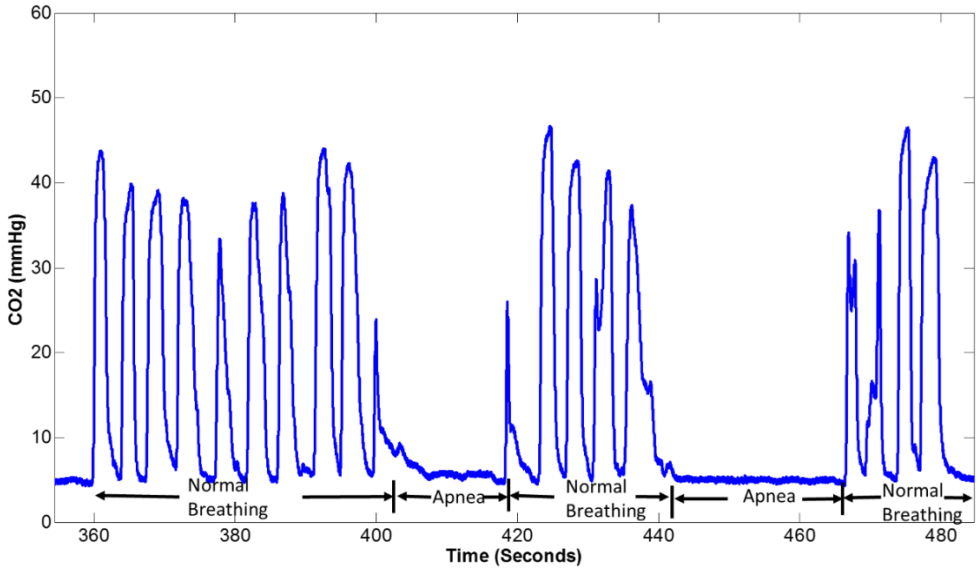

Figure 3-12 Capnogram during sleep apnea episodes and normal breathing

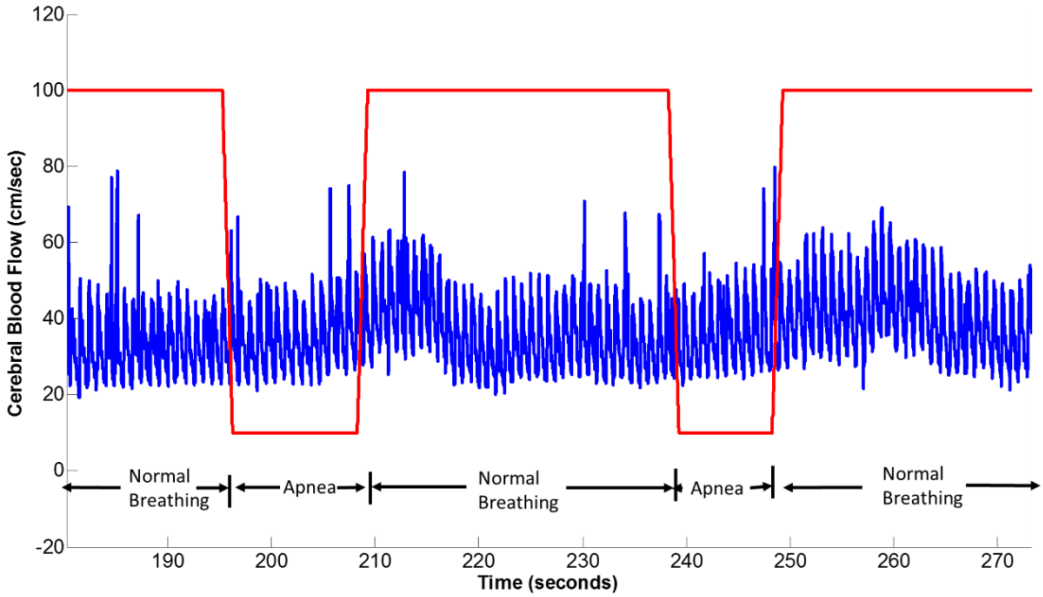

Figure 3-13 Cerebral Blood flow velocity waveform during apnea episodes and normal breathing

3.2.1. Comparison Metrics Means between Simulated Sleep Apnea and Nocturnal Sleep Apnea

For this study comparisons were made between nocturnal sleep study data and the protocol A and B in the supine position. Table 3-8 and Table 3-9 presents the findings from ANOVA test for exhaled CO_2 and CBFV metrics respectively. The definition of the metrics shown in tables are discussed in chapter 2 section 2.4.1.1.1. and 2.4.1.2.2. respectively. The p value marked with an asterisk indicates significance of < 0.05. This analysis was done by separating the data into the separate subject groups as mentioned before The results from the ANOVA test is mentioned in appendix E

Table 3-8 Results from ANOVA for the means of the metrics of exhaled CO_2 metrics between simulated apnea study and nocturnal sleep study data

ANOVA CO_2

Table 3-8: *Continued*

Metric	p	
	Group 1	Group2
$ETCO_2$	7.87×10^{-4}*	1.61×10^{-8}*
Delta $ETCO_2$	4.01×10^{-3}*	4.89×10^{-8}*

Table 3-9 Results from ANOVA for the means of the metrics of CBFV metrics between simulated apnea study and nocturnal sleep study data

ANOVA CBFV		
Metric	p	
	Group 1	Group2
Slope	8.73×10^{-1}	5.20×10^{-2}
Del_1	7.52×10^{-6}*	5.12×10^{-1}
PR_1	1.75×10^{-4}*	5.44×10^{-1}
Del_2	1.27×10^{-13}*	4.49×10^{-1}
Pr_2	1.51×10^{-3}*	6.72×10^{-1}
Del_3	2.44×10^{-16}*	5.68×10^{-2}
Pr_3	8.97×10^{-10}*	4.10×10^{-1}
$oDel_2$	8.03×10^{-15}*	1.9×10^{-1}
oPR_2	4.09×10^{-5}*	9.01×10^{-1}
PRArea	1.81×10^{-4}*	2.47×10^{-1}
Norm Area	2.86×10^{-24}*	6.51×10^{-10}*

3.2.1.1. Comparison of the mean of the exhaled CO_2 metrics between simulated sleep apnea and nocturnal sleep apnea

Table 3-10 shows the Tukey Kramer analysis for the means of the metrics derived from exhaled CO_2 metric between the simulated apnea study and the nocturnal sleep study. The p value marked with an asterisk indicates significance of < 0.05. SuA and SuB are short hand representation explained in subsection 2.3.1.

Table 3-10 Results from Tukey Kramer for means of the metrics derived from exhaled CO_2 metrics between simulated apnea study and nocturnal sleep study data

CO_2					
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	p
Group 1	$ETCO_2$	Sleep V/S SuA	0.95	5.03	1.74×10^{-3}*
		Sleep V/S SuB	0.12	4.61	3.62×10^{-2}*
	Delta $ETCO_2$	Sleep V/S SuB	0.52	4.45	8.38×10^{-3}*
Group 2	$ETCO_2$	Sleep V/S SuB	-7.08	-3.18	3.12×10^{-9}*
	Delta $ETCO_2$	Sleep V/S SuA	-6.07	-0.94	3.82×10^{-3}*
		Sleep V/S SuB	-6.26	-2.58	5.41×10^{-8}*

3.2.1.2. Comparison of the mean of the CBFV metrics for simulated sleep apnea and nocturnal sleep apnea

Table 3-11 shows the Tukey Kramer analysis for the means of the metrics derived from CBFV metric between the simulated apnea study and the nocturnal sleep study. The p value marked with an asterisk indicates significance of < 0.05.

Table 3-11 Results from ANOVA and Tukey Kramer for means of the metrics derived from CBFV metrics between simulated apnea study and nocturnal sleep study data

CBFV					
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	p
Group 1	Del_1	Sleep V/S SuA	-24.15	-6.6	1.18×10^{-4}*
		Sleep V/S SuB	-24.93	-5.59	6.30×10^{-4}*
	PR_1	Sleep V/S SuA	-26.35	-5.36	1.16×10^{-3}*
		Sleep V/S SuB	-26.76	-3.64	5.82×10^{-3}*
	Del_2	Sleep V/S SuA	-19.87	-9.34	1.19×10^{-9}*
		Sleep V/S SuB	-21.81	-10.20	1.25×10^{-9}*
	Pr_2	Sleep V/S SuB	-19.85	-3.31	2.95×10^{-3}*
	Del_3	Sleep V/S SuA	-23.24	-12.38	9.56×10^{-10}*
		Sleep V/S SuB	-23.26	-11.28	9.96×10^{-10}*
	Pr_3	Sleep V/S SuA	-22.38	-8.82	2.05×10^{-7}*
		Sleep V/S SuB	-24.13	-9.19	5.07×10^{-7}*
	$oDel_2$	Sleep V/S SuA	-21.6084	-10.5344	9.86×10^{-10}*
		Sleep V/S SuB	-23.9294	-11.7265	9.78×10^{-10}*

Table 3-11: *Continued*

	oPR_2	Sleep V/S SuA	-17.5011	-1.99026	9.06×10^{-3}*
		Sleep V/S SuB	-23.5522	-6.46006	1.14×10^{-4}*
	PRArea	Sleep V/S SuA	-32.56	-2.92	1.39×10^{-2}*
		Sleep V/S SuB	-42.32	-9.65	5.64×10^{-4}*
	Norm Area	Sleep V/S SuA	-1.14	-0.69	9.56×10^{-10}*
		Sleep V/S SuB	-1.17	-0.68	9.56×10^{-10}*
Group 2	Slope	Sleep V/S SuB	0.0057	0.52	4.37×10^{-2}*
	Norm Area	Sleep V/S SuA	-0.55	-0.21	6.05×10^{-7}*
		Sleep V/S SuB	-0.401	-0.16	2.61×10^{-7}*

Figure 3-14 represents the mean comparisons of the CBFV metrics between nocturnal sleep study data and simulated apnea study data.

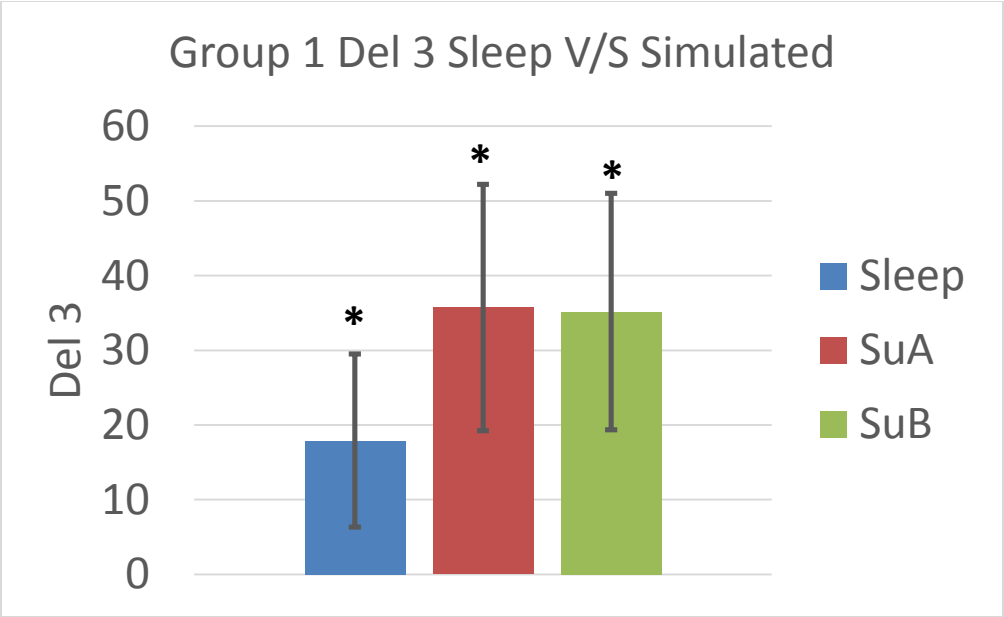

Figure 3-14 Mean Comparisons between Nocturnal Sleep Study and Simulated apnea study

3.2.2. Correlation of Delta $ETCO_2$ with Cerebral Blood Flow Velocity Metrics During Nocturnal Study

Examining the correlation between the change in the $ETCO_2$ with the CBFV parameters using Kendall's Tau indicated that Del_2, Del_3, PR_3, $oDel_2$ and Norm Area were not significant. Among the significant metrics none of them had a correlation greater than 50%. The highest correlation was with PRArea -0.25 ($p= 1.26x10^{-5}$*).

Spearman's Rho indicated that Del_2, Del_3, PR_3, $oDel_2$ and Norm Area were non-significant. Among the significant metrics none of them had a correlation greater than 50%. The highest correlation was with PRArea -0.36 ($p= 1.54x10^{-5}$*). The results for the correlation studies are reported in the appendix C

3.2.3. Correlation of $ETCO_2$ with Cerebral Blood Flow Velocity Metrics

Kendall's Tau and Spearman's Rho indicated no significant correlation between $ETCO_2$ and CBFV. The result for the correlation are presented in the appendix C

The next chapter discusses the above mentioned results. It also draws a conclusion based on these results. Along with this the next chapter also states the limitations of the study conducted.

Figure 3-15 represents the correlation between CO_2 and CBFV metrics in the nocturnal study.

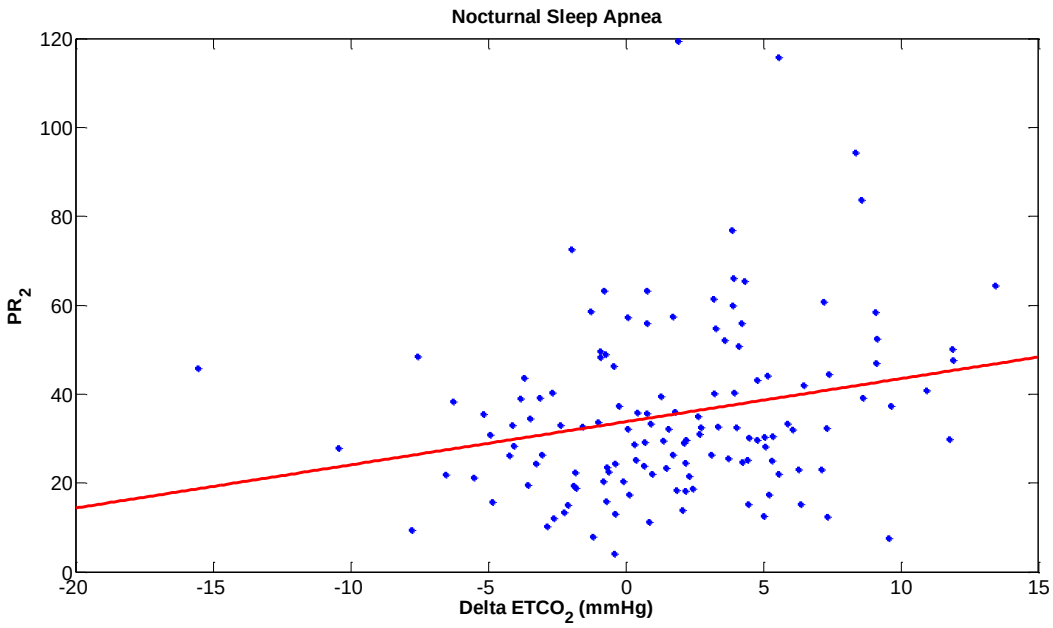

Figure 3-15 Correlation between Delta $ETCO_2$ and PR_2

Chapter 4

Discussion and Conclusion

This chapter discusses the results of the study, their significance, and physiological implications. The results of the both simulated sleep apnea and nocturnal sleep apnea studies will be discussed separately as well as together to highlight the differences and the similarities in the exhaled CO_2 and CBFV metrics and the level of correlation between them during apnea episodes. The results of simulated sleep apnea will be discussed first, followed by the discussion of the findings related to the nocturnal sleep apnea studies, and finally the comparison of the results obtained from these two studies.

4.1 Simulated Sleep Apnea Study

Analysis of the simulated apnea study focused on determining the effect of the frequency of apnea and the posture of the subject during simulated apnea. In the following sections, the responsiveness of each of the proposed metrics for exhaled CO_2 and cerebral blood flow velocity to the change in the frequency of apnea and the posture of the subject during apnea will be considered.

4.1.1. Comparison of Metrics Means Changes Due to Frequency of Apnea

The section below discusses the data from tables 3-1 to 3-3 which tabulates the result from ANOVA and Tukey-Kramer test for exhaled CO_2 and CBFV metrics according to the different apnea frequencies. This analysis was done for both the subject groups.

4.1.1.1. Comparison of Exhaled CO_2 Metrics Means

In the simulated apnea study for Group 1, the ANOVA results from exhaled CO_2 signal indicate that means of $ETCO_2$ did not differ between apnea frequencies and positions (3.1.1.). This was consistent with results obtained for Group 2 (3.1.1.) with the exception of the means of Delta $ETCO_2$ for Group 2. Tukey-Kramer analysis revealed

that Delta $ETCO_2$ did not differ between the apnea frequencies. This suggests that Delta $ETCO_2$ may not be sensitive to the frequency of apnea.

4.1.1.2. Comparison of Cerebral Blood Flow Velocity Metrics

ANOVA results from the CBFV metrics indicates that means of Norm Area in Group 1 and means of slope, Del_1, Del_2, Del_3, PR_3 and $oDel_2$ in Group 2 differed between apnea frequencies and positions (3.1.1.). Tukey-Kramer tests revealed that Del_3 in Group 2 differed for the two apnea frequencies that were tested within the supine position. The mean of Del_3 was greater in protocol A by 7.21 cm/sec (Appendix K). Since this metric did not differ in Group 1 and since Group 1 had more subject members, it is possible but not definitive, that these metrics may exhibit greater sensitivity to the frequency of apnea in the supine position for larger subject population.

In summary, neither of the metrics proposed for quantifying exhaled CO2 were sensitive to changes in frequency of apnea in simulated sleep apnea studies. Similarly, the metrics derived from CBFV indicated that the means of Del_3 may be sensitive to the changes in the apnea frequency in the supine position.

4.1.2. Comparison of Metrics Means Changes Due to Posture

The section below discusses the data from tables 3-1, 3-2, 3-4 and 3-5, which tabulate the results from ANOVA and Tukey-Kramer test for exhaled CO_2 metrics and CBFV metrics for the two postures tested. This analysis was done for both the subject groups: Group 1 and Group 2.

4.1.2.1. Comparison of Exhaled CO_2 Metrics Mean

As discussed above in the simulated apnea study, the ANOVA results from exhaled CO_2 metrics from both subject groups indicate that the means of $ETCO_2$ did not differ between apnea frequencies and positions. Means of Delta $ETCO_2$, however, did differ in Group 2 (3.1.1.). Tukey-Kramer analysis revealed that Delta $ETCO_2$ differed

within protocol A. The mean of Delta $ETCO_2$ was greater in the sitting position by 2.99 mmHg (Appendix K). Since these metrics did not exhibit sensitivity to posture in Group 1, it is possible but that Delta $ETCO_2$ is sensitive to position within the lower frequency of apnea.

4.1.2.2. Comparison of Cerebral Blood Flow Velocity Metrics

As discussed above, ANOVA results from the CBFV metrics indicate that means of Norm Area in Group 1 and the means of slope, Del_1, Del_2, Del_3, PR_3 and $oDel_2$ in Group 2 differed significantly ($p<0.05$) between apnea frequencies and positions (3.1.1.). Tukey-Kramer tests revealed that in Group 1, means of Norm Area differed within both apnea frequencies. The mean of Norm Area was greater in the supine position by 0.33 in protocol A. It was greater in the supine position by 0.36 in protocol B (Appendix K). This test, when performed on the data from Group 2 revealed that means of slope and Del_1 differed between the two postures within protocol A. The mean of slope was greater in the supine position by 0.41 cm/sec^2. The mean of Del_1 was greater in the supine position by 10.7 cm/sec (Appendix K). This test also indicated that means of Del_3 and $oDel_2$ differed between the two postures for both apnea frequencies. The mean of Del_3 was greater in the supine position by 9.24 cm/sec in protocol A and it was greater in the supine position by 6.06 cm/sec in protocol B. The mean of $oDel_2$ was greater in the supine position by 9.3 cm/sec in protocol A. It was also greater in the supine position by 5.97 cm/sec in protocol B. (Appendix K).Since the difference between the positions was not consistent between the two groups. One can speculate that Norm Area, Del_3 and $oDel_2$ are sensitive to the posture within both frequencies of apnea. It can also be inferred that slope and Del_1 are sensitive to the posture within lower frequencies of apnea.

In summary, metrics derived from exhaled CO_2 indicated that the means of Delta $ETCO_2$ may be sensitive to the changes in the posture within lower frequency of apnea.

Similarly the metrics derived from CBFV indicated that the means of Norm Area, Del_3 and $oDel_2$ may be sensitive to the changes in the posture within both frequencies of apnea. Moreover slope and Del_1 may be sensitive to the changes in the posture within lower frequencies of apnea.

4.1.3. Correlation between Delta $ETCO_2$ and CBFV metrics

The correlation between Delta $ETCO_2$ and the CBFV metrics is discussed below grouping them with different subject groups. Only the metrics with a correlation coefficient greater than 50% are considered here.

In Group 1, using Kendall's method, none of the metric pairs had a correlation coefficient greater than 50%. Using Spearman's method, PRArea had a correlation coefficient greater than 50% in protocol A with the supine position. In Group 2, using Kendall's method none of the metric pairs had a correlation coefficient greater than 50%. Using Spearman's method Del_1, PR_1, $oDel_2$ and Norm Area had a correlation coefficient greater than 50% in protocol A with the supine position. This method also indicated that Norm Area had a correlation coefficient greater than 50% in protocol B with supine position. Although these metrics correlation coefficient were greater than 50%, they were not consistent for all protocols. This indicates that they cannot be used for quantifying the CBFV with the changes in CO_2. The reason for this could be that other physiological parameters like blood pressure and sympathetic nerve activity during hypertension may have had an effect on this relationship.

Kolmogorov-Smirnov test indicated that none of the exhaled CO_2 and CBFV metrics had a Gaussian distribution (Appendix H). Therefore Pearson's Product-Moment correlation was not considered for the analysis. This method indicated that, in Group 1, none of the considered metric pairs had a correlation coefficient greater than 50%. In Group 2, this method indicated that Del_1, PR_1, $oDel_2$ and Norm Area had a correlation

coefficient greater than 50% in protocol A with the supine position. This method also indicated that Norm Area had a correlation coefficient greater than 50% in protocol B with supine position (Appendix A).

4.1.4. Correlation between $ETCO_2$ and CBFV metrics

In this section the emphasis is given to discussing the results pertaining to metrics with correlation coefficient greater than 50%.

In Group 1, using Kendall's method, none of the metric pairs had a correlation coefficient greater than 50%. However, using Spearman's method PR_1, PR_2, PR_3 and oPR_2 had a correlation coefficient greater than 50% in protocol B with supine position. This indicates that the analysis method does affect the findings. Kendall's method is more accurate with smaller sample sizes. The relationship between Spearman's rho and Kendall's tau can be expressed by $-1 \leq 3\tau - 2\rho \leq 1$ [36]. In Group 2, using Kendall's method, none of the metric pairs had a correlation coefficient greater than 50%. Using Spearman's method, Norm Area had a correlation coefficient greater than 50% in protocol A with supine position. Although these metrics have a correlation coefficient greater than 50%, they were not consistent for all protocols. This indicates that they cannot be used for quantifying the CBFV with the changes in CO_2. As stated above, the reason for this could be that other physiological parameters like blood pressure and sympathetic nerve activity during hypertension may have had an effect on this relationship.

As stated above, Kolmogorov-Smirnov test indicated that none of the exhaled CO_2 and CBFV metrics had a Gaussian distribution (Appendix H). Therefore Pearson's Product-Moment correlation was not considered for the analysis. This method indicated that, in Group 1, PR_1, PR_3 and oPR_2 had a correlation coefficient greater than 50% in protocol B with the supine position. In Group 2, this method indicated that Norm Area had

a correlation coefficient greater than 50% in protocol A with the supine position (Appendix A).

4.2 Comparison of Nocturnal Sleep Apnea and Simulated Apnea Study Results

Comparisons were made between data from the nocturnal sleep study and supine position data for both frequencies of simulate sleep apnea. The supine position data were considered, because it closely represents the posture during sleep. This was done to compare the results obtained from the simulated apnea study. Comparisons was made between sleep apnea data and both apnea frequencies.

4.2.1. Comparison Metrics Means between Simulated Sleep Apnea and Nocturnal Sleep Apnea

The section below discusses the result from tables 3-8 to 3-11, which tabulate the results from ANOVA and Tukey-Kramer tests for exhaled CO_2 and CBFV metrics. The nocturnal sleep apnea and both apnea frequencies in the supine position from simulated sleep apnea were considered. This analysis was done for both the subject groups in the simulated apnea study.

4.2.1.1. Comparison of Mean of Exhaled CO_2 Metrics between Simulated Sleep Apnea and Nocturnal Sleep Apnea

ANOVA tests for exhaled CO_2 between nocturnal sleep apnea and simulated apnea study revealed that in both the subject groups, the means of Delta $ETCO_2$ and $ETCO_2$ means differed among nocturnal sleep study and simulated apnea study. The Tukey-Kramer test indicated that in Group 1, means of $ETCO_2$ differed between nocturnal sleep apnea data and both apnea frequencies in the supine position (3.2.1.1). The mean of $ETCO_2$ was greater in the data from the sleep study by 2.99 mmHg when compared with data from protocol A in the supine position. It was greater in the data from the nocturnal sleep apnea study by 2.37 mmHg when compared with data from protocol B in

the supine position (Appendix K). This test also revealed that means of Delta $ETCO_2$ differed between nocturnal sleep apnea study and data from protocol B in the supine position (3.2.1.1). The mean of Delta $ETCO_2$ was greater in the data from the nocturnal sleep apnea study by 2.49 mmHg when compared with data from protocol B in the supine position (Appendix K). Within Group 2, means of $ETCO_2$ differed between nocturnal sleep apnea study and the data from protocol B in the supine position. The mean of $ETCO_2$ was greater in the data from protocol B in the supine position by 5.13 mmHg (Appendix K). In this group, the means of Delta $ETCO_2$ differed between nocturnal sleep apnea study and both apnea frequencies in the supine position (3.2.1.1). The mean of Delta $ETCO_2$ was greater in the data from protocol A in the supine position by 3.15 mmHg when compared with data from the nocturnal sleep apnea study. It was also greater in the data from protocol B in the supine position by 4.43 mmHg when compared with data from the nocturnal sleep apnea study (Appendix K).

4.2.1.2. Comparison of the Mean of the CBFV Metrics for Simulated Sleep Apnea and Nocturnal Sleep Apnea

ANOVA results for comparison of the CBFV metrics between nocturnal and simulated apnea study in Group 1 revealed that means of Del_1, PR_1, Del_2, PR_2, Del_3, PR_3, $oDel_2$, oPR_2, PRArea and Norm Area have a significant difference between nocturnal apnea study and simulated apnea study. These tests also showed that in Group 2, means of Norm Area has significant difference between nocturnal sleep apnea study and simulated apnea study. The Tukey-Kramer test for Group 1 indicates that means of Del_1, PR_1, Del_2, Del_3, PR_3, $oDel_2$, oPR_2, PRArea and Norm Area differed between nocturnal sleep apnea and both simulated sleep apnea in the supine position, irrespective of the frequency of simulated sleep apnea (3.2.1.2). The means of these metrics were greater in the data from the nocturnal sleep apnea study than from protocol A in the supine

position. The means of Del_1 was greater by 15.4 cm/sec, PR_1 was greater by 15.9 %, Del_2 was greater by 14.6 cm/sec, Del_3 was greater by 17.8 cm/sec, PR_3 was greater by 15.6 %, $oDel_2$ was greater by 16.1 cm/sec, oPR_2 was greater by 9.7 %, PRArea was greater by 17.7 % and Norm Area was greater by 0.91. The means of these metrics were greater in the data from the nocturnal sleep apnea study than from protocol B in the supine position. The means of Del_1 was greater by 15.3 cm/sec, PR_1 was greater by 15.2 %, Del_2 was greater by 16 cm/sec, Del_3 was greater by 17.3 cm/sec, PR_3 was greater by 16.7 %, $oDel_2$ was greater by 17.8 cm/sec, oPR_2 was greater by 15 %, PRArea was greater by 26 % and Norm Area was greater by 0.93 (Appendix K). This test also showed that means of PR_2 differed between nocturnal sleep apnea and protocol B in the supine position (3.2.1.2). The mean of PR_2 was greater in the data from the nocturnal sleep apnea study by 11.6 % when compared with data from protocol B in the supine position (Appendix K). The Tukey-Kramer test for Group 2 indicate that means of slope differed between nocturnal sleep apnea and protocol B in the supine position (3.2.1.2). The mean of slope was greater in the data from the nocturnal sleep apnea study by 0.26 cm/sec^2 when compared with data from protocol B in the supine position (Appendix K). This test also indicated that means of Norm Area differed between nocturnal sleep apnea and both apnea frequencies in the supine position (3.2.1.2). The mean of Norm Area was greater in the data from protocol A in the supine position by 0.37 when compared with data from the nocturnal sleep apnea study. It was greater in the data from protocol B in the supine position by 0.27 when compared with data from the nocturnal sleep apnea study (Appendix K). These differences could be due to the dissimilarities in the methodology of nocturnal sleep study and the simulated apnea study. In the simulated apnea study, the subjects made a conscious effort to hold their breath. This could have induced some physiological changes which may not be there in the nocturnal sleep study.

4.2.2. Correlation between CBFV Metrics Delta $ETCO_2$ in Nocturnal Apnea Subjects

In the nocturnal sleep apnea study, Kendall's method indicated that none of the CBFV Delta $ETCO_2$ metric pairs had a correlation coefficient greater than 50%. Spearman's method also indicated that none of the CBFV Delta $ETCO_2$ metric pairs had a correlation coefficient greater than 50%. This indicates that these metrics cannot be used to quantify the changes in CBFV with the changes in CO_2. The reason for this, as stated above, could be that other physiological changes like blood pressure and sympathetic nerve activity during hypertension could influence this relationship.

Kolmogorov-Smirnov test indicated that none of the exhaled CO_2 and CBFV metrics had a Gaussian distribution (Appendix H). Therefore Pearson's Product-Moment correlation was not considered for the analysis. This method indicates that none of the CBFV Delta $ETCO_2$ metric pairs had a correlation coefficient greater than 50% (Appendix A).

4.2.3. Correlation between CBFV Metrics $ETCO_2$ in Nocturnal Apnea Subjects

In the nocturnal sleep apnea study Kendall's method indicated that none of the CBFV $ETCO_2$ metric pairs had a correlation coefficient greater than 50%. The results was similar with Spearman's method. This indicates that these metrics cannot be used to quantify the changes in CBFV with the changes in CO_2. The reason for this could be that other physiological parameters like blood pressure and sympathetic nerve activity during hypertension could have influenced this relationship.

As stated above, Kolmogorov-Smirnov test indicated that none of the exhaled CO_2 and CBFV metrics had a Gaussian distribution (Appendix H). Therefore Pearson's Product-Moment correlation was not considered for the analysis. This method indicates that none of the CBFV $ETCO_2$ metric pairs had a correlation coefficient greater than 50% (Appendix A).

4.3 Comparison of the Results with the Previous Studies

Previous studies conducted by Battisti-Charbonney, et al [15], M. Cigada et al [23], Markwalder T.M. et al [24] and Tancredi F.B. et al [26], found a strong positive relationship between exhaled CO_2 and CBFV metrics. To evaluate this relationship, Battisti-Charbonney considered the following metrics - MCAv from CBF and $ETCO_2$ from exhaled CO_2. M. Cigada considered Vm and PI from CBF and $ETCO_2$ from exhaled CO_2. Markwalder T.M. considered Vmca from CBF and $ETCO_2$ from exhaled CO_2. Tancredi F.B. considered CBF using ASL from CBF and $ETCO_2$ from exhaled CO_2. The details of these metrics are explained in section 1.5. Studies conducted by Battisti-Charbonney, M. Cigada and Tancredi F.B. analyzed the data by finding the relationship between exhaled CO_2 and CBF metrics for individual subjects.

The study conducted by Markwalder T.M. grouped the data from the subjects and evaluated this relationship. Our study's aim was to find a more generalized and deductive relationship between exhaled CO_2 and CBFV metrics. This was done to find if this relationship can be used to discern the level of CBF from exhaled CO_2, which would be subject independent. In some of our protocols, there was a strong positive correlation between some of the considered CO_2 and CBFV metric pairs. But these were not consistent. The probable reasons for this could be that the relationship between the two physiological signals may be subject dependent and influenced by other physiological effects such as hypoxia.

Although the study conducted by Markwalder T.M. showed a strong positive relationship between exhaled CO_2 and CBF, when the data from all the subjects were grouped together, our study did not concur with this result. This inconsistency could be due to the differences in the considered metrics. They utilized Vmca from CBFV, which was recorded for 3-5 minutes. Post this they found the relationship between the change

in Vmca and $ETCO_2$. Our study used the change in the systolic values during the apnea, the area under the curve and the area under the systolic points. These changes were found using multiple methods as stated in subsection 2.4.1.2.2. These could be the probable reasons for the differences in the results to quantify the relationship between exhaled CO_2 and CBF between the two studies.

4.4 Limitations

Simulated apnea study involved voluntary breath hold in awake subjects. The conscious effort of holding the breath may affect the physiological signals studied, since the subject has control over the duration and method of breath holding under such circumstances. This may not be the case in nocturnal sleep apnea where the apnea occurs at the end of the breath.

4.5 Conclusion

Although some of the considered exhaled CO_2 and CBFV metric pairs in the simulated sleep study have a correlation coefficient greater than 50%, these were not consistent, indicating that they cannot be used to quantify the relationship between the two. Moreover, in the nocturnal sleep study the metrics did not have a correlation coefficient greater than 50%. Hence, this study does not support the use of any of the considered exhaled CO_2 and CBFV metric pairs to predict the changes in CBFV via the changes in exhaled CO_2. Further study, using different exhaled CO_2 and CBFV metrics and by analyzing this relationship within a subject, is warranted to find the possible existence of a relation between the exhaled CO2 and CBFV.

Appendix A

RESULTS FROM PEARSON'S PRODUCT MOMENT CORRELATION

The tables below shows the Pearson's correlation between CO_2 and the CBFV metrics in simulated apnea study in Group 1.

Table A-1 Pearson's Correlation between $ETCO_2$ and CBFV metrics in simulated apnea study for Group 1

	$ETCO_2$							
	SiA		SiB		SuA		SuB	
	p	r	p	r	p	r	p	r
Slope	3.66 x10^{-1}	1.19 x10^{-1}	3.34 x10^{-1}	1.22 x10^{-1}	7.53 x10^{-1}	-4.83 x10^{-2}	2.80 x10^{-1}	-1.88 x10^{-1}
Del_1	1.74 x10^{-1}	1.78 x10^{-1}	3.82 x10^{-1}	1.10 x10^{-1}	8.11 x10^{-1}	3.67 x10^{-2}	4.09 x10^{-2}*	-3.47 x10^{-1}
PR_1	5.57 x10^{-1}	7.73 x10^{-2}	9.41 x10^{-1}	9.37 x10^{-3}	5.62 x10^{-1}	-8.88 x10^{-2}	5.82 x10^{-4}*	-5.52 x10^{-1}
Del_2	3.18 x10^{-1}	1.31 x10^{-1}	9.04 x10^{-1}	-1.52 x10^{-2}	8.94 x10^{-1}	-2.04 x10^{-2}	9.46 x10^{-2}	-2.87 x10^{-1}
Pr_2	8.96 x10^{-1}	-1.72 x10^{-2}	3.46 x10^{-2}*	-2.63 x10^{-1}	4.46 x10^{-2}*	-3.01 x10^{-1}	2.69 x10^{-3}*	-4.92 x10^{-1}
Del_3	1.33 x10^{-1}	1.96 x10^{-1}	4.31 x10^{-1}	9.95 x10^{-2}	6.09 x10^{-1}	7.84 x10^{-2}	4.96 x10^{-2}*	-3.34 x10^{-1}
Pr_3	3.95 x10^{-1}	1.12 x10^{-1}	8.89 x10^{-1}	1.77 x10^{-2}	9.57 x10^{-1}	-8.30 x10^{-3}	1.79 x10^{-3}*	-5.09 x10^{-1}
$oDel_2$	3.24 x10^{-1}	1.29 x10^{-1}	8.89 x10^{-1}	1.76 x10^{-2}	9.94 x10^{-1}	1.20 x10^{-3}	7.03 x10^{-2}	-3.10 x10^{-1}

Table A-1: *Continued*

oPr_2	8.06 $x10^{-1}$	-3.24 $x10^{-2}$	7.64 $x10^{-2}$	-2.21 $x10^{-1}$	2.27 $x10^{-2}$*	-3.39 $x10^{-1}$	7.86 $x10^{-4}$*	-5.41 $x10^{-1}$
PRArea	9.07 $x10^{-1}$	1.54 $x10^{-2}$	9.79 $x10^{-1}$	-3.38 $x10^{-3}$	4.03 $x10^{-1}$	-1.28 $x10^{-1}$	1.09 $x10^{-2}$*	-4.25 $x10^{-1}$
Norm Area	5.65 $x10^{-1}$	7.58 $x10^{-2}$	6.68 $x10^{-1}$	5.43 $x10^{-2}$	1.29 $x10^{-1}$	2.30 $x10^{-1}$	1.79 $x10^{-2}$*	3.98 $x10^{-1}$

Table A-2 Pearson's Correlation between Delta $ETCO_2$ and CBFV metrics in simulated apnea study for Group 1

	Delta $ETCO_2$							
	SiA		SiB		SuA		SuB	
	p	r	p	r	p	r	p	r
Slope	2.75 $x10^{-1}$	1.43 $x10^{-1}$	9.72 $x10^{-1}$	4.43 $x10^{-3}$	4.96 $x10^{-1}$	-1.04 $x10^{-1}$	9.92 $x10^{-1}$	-1.77 $x10^{-3}$
Del_1	3.61 $x10^{-1}$	1.20 $x10^{-1}$	8.05 $x10^{-1}$	3.12 $x10^{-2}$	9.98 $x10^{-1}$	2.98 $x10^{-4}$	6.25 $x10^{-1}$	-8.56 $x10^{-2}$
PR_1	5.18 $x10^{-1}$	8.51 $x10^{-2}$	8.17 $x10^{-1}$	2.93 $x10^{-2}$	6.25 $x10^{-1}$	7.48 $x10^{-2}$	1.25 $x10^{-1}$	-2.65 $x10^{-1}$
Del_2	5.89 $x10^{-1}$	7.12 $x10^{-2}$	4.38 $x10^{-1}$	-9.78 $x10^{-2}$	2.88 $x10^{-1}$	-1.62 $x10^{-1}$	7.82 $x10^{-1}$	-4.85 $x10^{-2}$
Pr_2	6.76 $x10^{-1}$	-5.50 $x10^{-2}$	4.64 $x10^{-2}$*	-2.48 $x10^{-1}$	8.79 $x10^{-2}$	-2.57 $x10^{-1}$	5.94 $x10^{-2}$	-3.22 $x10^{-1}$

Table A-2: *Continued*

Del_3	2.26 x10^{-1}	1.59 x10^{-1}	9.78 x10^{-1}	3.45 x10^{-3}	9.73 x10^{-1}	5.26 x10^{-3}	7 x10^{-1}	-6.75 x10^{-2}
Pr_3	2.49 x10^{-1}	1.51 x10^{-1}	9.02 x10^{-1}	-1.55 x10^{-2}	6.20 x10^{-1}	7.59 x10^{-2}	1.64 x10^{-1}	-2.40 x10^{-1}
$oDel_2$	5 x10^{-1}	8.88 x10^{-2}	4.79 x10^{-1}	-8.95 x10^{-2}	2.42 x10^{-1}	-1.78 x10^{-1}	6.97 x10^{-1}	-6.83 x10^{-2}
oPr_2	8.06 x10^{-1}	-3.24 x10^{-2}	5.27 x10^{-2}	-2.41 x10^{-1}	2.32 x10^{-2}*	-3.38 x10^{-1}	3.55 x10^{-2}*	-3.57 x10^{-1}
PRArea	4.21 x10^{-1}	-1.06 x10^{-1}	3.44 x10^{-1}	-1.19 x10^{-1}	3.08 x10^{-3}*	-4.32 x10^{-1}	8.95 x10^{-1}	-2.31 x10^{-2}
Norm Area	6.37 x10^{-1}	-6.22 x10^{-2}	7.14 x10^{-1}	4.63 x10^{-2}	1.60 x10^{-1}	2.13 x10^{-1}	6.12 x10^{-1}	8.88 x10^{-2}

The tables below shows the Pearson's correlation between CO_2 and the CBFV metrics in simulated apnea study in Group 2.

Table A-3 Pearson's Correlation between $ETCO_2$ and CBFV metrics in simulated apnea study for Group 2

	$ETCO_2$							
	SiA		SiB		SuA		SuB	
	p	r	p	r	p	r	p	r
Slope	5.76 x10^{-1}	-1.06 x10^{-1}	4.09 x10^{-1}	-1.57 x10^{-1}	7.05 x10^{-1}	9.02 x10^{-2}	9.97 x10^{-1}	5.17 x10^{-4}

Table A-3:*Continued*

Del_1	5.94 x10^{-2}	-3.48 x10^{-1}	4.55 x10^{-1}	1.42 x10^{-1}	3.89 x10^{-2}*	4.65 x10^{-1}	2.29 x10^{-1}	1.83 x10^{-1}
PR_1	1.51 x10^{-1}	-2.69 x10^{-1}	8.15 x10^{-1}	-4.47 x10^{-2}	3.73 x10^{-2}*	4.68 x10^{-1}	2.35 x10^{-1}	1.81 x10^{-1}
Del_2	2.17 x10^{-1}	-2.32 x10^{-1}	7.30 x10^{-1}	6.57 x10^{-2}	1.47 x10^{-1}	3.36 x10^{-1}	7.62 x10^{-2}	2.67 x10^{-1}
Pr_2	3.62 x10^{-1}	-1.72 x10^{-1}	6.13 x10^{-1}	-9.62 x10^{-2}	3.54 x10^{-1}	2.19 x10^{-1}	8.82 x10^{-2}	2.57 x10^{-1}
Del_3	2.42 x10^{-2}*	-4.11 x10^{-1}	3.15 x10^{-1}	1.90 x10^{-1}	6.59 x10^{-2}	4.19 x10^{-1}	1.77 x10^{-1}	2.05 x10^{-1}
Pr_3	1.03 x10^{-1}	-3.04 x10^{-1}	9.32 x10^{-1}	1.62 x10^{-2}	8.29 x10^{-2}	3.97 x10^{-1}	1.97 x10^{-1}	1.96 x10^{-1}
$oDel_2$	1.97 x10^{-1}	-2.43 x10^{-1}	5.94 x10^{-1}	1.01 x10^{-1}	4.41 x10^{-2}*	4.54 x10^{-1}	5.11 x10^{-2}	2.93 x10^{-1}
oPr_2	3.06 x10^{-1}	-1.93 x10^{-1}	8.37 x10^{-1}	-3.93 x10^{-2}	1.67 x10^{-1}	3.21 x10^{-1}	4.82 x10^{-2}*	2.96 x10^{-1}
PRArea	1.56 x10^{-2}*	-4.38 x10^{-1}	8.63 x10^{-1}	-3.30 x10^{-2}	5.60 x10^{-1}	-1.39 x10^{-1}	4.40 x10^{-2}*	-3.02 x10^{-1}
Norm Area	2.44 x10^{-1}	-2.20 x10^{-1}	4.91 x10^{-2}*	3.62 x10^{-1}	2.26 x10^{-3}*	6.42 x10^{-1}	4.65 x10^{-2}*	2.98 x10^{-1}

Table A-4 Pearson's Correlation between Delta $ETCO_2$ and CBFV metrics in simulated apnea study for Group 2

	Delta $ETCO_2$							
	SiA		SiB		SuA		SuB	
	p	r	p	r	p	r	p	r
Slope	7.87 x10^{-1}	5.15 x10^{-2}	8.47 x10^{-1}	3.69 x10^{-2}	5.62 x10^{-1}	1.38 x10^{-1}	3.68 x10^{-1}	-1.38 x10^{-1}
Del_1	3.49 x10^{-1}	-1.77 x10^{-1}	4.93 x10^{-1}	1.30 x10^{-1}	1.87 x10^{-2}*	5.20 x10^{-1}	1.74 x10^{-1}	2.06 x10^{-1}
PR_1	3.06 x10^{-1}	-1.94 x10^{-1}	8.24 x10^{-1}	4.24 x10^{-2}	1.09 x10^{-2}*	5.56 x10^{-1}	4.53 x10^{-2}*	3 x10^{-1}
Del_2	7.94 x10^{-1}	4.98 x10^{-2}	4.54 x10^{-1}	1.42 x10^{-1}	7.60 x10^{-2}	4.06 x10^{-1}	2.79 x10^{-1}	1.65 x10^{-1}
Pr_2	9.95 x10^{-1}	1.31 x10^{-3}	7.61 x10^{-1}	5.79 x10^{-2}	1.97 x10^{-1}	3.01 x10^{-1}	2.11 x10^{-1}	1.90 x10^{-1}
Del_3	2.43 x10^{-1}	-2.20 x10^{-1}	4.34 x10^{-1}	1.48 x10^{-1}	3.38 x10^{-2}*	4.76 x10^{-1}	9.15 x10^{-2}	2.55 x10^{-1}
Pr_3	2.37 x10^{-1}	-2.23 x10^{-1}	7.18 x10^{-1}	6.89 x10^{-2}	2.91 x10^{-2}*	4.88 x10^{-1}	1.35 x10^{-2}*	3.66 x10^{-1}
$oDel_2$	7.35 x10^{-1}	6.45 x10^{-2}	4.33 x10^{-1}	1.49 x10^{-1}	2.14 x10^{-2}*	5.11 x10^{-1}	2.50 x10^{-1}	1.75 x10^{-1}
oPr_2	9.39 x10^{-1}	1.47 x10^{-2}	6.87 x10^{-1}	7.67 x10^{-2}	1.02 x10^{-1}	3.77 x10^{-1}	1.50 x10^{-1}	2.18 x10^{-1}

Table A-4: *Continued*

PRArea	1.15 x10^{-1}	-2.94 x10^{-1}	3.20 x10^{-1}	-1.88 x10^{-1}	1.99 x10^{-1}	-3 x10^{-1}	6.41 x10^{-2}	-2.78 x10^{-1}
Norm Area	7.46 x10^{-1}	-6.18 x10^{-2}	3.95 x10^{-1}	1.61 x10^{-1}	5.16 x10^{-6}*	8.33 x10^{-1}	6.52 x10^{-7}*	6.64 x10^{-1}

The table below shows the Pearson's correlation between CO_2 and the CBFV metrics in nocturnal sleep apnea study.

Table A-5 Pearson's Correlation of Delta $ETCO_2$ and $ETCO_2$ with CBFV metrics in nocturnal sleep apnea study

	Pearson			
	$ETCO_2$		Del $ETCO_2$	
	p	r	p	r
Slope	4.80 x10^{-1}	6.15 x10^{-2}	1.20 x10^{-2}*	-2.16 x10^{-1}
Del_1	2.34 x10^{-3}*	2.61 x10^{-1}	6.10 x10^{-3}*	-2.36 x10^{-1}
PR_1	1.38 x10^{-2}*	2.12 x10^{-1}	2.48 x10^{-2}*	-1.94 x10^{-1}
Del_2	3.11 x10^{-1}	8.82 x10^{-2}	4.61 x10^{-1}	-6.42 x10^{-2}
Pr_2	7.69 x10^{-1}	2.56 x10^{-2}	6.40 x10^{-3}*	2.34 x10^{-1}
Del_3	5.13 x10^{-1}	5.71 x10^{-2}	1.37 x10^{-1}	-1.29 x10^{-1}
Pr_3	8.93 x10^{-1}	1.18 x10^{-2}	5.97 x10^{-2}	1.63 x10^{-1}
$oDel_2$	2.48 x10^{-1}	1 x10^{-1}	1.51 x10^{-1}	-1.25 x10^{-1}
oPr_2	8.44 x10^{-1}	1.72 x10^{-2}	4.37 x10^{-2}*	1.75 x10^{-1}
PRArea	7.76 x10^{-1}	2.48 x10^{-2}	2.25 x10^{-3}*	-2.62 x10^{-1}
Norm Area	4.50 x10^{-1}	6.59 x10^{-2}	7.45 x10^{-1}	2.84 x10^{-2}

Appendix B

RESULTS FROM KENDALL'S RANK CORRELATION AND SPEARMAN'S RANK-ORDER CORRELATION IN SIMULATED APNEA STUDY

The table below shows the correlation between $ETCO_2$ and the CBFV metrics under Kendall and Spearman's method for Group 1 and Group 2.

Table B-1 Kendall's correlation between $ETCO_2$ and CBFV metrics for Group 1

	Kendall							
	SiA		SiB		SuA		SuB	
	p	τ	p	τ	p	τ	p	τ
Slope	3.89 $x10^{-1}$	7.68 $x10^{-2}$	1.95 $x10^{-1}$	1.11 $x10^{-1}$	9.77 $x10^{-1}$	-4.04 $x10^{-3}$	1.06 $x10^{-1}$	-1.93 $x10^{-1}$
Del_1	3.62 $x10^{-1}$	8.14 $x10^{-2}$	3.68 $x10^{-1}$	7.69 $x10^{-2}$	9.30 $x10^{-1}$	-1.01 $x10^{-2}$	1.57 $x10^{-1}$	-1.70 $x10^{-1}$
PR_1	6.51 $x10^{-1}$	4.07 $x10^{-2}$	6.14 $x10^{-1}$	4.33 $x10^{-2}$	5.66 $x10^{-1}$	-6.06 $x10^{-2}$	7.57 $x10^{-4}$*	-3.92 $x10^{-1}$
Del_2	3.29 $x10^{-1}$	8.70 $x10^{-2}$	8.96 $x10^{-1}$	1.15 $x10^{-2}$	7.93 $x10^{-1}$	-2.83 $x10^{-2}$	7.81 $x10^{-2}$	-2.10 $x10^{-1}$
Pr_2	9.24 $x10^{-1}$	-9.04 $x10^{-3}$	1.28 $x10^{-1}$	-1.30 $x10^{-1}$	4.04 $x10^{-2}$*	-2.12 $x10^{-1}$	2.97 $x10^{-3}$*	-3.48 $x10^{-1}$
Del_3	4.48 $x10^{-1}$	6.78 $x10^{-2}$	3.93 $x10^{-1}$	7.31 $x10^{-2}$	7.78 $x10^{-1}$	3.03 $x10^{-2}$	1.65 $x10^{-1}$	-1.66 $x10^{-1}$
Pr_3	5.88 $x10^{-1}$	4.86 $x10^{-2}$	6.38 $x10^{-1}$	4.04 $x10^{-2}$	7.04 $x10^{-1}$	-4.04 $x10^{-2}$	2.97 $x10^{-3}$*	-3.48 $x10^{-1}$
$oDel_2$	3.55 $x10^{-1}$	8.25 $x10^{-2}$	8.43 $x10^{-1}$	1.73 $x10^{-2}$	9.61 $x10^{-1}$	-6.06 $x10^{-3}$	8.32 $x10^{-2}$	-2.07 $x10^{-1}$
oPr_2	7.84 $x10^{-1}$	-2.49 $x10^{-2}$	1.69 $x10^{-1}$	-1.17 $x10^{-1}$	4.04 $x10^{-2}$*	-2.12 $x10^{-1}$	9.45 $x10^{-4}$*	-3.85 $x10^{-1}$

Table B-1:*Continued*

PRArea	4.48 x10^{-1}	6.78 x10^{-2}	8.96 x10^{-1}	1.15 x10^{-2}	3.16 x10^{-1}	-1.05 x10^{-1}	1.62 x10^{-2}*	-2.84 x10^{-1}
Norm Area	7.35 x10^{-1}	3.05 x10^{-2}	8.79 x10^{-1}	1.35 x10^{-2}	6.90 x10^{-1}	-4.24 x10^{-2}	2.46 x10^{-1}	1.39 x10^{-1}

Table B-2 Spearman's correlation between $ETCO_2$ and CBFV metrics for Group 1

	Spearman							
	SiA		SiB		SuA		SuB	
	p	ρ	p	ρ	p	ρ	p	ρ
Slope	5.11 x10^{-1}	8.64 x10^{-2}	1.14 x10^{-1}	1.98 x10^{-1}	9.61 x10^{-1}	7.51 x10^{-3}	1.18 x10^{-1}	-2.69 x10^{-1}
Del_1	3.82 x10^{-1}	1.15 x10^{-1}	4.03 x10^{-1}	1.05 x10^{-1}	1	0	1.44 x10^{-1}	-2.52 x10^{-1}
PR_1	6.87 x10^{-1}	5.29 x10^{-2}	4.82 x10^{-1}	8.86 x10^{-2}	6.36 x10^{-1}	-7.23 x10^{-2}	1.63 x10^{-4}*	-6.04 x10^{-1}
Del_2	3.40 x10^{-1}	1.25 x10^{-1}	9.83 x10^{-1}	2.71 x10^{-3}	8.38 x10^{-1}	-3.14 x10^{-2}	1.09 x10^{-1}	-2.76 x10^{-1}
Pr_2	9.28 x10^{-1}	-1.19 x10^{-2}	1.36 x10^{-1}	-1.87 x10^{-1}	5.54 x10^{-2}	-2.88 x10^{-1}	1.58 x10^{-3}*	-5.20 x10^{-1}
Del_3	4.68 x10^{-1}	9.53 x10^{-2}	4.13 x10^{-1}	1.03 x10^{-1}	7.19 x10^{-1}	5.51 x10^{-2}	1.37 x10^{-1}	-2.57 x10^{-1}
Pr_3	6.56 x10^{-1}	5.85 x10^{-2}	5.15 x10^{-1}	8.20 x10^{-2}	7.66 x10^{-1}	-4.55 x10^{-2}	8.98 x10^{-4}*	-5.43 x10^{-1}

Table B-2: *Continued*

$oDel_2$	3.56 x10^{-1}	1.21 x10^{-1}	9.45 x10^{-1}	8.65 x10^{-3}	9.50 x10^{-1}	-9.62 x10^{-3}	1.03 x10^{-1}	-2.80 x10^{-1}
oPr_2	8.69 x10^{-1}	-2.17 x10^{-2}	1.69 x10^{-1}	-1.73 x10^{-1}	4.05 x10^{-2}*	-3.07 x10^{-1}	6.98 x10^{-4}*	-5.53 x10^{-1}
PRArea	5.57 x10^{-1}	7.71 x10^{-2}	7.92 x10^{-1}	3.33 x10^{-2}	4.01 x10^{-1}	-1.28 x10^{-1}	6.92 x10^{-3}*	-4.52 x10^{-1}
Norm Area	3.66 x10^{-1}	1.19 x10^{-1}	5.20 x10^{-1}	8.11 x10^{-2}	7.18 x10^{-1}	-5.52 x10^{-2}	2.68 x10^{-1}	1.92 x10^{-1}

Table B-3 Kendall's correlation between $ETCO_2$ and CBFV metrics for Group 2

	Kendall							
	SiA		SiB		SuA		SuB	
	p	τ	p	τ	p	τ	p	τ
Slope	3.76E-01	-1.17E-01	6.71E-01	-5.75E-02	6.77E-01	7.37E-02	5.27E-01	6.67E-02
Del_1	2.71E-01	-1.45E-01	5.01E-01	8.97E-02	6.38E-02	3.05E-01	3.55E-01	9.70E-02
PR_1	5.47E-01	-8.05E-02	1.00E+00	2.30E-03	7.40E-02	2.95E-01	3.97E-01	8.89E-02
Del_2	2.71E-01	-1.45E-01	8.32E-01	2.99E-02	2.33E-01	2.00E-01	1.16E-01	1.64E-01
Pr_2	7.50E-01	-4.37E-02	9.16E-01	1.61E-02	3.86E-01	1.47E-01	2.62E-01	1.17E-01

Table B-3: *Continued*

Del_3	4.91E-02*	-2.55E-01	3.95E-01	1.13E-01	9.83E-02	2.74E-01	3.16E-01	1.05E-01
Pr_3	2.14E-01	-1.63E-01	7.50E-01	4.37E-02	1.13E-01	2.63E-01	3.65E-01	9.49E-02
$oDel_2$	1.77E-01	-1.77E-01	5.71E-01	7.59E-02	7.40E-02	2.95E-01	8.69E-02	1.78E-01
oPr_2	4.15E-01	-1.08E-01	9.16E-01	1.61E-02	7.40E-02	2.95E-01	1.07E-01	1.68E-01
PRArea	1.43E-02*	-3.15E-01	8.88E-01	2.07E-02	6.77E-01	7.37E-02	7.02E-02	-1.88E-01
Norm Area	6.20E-01	-6.67E-02	4.12E-02*	2.64E-01	7.40E-02	2.95E-01	1.25E-03*	3.29E-01

Table B-4 Spearman's correlation between ETCO2 and CBFV metrics for Group 2

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	Spearman							
	SiA		SiB		SuA		SuB	
	p	ρ	p	ρ	p	ρ	p	ρ
Slope	5.11 x10^{-1}	-1.24 x10^{-1}	6.89 x10^{-1}	-7.59 x10^{-2}	9.77 x10^{-1}	-7.52 x10^{-3}	6.72 x10^{-1}	6.47 x10^{-2}
Del_1	1.99 x10^{-1}	-2.41 x10^{-1}	4.34 x10^{-1}	1.48 x10^{-1}	1.20 x10^{-1}	3.59 x10^{-1}	2.66 x10^{-1}	1.69 x10^{-1}
PR_1	4.53 x10^{-1}	-1.42 x10^{-1}	9.66 x10^{-1}	8.23 x10^{-3}	1.03 x10^{-1}	3.76 x10^{-1}	4.35 x10^{-1}	1.19 x10^{-1}

Table B-4: *Continued*

Del_2	2.98 $x10^{-1}$	-1.96 $x10^{-1}$	8.22 $x10^{-1}$	4.29 $x10^{-2}$	3.34 $x10^{-1}$	2.27 $x10^{-1}$	1.22 $x10^{-1}$	2.34 $x10^{-1}$
Pr_2	7.55 $x10^{-1}$	-5.94 $x10^{-2}$	9.72 $x10^{-1}$	-6.90 $x10^{-3}$	3.68 $x10^{-1}$	2.12 $x10^{-1}$	2.47 $x10^{-1}$	1.76 $x10^{-1}$
Del_3	4.60 $x10^{-2}$*	-3.68 $x10^{-1}$	3.84 $x10^{-1}$	1.64 $x10^{-1}$	1.99 $x10^{-1}$	2.99 $x10^{-1}$	2.66 $x10^{-1}$	1.69 $x10^{-1}$
Pr_3	2.07 $x10^{-1}$	-2.37 $x10^{-1}$	7.51 $x10^{-1}$	6.03 $x10^{-2}$	1.97 $x10^{-1}$	3.01 $x10^{-1}$	4.16 $x10^{-1}$	1.24 $x10^{-1}$
$oDel_2$	1.67 $x10^{-1}$	-2.59 $x10^{-1}$	6.33 $x10^{-1}$	9.05 $x10^{-2}$	1 $x10^{-1}$	3.79 $x10^{-1}$	1.01 $x10^{-1}$	2.48 $x10^{-1}$
oPr_2	4.83 $x10^{-1}$	-1.33 $x10^{-1}$	9.14 $x10^{-1}$	2.07 $x10^{-2}$	6.48 $x10^{-2}$	4.23 $x10^{-1}$	1.50 $x10^{-1}$	2.18 $x10^{-1}$
PRArea	1.77 $x10^{-2}$*	-4.33 $x10^{-1}$	8.23 $x10^{-1}$	4.25 $x10^{-2}$	5.94 $x10^{-1}$	1.26 $x10^{-1}$	6.77 $x10^{-2}$	-2.75 $x10^{-1}$
Norm Area	6.70 $x10^{-1}$	-8.08 $x10^{-2}$	4.72 $x10^{-2}$*	3.66 $x10^{-1}$	1.01 $x10^{-2}$*	5.68 $x10^{-1}$	7.39 $x10^{-4}$*	4.90 $x10^{-1}$

The table below shows the correlation between Delta $ETCO_2$ and the CBFV metrics under Kendall and Spearman's method for Group 1 and Group 2.

Table B-5 Kendall's correlation between Delta $ETCO_2$ and CBFV metrics for Group 1

	Kendall							
	SiA		SiB		SuA		SuB	
	p	τ	p	τ	p	τ	p	τ
Slope	4.33 x10^{-1}	7.01 x10^{-2}	6.47 x10^{-1}	3.94 x10^{-2}	5.93 x10^{-1}	-5.66 x10^{-2}	3.09 x10^{-1}	-1.23 x10^{-1}
Del_1	3.89 x10^{-1}	7.68 x10^{-2}	7.90 x10^{-1}	2.31 x10^{-2}	5.79 x10^{-1}	-5.86 x10^{-2}	6.72 x10^{-1}	-5.21 x10^{-2}
PR_1	2.23 x10^{-1}	1.08 x10^{-1}	4.65 x10^{-1}	6.25 x10^{-2}	9.77 x10^{-1}	-4.04 x10^{-3}	1.33 x10^{-1}	-1.80 x10^{-1}
Del_2	9.34 x10^{-1}	7.91 x10^{-3}	4.31 x10^{-1}	-6.73 x10^{-2}	1.30 x10^{-1}	-1.58 x10^{-1}	4.46 x10^{-1}	-9.24 x10^{-2}
Pr_2	4.63 x10^{-1}	-6.55 x10^{-2}	3.47 x10^{-2}*	-1.80 x10^{-1}	3.67 x10^{-2}*	-2.16 x10^{-1}	6.05 x10^{-2}	-2.24 x10^{-1}
Del_3	4.48 x10^{-1}	6.78 x10^{-2}	8.79 x10^{-1}	1.35 x10^{-2}	6.62 x10^{-1}	-4.65 x10^{-2}	8.66 x10^{-1}	-2.18 x10^{-2}
Pr_3	1.18 x10^{-1}	1.39 x10^{-1}	7.04 x10^{-1}	3.27 x10^{-2}	9.15 x10^{-1}	-1.21 x10^{-2}	3.09 x10^{-1}	-1.23 x10^{-1}
$oDel_2$	7.94 x10^{-1}	2.37 x10^{-2}	3.44 x10^{-1}	-8.08 x10^{-2}	9.07 x10^{-2}	-1.76 x10^{-1}	3.97 x10^{-1}	-1.03 x10^{-1}
oPr_2	5.97 x10^{-1}	-4.75 x10^{-2}	2.85 x10^{-2}*	-1.87 x10^{-1}	3.76 x10^{-3}*	-2.97 x10^{-1}	6.46 x10^{-2}	-2.20 x10^{-1}
PRArea	9.24 x10^{-1}	9.04 x10^{-3}	2.80 x10^{-1}	-9.23 x10^{-2}	1.78 x10^{-3}*	-3.19 x10^{-1}	8.44 x10^{-1}	-2.52 x10^{-2}

Table B-5: *Continued*

Norm Area	5.36 x10^{-1}	-5.54 x10^{-2}	9.68 x10^{-1}	-3.85 x10^{-3}	9.92 x10^{-1}	2.02 x10^{-3}	3.66 x10^{-1}	1.09 x10^{-1}

Table B-6 Spearman's correlation between Delta $ETCO_2$ and CBFV metrics for Group 1

	Spearman							
	SiA		SiB		SuA		SuB	
	p	ρ	p	ρ	p	ρ	p	ρ
Slope	4.10 x10^{-1}	1.08 x10^{-1}	5.51 x10^{-1}	7.52 x10^{-2}	3.42 x10^{-1}	-1.45 x10^{-1}	2.73 x10^{-1}	-1.90 x10^{-1}
Del_1	3.92 x10^{-1}	1.12 x10^{-1}	7.80 x10^{-1}	3.53 x10^{-2}	5.22 x10^{-1}	-9.76 x10^{-2}	7.45 x10^{-1}	-5.69 x10^{-2}
PR_1	2.28 x10^{-1}	1.58 x10^{-1}	4.28 x10^{-1}	9.98 x10^{-2}	8.95 x10^{-1}	2.03 x10^{-2}	1.26 x10^{-1}	-2.63 x10^{-1}
Del_2	9.03 x10^{-1}	1.60 x10^{-2}	4.22 x10^{-1}	-1.01 x10^{-1}	6.78 x10^{-2}	-2.75 x10^{-1}	4.87 x10^{-1}	-1.21 x10^{-1}
Pr_2	3.71 x10^{-1}	-1.17 x10^{-1}	2.40 x10^{-2}*	-2.80 x10^{-1}	2.72 x10^{-2}*	-3.30 x10^{-1}	4.93 x10^{-2}*	-3.36 x10^{-1}
Del_3	4.32 x10^{-1}	1.03 x10^{-1}	8.24 x10^{-1}	2.81 x10^{-2}	5.70 x10^{-1}	-8.67 x10^{-2}	9.02 x10^{-1}	-2.16 x10^{-2}
Pr_3	1.25 x10^{-1}	2 x10^{-1}	6.52 x10^{-1}	5.69 x10^{-2}	9.61 x10^{-1}	7.51 x10^{-3}	2.32 x10^{-1}	-2.07 x10^{-1}
$oDel_2$	8.06 x10^{-1}	3.23 x10^{-2}	3.71 x10^{-1}	-1.13 x10^{-1}	5.59 x10^{-2}	-2.87 x10^{-1}	3.89 x10^{-1}	-1.50 x10^{-1}

Table B-6: *Continued*

oPr_2	6.68 $x10^{-1}$	-5.63 $x10^{-2}$	2.65 $x10^{-2}$*	-2.76 $x10^{-1}$	3.90 $x10^{-3}$*	-4.25 $x10^{-1}$	6.84 $x10^{-2}$	-3.12 $x10^{-1}$
PRArea	8.74 $x10^{-1}$	2.08 $x10^{-2}$	2.80 $x10^{-1}$	-1.36 $x10^{-1}$	3.40 $x10^{-4}$*	-5.17 $x10^{-1}$	7.94 $x10^{-1}$	-4.57 $x10^{-2}$
Norm Area	5.61 $x10^{-1}$	-7.64 $x10^{-2}$	8.65 $x10^{-1}$	2.15 $x10^{-2}$	9.01 $x10^{-1}$	1.90 $x10^{-2}$	3.19 $x10^{-1}$	1.73 $x10^{-1}$

Table B-7 Kendall's correlation between Delta $ETCO_2$ and CBFV metrics for Group 2

	Kendall							
	SiA		SiB		SuA		SuB	
	p	τ	p	τ	p	τ	p	τ
Slope	9.16 $x10^{-1}$	1.61 $x10^{-2}$	5.96 $x10^{-1}$	7.13 $x10^{-2}$	2.88 $x10^{-1}$	1.79 $x10^{-1}$	1.88 $x10^{-1}$	-1.37 $x10^{-1}$
Del_1	1	-2.30 $x10^{-3}$	3.76 $x10^{-1}$	1.17 $x10^{-1}$	1.11 $x10^{-2}$*	4.11 $x10^{-1}$	2.88 $x10^{-1}$	1.11 $x10^{-1}$
PR_1	7.24 $x10^{-1}$	-4.83 $x10^{-2}$	7.77 $x10^{-1}$	3.91 $x10^{-2}$	1.35 $x10^{-2}$*	4 $x10^{-1}$	2.54 $x10^{-1}$	1.19 $x10^{-1}$
Del_2	2.71 $x10^{-1}$	1.45 $x10^{-1}$	3.21 $x10^{-1}$	1.31 $x10^{-1}$	6.38 $x10^{-2}$	3.05 $x10^{-1}$	5.40 $x10^{-1}$	6.46 $x10^{-2}$
Pr_2	4.57 $x10^{-1}$	9.89 $x10^{-2}$	3.04 $x10^{-1}$	1.36 $x10^{-1}$	1.28 $x10^{-1}$	2.53 $x10^{-1}$	8.08 $x10^{-1}$	2.63 $x10^{-2}$
Del_3	4.36 $x10^{-1}$	-1.03 $x10^{-1}$	5.24 $x10^{-1}$	8.51 $x10^{-2}$	1.98 $x10^{-2}$*	3.79 $x10^{-1}$	1.94 $x10^{-1}$	1.35 $x10^{-1}$

Table B-7: *Continued*

Pr_3	3.95×10^{-1}	-1.13×10^{-1}	6.97×10^{-1}	5.29×10^{-2}	2.37×10^{-2}*	3.68×10^{-1}	1.51×10^{-1}	1.49×10^{-1}
$oDel_2$	4.36×10^{-1}	1.03×10^{-1}	2.27×10^{-1}	1.59×10^{-1}	1.35×10^{-2}*	4×10^{-1}	3.06×10^{-1}	1.07×10^{-1}
oPr_2	5.96×10^{-1}	7.13×10^{-2}	3.38×10^{-1}	1.26×10^{-1}	7.40×10^{-2}	2.95×10^{-1}	5.14×10^{-1}	6.87×10^{-2}
PRArea	3.44×10^{-2}*	-2.74×10^{-1}	4.57×10^{-1}	-9.89×10^{-2}	9.74×10^{-1}	-1.05×10^{-2}	1.40×10^{-1}	-1.54×10^{-1}
Norm Area	1	2.30×10^{-3}	4.57×10^{-1}	9.89×10^{-2}	1.35×10^{-2}*	4×10^{-1}	1.25×10^{-6}*	4.81×10^{-1}

Table B-8 Spearman's correlation between Delta $ETCO_2$ and CBFV metrics for Group 2

	Spearman							
	SiA		SiB		SuA		SuB	
	p	ρ	p	ρ	p	ρ	p	ρ
Slope	8.53×10^{-1}	3.54×10^{-2}	5.45×10^{-1}	1.15×10^{-1}	4.80×10^{-1}	1.67×10^{-1}	2.69×10^{-1}	-1.68×10^{-1}
Del_1	7.49×10^{-1}	-6.07×10^{-2}	4.32×10^{-1}	1.48×10^{-1}	1.51×10^{-2}*	5.41×10^{-1}	2.74×10^{-1}	1.66×10^{-1}
PR_1	4.78×10^{-1}	-1.34×10^{-1}	7.02×10^{-1}	7.27×10^{-2}	1.26×10^{-2}*	5.53×10^{-1}	1.68×10^{-1}	2.09×10^{-1}
Del_2	4.94×10^{-1}	1.29×10^{-1}	3.59×10^{-1}	1.73×10^{-1}	9.46×10^{-2}	3.85×10^{-1}	5.34×10^{-1}	9.49×10^{-2}

Table B-8: *Continued*

Pr_2	5.40 x10^{-1}	1.16 x10^{-1}	3.15 x10^{-1}	1.89 x10^{-1}	1.66 x10^{-1}	3.22 x10^{-1}	7.84 x10^{-1}	4.19 x10^{-2}
Del_3	3.86 x10^{-1}	-1.64 x10^{-1}	4.90 x10^{-1}	1.31 x10^{-1}	2.92 x10^{-2}*	4.92 x10^{-1}	1.74 x10^{-1}	2.06 x10^{-1}
Pr_3	2.90 x10^{-1}	-1.99 x10^{-1}	6 x10^{-1}	9.94 x10^{-2}	3.15 x10^{-2}*	4.86 x10^{-1}	7.64 x10^{-2}	2.67 x10^{-1}
$oDel_2$	6.03 x10^{-1}	9.86 x10^{-2}	3.13 x10^{-1}	1.90 x10^{-1}	2.01 x10^{-2}*	5.20 x10^{-1}	3.77 x10^{-1}	1.35 x10^{-1}
oPr_2	6.64 x10^{-1}	8.25 x10^{-2}	3.90 x10^{-1}	1.62 x10^{-1}	6.68 x10^{-2}	4.20 x10^{-1}	5.92 x10^{-1}	8.18 x10^{-2}
PRArea	4.92 x10^{-2}*	-3.63 x10^{-1}	4.97 x10^{-1}	-1.28 x10^{-1}	9.32 x10^{-1}	2.11 x10^{-2}	7.13 x10^{-2}	-2.72 x10^{-1}
Norm Area	8.69 x10^{-1}	-3.14 x10^{-2}	4.48 x10^{-1}	1.43 x10^{-1}	2 x10^{-3}*	6.60 x10^{-1}	7.96 x10^{-7}*	6.77 x10^{-1}

Appendix C

RESULTS FROM KENDALL'S RANK CORRELATION AND SPEARMAN'S RANK-ORDER CORRELATION IN NOCTURNAL SLEEP APNEA STUDY

The table below shows the correlation between CO_2 metrics and the CBFV metrics under Kendall and Spearman's method in nocturnal sleep apnea study.

Table C-1 Kendall's correlation between CO_2 and CBFV metrics

	Kendall			
	$ETCO_2$		Delta $ETCO_2$	
	p	τ	p	τ
Slope	8.22×10^{-1}	-1.32×10^{-2}	2.67×10^{-2}*	-1.29×10^{-1}
Del_1	2.34×10^{-1}	6.96×10^{-2}	3.25×10^{-3}*	-1.72×10^{-1}
PR_1	1.85×10^{-1}	7.74×10^{-2}	7.25×10^{-3}*	-1.57×10^{-1}
Del_2	5.50×10^{-1}	3.50×10^{-2}	3.19×10^{-1}	-5.82×10^{-2}
Pr_2	6.18×10^{-1}	2.92×10^{-2}	7.86×10^{-3}*	1.55×10^{-1}
Del_3	7.77×10^{-1}	-1.66×10^{-2}	1.25×10^{-1}	-8.97×10^{-2}
Pr_3	9.43×10^{-1}	-4.26×10^{-3}	2.15×10^{-1}	7.24×10^{-2}
$oDel_2$	6.37×10^{-1}	2.76×10^{-2}	2.18×10^{-1}	-7.19×10^{-2}
oPr_2	5.24×10^{-1}	3.73×10^{-2}	3.47×10^{-2}*	1.23×10^{-1}
PRArea	7.48×10^{-1}	-1.89×10^{-2}	1.26×10^{-5}*	-2.55×10^{-1}
Norm Area	5.60×10^{-1}	3.41×10^{-2}	9.42×10^{-1}	-4.38×10^{-3}

Table C-2 Spearman's correlation between CO_2 and CBFV metrics

	Spearman			
	$ETCO_2$		Del $ETCO_2$	
	p	ρ	p	ρ
Slope	9.17×10^{-1}	-9.09×10^{-3}	2.86×10^{-2}*	-1.89×10^{-1}
Del_1	2.23×10^{-1}	1.06×10^{-1}	3.89×10^{-3}*	-2.48×10^{-1}

Table C-2: *Continued*

PR_1	1.59×10^{-1}	1.22×10^{-1}	9.22×10^{-3}*	-2.25×10^{-1}
Del_2	5.80×10^{-1}	4.82×10^{-2}	3.21×10^{-1}	-8.62×10^{-2}
Pr_2	6.32×10^{-1}	4.17×10^{-2}	8.13×10^{-3}*	2.28×10^{-1}
Del_3	7.52×10^{-1}	-2.75×10^{-2}	1.31×10^{-1}	-1.31×10^{-1}
Pr_3	9.87×10^{-1}	1.38×10^{-3}	1.79×10^{-1}	1.17×10^{-1}
$oDel_2$	6.37×10^{-1}	4.11×10^{-2}	2.01×10^{-1}	-1.11×10^{-1}
oPr_2	6.10×10^{-1}	4.44×10^{-2}	4.09×10^{-2}*	1.77×10^{-1}
PRArea	8.54×10^{-1}	-1.60×10^{-2}	1.54×10^{-5}*	-3.66×10^{-1}
Norm Area	5.48×10^{-1}	5.23×10^{-2}	9.37×10^{-1}	-6.87×10^{-3}

Appendix D

ANOVA TABLE FOR CO_2 AND CBFV IN THE SIMULATED SLEEP APNEA STUDY

The tables below shows the ANOVA tables for the CO_2 metrics in the simulated sleep apnea study for both groups.

Table D-1 $ETCO_2$ ANOVA Table for Group 1

	$ETCO_2$				
Source	SS	Df	MS	F	Prob>F
Groups	3.33×10^{1}	3	11.1	3.42×10^{-1}	7.95×10^{-1}
Error	6.54×10^{3}	2.01×10^{2}	32.5		
Total	6.57×10^{3}	2.04×10^{2}			

Table D-2 Delta $ETCO_2$ ANOVA Table for Group 1

	Delta $ETCO_2$				
Source	SS	df	MS	F	Prob>F
Groups	22.6	3	7.53	4.73×10^{-1}	7.01×10^{-1}
Error	3.20×10^{3}	2.01×10^{2}	15.9		
Total	3.22×10^{3}	2.04×10^{2}			

Table D-3 $ETCO_2$ ANOVA Table for Group 2

	$ETCO_2$				
Source	SS	Df	MS	F	Prob>F
Groups	163	3	54.4	2.62	5.40×10^{-2}
Error	2.51×10^{3}	121	20.8		
Total	2.68×10^{3}	124			

Table D-4 Delta $ETCO_2$ ANOVA Table for Group 2

	Delta $ETCO_2$				
Source	SS	df	MS	F	Prob>F
Groups	126	3	42.1	2.90	3.77×10^{-2}*
Error	1.76×10^{3}	121	14.5		
Total	1.88×10^{3}	124			

The tables below shows the ANOVA tables for the CBFV metrics in the simulated sleep apnea study for both groups.

Table D-5 Slope ANOVA Table for Group 1

	Slope				
Source	SS	Df	MS	F	Prob>F
Groups	2.29×10^{-1}	3	7.63×10^{-2}	2.82×10^{-1}	8.39×10^{-1}
Error	54.4	201	2.71×10^{-1}		
Total	54.7	204			

Table D-6 Del_1 ANOVA Table for Group 1

	Del_1				
Source	SS	Df	MS	F	Prob>F
Groups	567	3	189	7.17×10^{-1}	5.43×10^{-1}
Error	5.30×10^{4}	201	264		
Total	5.35×10^{4}	204			

Table D-7 PR_1 ANOVA Table for Group 1

	PR_1				
Source	SS	Df	MS	F	Prob>F
Groups	1.18×10^{3}	3	393	1.67	1.75×10^{-1}
Error	4.74×10^{4}	201	236		
Total	4.85×10^{4}	204			

Table D-8 Del_2 ANOVA Table for Group 1

	Del_2				
Source	SS	Df	MS	F	Prob>F
Groups	449	3	150	5.76×10^{-1}	6.32×10^{-1}
Error	5.23×10^{4}	201	260		
Total	5.27×10^{4}	204			

Table D-9 PR_2 ANOVA Table for Group 1

	PR_2				
Source	SS	Df	MS	F	Prob>F
Groups	1.38×10^{3}	3	459	1.87	1.36×10^{-1}
Error	4.94×10^{4}	201	246		
Total	5.08×10^{4}	204			

Table D-10 Del_3 ANOVA Table for Group 1

	Del_3				
Source	SS	Df	MS	F	Prob>F
Groups	870	3	290	1.16	3.27×10^{-1}
Error	5.04×10^{4}	201	251		
Total	5.12×10^{4}	204			

Table D-11 PR_3 ANOVA Table for Group 1

	PR_3				
Source	SS	Df	MS	F	Prob>F
Groups	1.84×10^{3}	3	613	2.31	7.76×10^{-2}
Error	5.34×10^{4}	201	265		
Total	5.52×10^{4}	204			

Table D-12 $oDel_2$ ANOVA Table for Group 1

	$oDel_2$				
Source	SS	Df	MS	F	Prob>F
Groups	256	3	85.4	2.82×10^{-1}	8.38×10^{-1}
Error	6.08×10^{4}	201	302		
Total	6.10×10^{4}	204			

Table D-13 oPR_2 ANOVA Table for Group 1

	oPR_2				
Source	SS	df	MS	F	Prob>F
Groups	965	3	322	1.06	3.67×10^{-1}
Error	6.10×10^{4}	201	303		
Total	6.19×10^{4}	204			

Table D-14 PRArea ANOVA Table for Group 1

	PRArea				
Source	SS	df	MS	F	Prob>F
Groups	2.47×10^{3}	3	823	7.38×10^{-1}	5.30×10^{-1}
Error	2.24×10^{5}	201	1.12×10^{3}		
Total	2.27×10^{5}	204			

Table D-15 Norm Area ANOVA Table for Group 1

	Norm Area				
Source	SS	df	MS	F	Prob>F
Groups	5.96	3	1.99	5.73	8.81×10^{-4}*
Error	69.7	201	3.47×10^{-1}		
Total	75.6	204			

Table D-16 Slope ANOVA Table for Group 2

	Slope				
Source	SS	Df	MS	F	Prob>F
Groups	2.85	3	9.51×10^{-1}	7.15	1.83×10^{-4}*
Error	16.1	121	1.33×10^{-1}		
Total	18.9	124			

Table D-17 Del_1 ANOVA Table for Group 2

	Del_1				
Source	SS	Df	MS	F	Prob>F
Groups	1.70×10^{3}	3	565	5.08	2.41×10^{-3}*
Error	1.35×10^{4}	121	111		
Total	1.52×10^{4}	124			

Table D-18 PR_1 ANOVA Table for Group 2

	PR_1				
Source	SS	Df	MS	F	Prob>F
Groups	884	3	295	9.95×10^{-1}	3.98×10^{-1}
Error	3.58×10^{4}	121	296		
Total	3.67×10^{4}	124			

Table D-19 Del_2 ANOVA Table for Group 2

	Del_2				
Source	SS	Df	MS	F	Prob>F
Groups	1.06×10^{3}	3	352	3.72	1.33×10^{-2}*
Error	1.14×10^{4}	121	94.5		
Total	1.25×10^{4}	124			

Table D-20 PR_2 ANOVA Table for Group 2

	PR_2				
Source	SS	Df	MS	F	Prob>F
Groups	478	3	159	6.32×10^{-1}	5.96×10^{-1}
Error	3.05×10^{4}	121	252		
Total	3.09×10^{4}	124			

Table D-21 Del_3 ANOVA Table for Group 2

	Del_3				
Source	SS	Df	MS	F	Prob>F
Groups	2.19×10^{3}	3	730	7.83	8.04×10^{5}*
Error	1.13×10^{4}	121	93.2		
Total	1.35×10^{4}	124			

Table D-22 PR_3 ANOVA Table for Group 2

	PR_3				
Source	SS	df	MS	F	Prob>F
Groups	3.21×10^{3}	3	1.07×10^{3}	3.73	1.32×10^{-2}*
Error	3.47×10^{4}	121	287		
Total	3.79×10^{4}	124			

Table D-23 $oDel_2$ ANOVA Table for Group 2

	$oDel_2$				
Source	SS	df	MS	F	Prob>F
Groups	1.72×10^{3}	3	573	6.19	5.97×10^{-4}*
Error	1.12×10^{4}	121	92.6		
Total	1.29×10^{4}	124			

Table D-24 oPR_2 ANOVA Table for Group 2

	oPR_2				
Source	SS	df	MS	F	Prob>F
Groups	1.65×10^{3}	3	549	2.19	9.29×10^{-2}
Error	3.03×10^{4}	121	251		
Total	3.20×10^{4}	124			

Table D-25 PRArea ANOVA Table for Group 2

	PRArea				
Source	SS	df	MS	F	Prob>F
Groups	6.46×10^{3}	3	2.15×10^{3}	2.66	5.12×10^{-2}
Error	9.80×10^{4}	121	810		
Total	1.04×10^{5}	124			

Table D-26 Norm Area ANOVA Table for Group 2

	Norm Area				
Source	SS	df	MS	F	Prob>F
Groups	1.04	3	3.47×10^{-1}	1.97	1.22×10^{-1}
Error	21.2	121	1.76×10^{-1}		
Total	22.3	124			

Appendix E

ANOVA TABLE FOR CO_2 AND CBFV IN THE NOCTURNAL SLEEP APNEA STUDY

The tables below shows the ANOVA tables for the CO_2 metrics between the nocturnal sleep apnea study and simulated apnea study in both groups.

Table E-1 $ETCO_2$ ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	$ETCO_2$				
Source	SS	df	MS	F	Prob>F
Groups	378	2	189	7.39	7.87×10^{-4}*
Error	5.42×10^{3}	212	256		
Total	5.80×10^{3}	214			

Table E-2 Delta $ETCO_2$ ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	Delta $ETCO_2$				
Source	SS	df	MS	F	Prob>F
Groups	221	2	111	5.67	4.01×10^{-3}*
Error	4.14×10^{3}	212	19.5		
Total	4.36×10^{3}	214			

Table E-3 $ETCO_2$ ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	$ETCO_2$				
Source	SS	df	MS	F	Prob>F
Groups	922	2	461	19.7	1.61×10^{-8}*
Error	4.62×10^{3}	197	23.4		
Total	5.54×10^{3}	199			

Table E-4 Delta $ETCO_2$ ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	Delta $ETCO_2$				
Source	SS	df	MS	F	Prob>F
Groups	765	2	382	18.4	4.89×10^{-8}*
Error	4.10×10^{3}	197	20.8		
Total	4.87×10^{3}	199			

The tables below shows the ANOVA tables for the CBFV between the nocturnal sleep apnea study and simulated apnea study in both groups.

Table E-5 Slope ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	Slope				
Source	SS	df	MS	F	Prob>F
Groups	1.12×10^{-1}	2	5.62×10^{-2}	1.36×10^{-1}	8.73×10^{-1}
Error	87.9	212	4.15×10^{-1}		
Total	88	214			

Table E-6 Del_1 ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	Del_1				
Source	SS	df	MS	F	Prob>F
Groups	1.18×10^{4}	2	5.90×10^{3}	12.5	7.52×10^{-6}*
Error	1.00×10^{5}	212	473		
Total	1.12×10^{5}	214			

Table E-7 PR_1 ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	PR_1				
Source	SS	df	MS	F	Prob>F
Groups	1.22×10^4	2	6.10×10^3	9.01	1.75×10^{-4}*
Error	1.43×10^5	212	676		
Total	1.56×10^5	214			

Table E-8 Del_2 ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	Del_2				
Source	SS	df	MS	F	Prob>F
Groups	1.17×10^4	2	5.84×10^3	34.3	1.27×10^{-13}*
Error	3.61×10^4	212	170		
Total	4.78×10^4	214			

Table E-9 PR_2 ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	PR_2				
Source	SS	df	MS	F	Prob>F
Groups	4.63×10^{3}	2	2.32×10^{3}	6.70	1.51×10^{-3}*
Error	7.34×10^{4}	212	346		
Total	7.80×10^{4}	214			

Table E-10 Del_3 ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	Del_3				
Source	SS	df	MS	F	Prob>F
Groups	1.55×10^{4}	2	7.76×10^{3}	42.8	2.44×10^{-16}*
Error	3.84×10^{4}	212	181		
Total	5.40×10^{4}	214			

Table E-11 PR_3 ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	PR_3				
Source	SS	df	MS	F	Prob>F
Groups	1.30×10^4	2	6.49×10^3	23	8.97×10^{-10}*
Error	5.98×10^4	212	282		
Total	7.28×10^4	214			

Table E-12 $oDel_2$ ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	$oDel_2$				
Source	SS	df	MS	F	Prob>F
Groups	1.43×10^4	2	7.15×10^3	38	8.03×10^{-15}*
Error	3.99×10^4	212	188		
Total	5.42×10^4	214			

Table E-13 oPR_2 ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	oPR_2				
Source	SS	df	MS	F	Prob>F
Groups	7.84×10^3	2	3.92×10^3	10.6	4.09×10^{-5}*
Error	7.83×10^4	212	370		
Total	8.62×10^4	214			

Table E-14 PRArea ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	PRArea				
Source	SS	df	MS	F	Prob>F
Groups	2.42×10^{4}	2	1.21×10^{4}	8.98	1.81×10^{-4}*
Error	2.86×10^{5}	212	1.35×10^{3}		
Total	3.10×10^{5}	214			

Table E-15 Norm Area ANOVA Table between Nocturnal Sleep Apnea and Group 1 in Simulated Apnea

	Norm Area				
Source	SS	df	MS	F	Prob>F
Groups	42.8	2	21.4	70.8	2.86×10^{-24}*
Error	64.1	212	3.02×10^{-1}		
Total	107	214			

Table E-16 Slope ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	Slope				
Source	SS	df	MS	F	Prob>F
Groups	2.44	2	1.22	3	5.20×10^{-2}
Error	80	197	4.06×10^{-1}		
Total	82.4	199			

Table E-17 Del_1 ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	Del_1				
Source	SS	df	MS	F	Prob>F
Groups	594	2	297	6.73×10^{-1}	5.12×10^{-1}
Error	8.70×10^{4}	197	442		
Total	8.76×10^{4}	199			

Table E-18 PR_1 ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	PR_1				
Source	SS	Df	MS	F	Prob>F
Groups	813	2	406	6.11×10^{-1}	5.44×10^{-1}
Error	1.31×10^{5}	197	665		
Total	1.32×10^{5}	199			

Table E-19 Del_2 ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	Del_2				
Source	SS	df	MS	F	Prob>F
Groups	203	2	101	8.03×10^{-1}	4.49×10^{-1}
Error	2.49×10^{4}	197	126		
Total	2.51×10^{4}	199			

Table E-20 PR_2 ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	PR_2				
Source	SS	df	MS	F	Prob>F
Groups	271	2	136	3.98×10^{-1}	6.72×10^{-1}
Error	6.72×10^{4}	197	341		
Total	6.74×10^{4}	199			

Table E-21 Del_3 ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	Del_3				
Source	SS	df	MS	F	Prob>F
Groups	776	2	388	2.91	5.68×10^{-2}
Error	2.63×10^{4}	197	133		
Total	2.71×10^{4}	199			

Table E-22 PR_3 ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	PR_3				
Source	SS	df	MS	F	Prob>F
Groups	472	2	236	8.97×10^{-1}	4.10×10^{-1}
Error	5.19×10^{4}	197	263		
Total	5.23×10^{4}	199			

Table E-23 $oDel_2$ ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	$oDel_2$				
Source	SS	df	MS	F	Prob>F
Groups	437	2	218	1.67	1.90×10^{-1}
Error	2.57×10^{4}	197	131		
Total	2.62×10^{4}	199			

Table E-24 oPR_2 ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	oPR_2				
Source	SS	df	MS	F	Prob>F
Groups	67.6	2	33.8	1.04×10^{-1}	9.01×10^{-1}
Error	6.41×10^{4}	197	326		
Total	6.42×10^{4}	199			

Table E-25 PRArea ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	PRArea				
Source	SS	df	MS	F	Prob>F
Groups	3.18×10^{3}	2	1.59×10^{3}	1.41	2.47×10^{-1}
Error	2.22×10^{5}	197	1.13×10^{3}		
Total	2.25×10^{5}	199			

Table E-26 Norm Area ANOVA Table between Nocturnal Sleep Apnea and Group 2 in Simulated Apnea

	Norm Area				
Source	SS	df	MS	F	Prob>F
Groups	4.34	2	2.17	23.6	6.51×10^{-10}*
Error	18.1	197	9.19×10^{-2}		
Total	22.4	199			

Appendix F

CAPNOGRAM VALIDATION STUDIES

Studies have been done to validate capnography as a method to judge the level of CO_2 in exhaled air. A study conducted by B. You, *et al* [39] compared the readings from a capnogram with those from a spirometer. They tested the sensitivity of capnogram to airway obstruction. The study had 10 healthy and 30 asthmatic subjects. The result showed a strong correlation between the capnography data and spirometry data. A study done by Richard H Kallet MSc, *et al* [40] compared the readings from the capnogram to that of the 'Metabolic Monitor Method' in 23 patients with Acute Respiratory Distress Syndrome (ARDS). Dead space to tidal volume ratio (V_D/V_T) was analyzed by both of the methods. This was calculated using Enghoff modification of Bohr equation, $V_D/V_T = [P_{aCO2} – P_{eCO2}] / P_{aCO2}$. Mean P_{eCO2} was corrected for compression volume dilution by $P_{eCO2} = P_{eCO2} * (V_T / [V_T – \text{compression volume}])$ It was concluded that the data from the capnogram highly correlates with the data from the metabolic monitor method (uncorrected data from the metabolic monitor method: $r^2=0.93$, $p < 0.0001$, corrected: $r^2=0.89$, $p < 0.0001$).

Appendix G

TCD VALIDATION STUDIES

Studies have been done to validate the readings from the transracial Doppler. A study, conducted by Georgios Tsivgoulis, MD, RVT et al, compares the TCD with spiral computed tomography angiography (CTA) in Acute Cerebral Ischemia [41]. CTA was performed on the subjects. Within two hours TCD data was recorded. This study was done on 132 patients. From that 34 were true-positive, 9 false-negative, 5 false-positive, and 84 true-negative studies. They found that CTA corroborated TCD data. Rocco Totaro et al. conducted a study to study the reproducibility of the TCD [42]. TCD measurements on thirty six subjects were done in the anterior, middle and posterior cerebral, and basilar arteries. They took three measurements with a one hour time interval between the first and the second reading and a twenty four hour interval between the first and the third. They found that in most cases TCD had a good reproducibility ($r=0.78–0.97$; $p<0.001$) except in the case where the velocity in the MCA was low. In that case the reproducibility for the posterior artery was poorer ($r=0.42–0.54$).

Appendix H

RESULTS FROM KOLMOGOROV-SMIRNOV TEST

The Tables below represents the results from the normality test for the CO_2 and the CBFV metrics for simulated apnea study in both the groups. A Kolmogorov-Smirnov Test was used for this. P value less than 0.05 indicates that the data from that metric is not normal.

Table H-1 Results from Kolmogorov-Smirnov Test for CO_2 metrics in Group 1

	CO_2			
	SiA	SiB	SuA	SuB
	p	p	p	p
$ETCO_2$	2.87E-54*	1.17E-58*	4.33E-41*	2.74E-32*
Delta $ETCO_2$	5.09E-09*	4.46E-11*	1.02E-05*	3.59E-06*

Table H-2 Results from Kolmogorov-Smirnov Test for CO_2 metrics in Group 2

	CO_2			
	SiA	SiB	SuA	SuB
	p	p	p	p
$ETCO_2$	6.97E-28*	6.97E-28*	4.72E-19*	4.33E-41*
Delta $ETCO_2$	2.40E-25*	1.04E-24*	2.34E-09*	7.22E-24*

Table H-3 Results from Kolmogorov-Smirnov Test for CBFV metrics in Group 1

	CBFV			
	SiA	SiB	SuA	SuB
	p	p	p	p
Slope	1.23E-18*	6.05E-19*	1.30E-13*	1.08E-09*

Table H-3: *Continued*

Del_1	2.87E-54*	1.17E-58*	1.75E-39*	9.43E-29*
PR_1	2.87E-54*	1.17E-58*	4.33E-41*	9.43E-29*
Del_2	2.87E-54*	1.17E-58*	2.66E-39*	1.71E-30*
PR_2	2.87E-54*	1.17E-58*	2.66E-39*	3.19E-32*
Del_3	2.87E-54*	1.17E-58*	4.33E-41*	1.71E-30*
PR_3	2.87E-54*	1.17E-58*	4.33E-41*	1.71E-30*
$oDel_2$	2.87E-54*	1.17E-58*	4.33E-41*	1.71E-30*
oPR_2	2.87E-54*	1.17E-58*	4.33E-41*	3.28E-32*
PRArea	2.87E-54*	1.17E-58*	3.51E-34*	2.74E-32*
Norm Area	2.21E-25*	9.63E-28*	5.23E-18*	1.85E-19*

Table H-4 Results from Kolmogorov-Smirnov Test for CBFV metrics in Group 2

		CBFV		
	SiA	SiB	SuA	SuB
	p	p	p	p
Slope	6.06E-08*	7.53E-08*	1.74E-04*	5.27E-10*
Del_1	1.66E-25*	8.34E-28*	2.40E-12*	7.56E-36*
PR_1	1.85E-27*	7.03E-28*	2.40E-12*	1.49E-37*
Del_2	6.97E-28*	6.97E-28*	1.63E-15*	7.55E-36*
PR_2	6.97E-28*	6.97E-28*	8.91E-17*	7.55E-36*
Del_3	6.99E-28*	4.47E-26*	1.68E-15*	7.55E-36*
PR_3	6.97E-28*	4.40E-26*	1.63E-15*	7.55E-36*
$oDel_2$	6.97E-28*	6.97E-28*	1.63E-15*	1.49E-37*
oPR_2	6.97E-28*	6.97E-28*	1.63E-15*	7.64E-41*

Table H-4: *Continued*

PRArea	6.22E-26*	7.79E-28*	3.09E-17*	4.34E-41*
Norm Area	8.88E-13*	1.35E-12*	8.81E-09*	2.37E-16*

The Tables below represents the results from the normality test for the CO_2 and the CBFV metrics for nocturnal sleep apnea study. A Kolmogorov-Smirnov Test was used for this. P value less than 0.05 indicates that the data from that metric is not normal.

Table H-5 Results from Kolmogorov-Smirnov Test for CO_2 metrics in Nocturnal Sleep Apnea Study

	CO_2
	p
$ETCO_2$	4.27E-119*
Delta $ETCO_2$	4.51E-30*

Table H-6 Results from Kolmogorov-Smirnov Test for CBFV metrics in Nocturnal Sleep Apnea Study

	CBFV
	p
Slope	1.09E-32*
Del_1	6.32E-77*
PR_1	1.46E-81*
Del_2	4.29E-119*
PR_2	4.33E-119*

Table H-6:*Continued*

Del_3	2.03E-114*
PR_3	7.10E-117*
$oDel_2$	4.28E-119*
oPR_2	4.33E-119*
PRArea	3.20E-83*
Norm Area	6.14E-35*

Appendix I

TWO WAY ANOVA FOR SIMULATED APNEA

Two Way ANOVA was performed on the data from the simulated apnea study. For this test frequency was considered as one effect and posture was considered as another effect. Since in the simulated apnea study some subject's data in some protocols had to be removed from the analysis this led to an imbalanced data sets. Due to this for this test subjects who had usable data from all protocols was considered. There were 6 subjects which had usable data from all protocols. These subjects were from Group 1. Tables I-1 to I-3 represents the two way ANOVA and Tukey-Kramer results from the six subjects.

Table I-1 Results from Two Way ANOVA for the means of the metrics of exhaled CO_2 across all apnea frequencies and positions

CO_2		
Metric	p	
	Posture	Frequency
$ETCO_2$	1.83×10^{-1}	6.93×10^{-1}
Delta $ETCO_2$	1.14×10^{-1}	4.76×10^{-1}

Table I-2 Results from Two Way ANOVA for the means of the metrics of exhaled CBFV across all apnea frequencies and positions

CBFV		
Metric	p	
	Posture	Frequency
Slope	5.46×10^{-2}	9.60×10^{-1}
Del_1	2.18×10^{-1}	4.50×10^{-1}
PR_1	5.98×10^{-1}	6.99×10^{-1}
Del_2	1.28×10^{-1}	3.75×10^{-1}

Table I-2: *Continued*

PR_2	9.20×10^{-1}	6.43×10^{-1}
Del_3	4.31×10^{-1}	3.08×10^{-2}*
PR_3	2.94×10^{-1}	2.68×10^{-3}*
$oDel_2$	4.67×10^{-2}*	3.43×10^{-1}
oPR_2	2.12×10^{-1}	6.20×10^{-1}
PRArea	7.22×10^{-1}	8.49×10^{-1}
Norm Area	7.25×10^{-3}*	7.08×10^{-1}

Table I-3 Results from Tukey Kramer for comparing the means of metrics derived from CBFV metrics

CBFV					
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	p
Group 2	Del_3	SiA V/S SuA	-9.62	12.1	9.91×10^{-1}
		SiA V/S SiB	-5.51	16.2	5.77×10^{-1}
		SuA V/S SuB	-3.31	18.4	2.74×10^{-1}
		SiB V/S SuB	-7.42	14.3	8.43×10^{-1}
	PR_3	SiA V/S SuA	-11.5	8.51	9.79×10^{-1}
		SiA V/S SiB	-3.25×10^{-1}	19.7	6.17×10^{-2}
		SuA V/S SuB	-3.03	17	2.70×10^{-1}
		SiB V/S SuB	-14.2	5.80	6.92×10^{-1}
	$oDel_2$	SiA V/S SuA	-7.18	16.2	7.45×10^{-1}

Table I-3: *Continued*

		SiA V/S SiB	-10.5	12.9	9.94×10^{-1}
		SuA V/S SuB	-6.83	1.66E+01	6.99×10^{-1}
		SiB V/S SuB	-3.47	2.00E+01	2.62×10^{-1}
	Norm Area	SiA V/S SuA	-8.87×10^{-1}	3.70×10^{-2}	8.32×10^{-2}
		SiA V/S SiB	-4.97×10^{-1}	4.26×10^{-1}	9.97×10^{-1}
		SuA V/S SuB	-3.32×10^{-1}	5.91×10^{-1}	8.85×10^{-1}
		SiB V/S SuB	-7.22×10^{-1}	2.02×10^{-1}	4.60×10^{-1}

Appendix J

RESULTS FROM TUKEY-KRAMER ANALYSIS

Table J-1 Results from Tukey-Kramer Analysis for Exhaled CO_2 metrics in Simulated Apnea

		Exhaled CO_2			
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	P Value
Group 2	Delta $ETCO_2$	SiA V/S SiB	-7.60×10^{-1}	4.29	2.75×10^{-1}
		SiA V/S SuA	1.68×10^{-1}	5.82	3.29×10^{-2}
		SiB V/S SuB	-2	2.62	9.86×10^{-1}
		SuA V/S SuB	-3.55	1.71	8.07×10^{-1}

Table J-2 Results from Tukey-Kramer Analysis for CBFV metrics in Simulated Apnea

		CBFV			
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	P Value
Group 1	Norm Area	SiA V/S SiB	-2.52×10^{-1}	2.89×10^{-1}	9.98×10^{-1}
		SiA V/S SuA	-6.31×10^{-1}	-3.49×10^{-2}	2.14×10^{-2}
		SiB V/S SuB	-6.83×10^{-1}	-4.89×10^{-2}	1.60×10^{-2}
		SuA V/S SuB	-3.55×10^{-1}	3.26×10^{-1}	1
Group 2	Slope	SiA V/S SiB	-3.45×10^{-1}	1.38×10^{-1}	6.90×10^{-1}
		SiA V/S SuA	-6.88×10^{-1}	-1.47×10^{-1}	4.23×10^{-4}
		SiB V/S SuB	-4.15×10^{-1}	2.68×10^{-2}	1.08×10^{-1}
		SuA V/S SuB	-1.32×10^{-1}	3.72×10^{-1}	6.10×10^{-1}

Table J-2: *Continued*

	Del_1	SiA V/S SiB	-7.78	6.22	9.92×10^{-1}
		SiA V/S SuA	-18.6	-2.92	2.38×10^{-3}
		SiB V/S SuB	-10.3	2.53	4.07×10^{-1}
		SuA V/S SuB	-1.19	13.4	1.37×10^{-1}
	Del_2	SiA V/S SiB	-5.38	7.51	9.75×10^{-1}
		SiA V/S SuA	-14.2	1.86×10^{-1}	5.95×10^{-2}
		SiB V/S SuB	-10.8	9.45×10^{-1}	1.36×10^{-1}
		SuA V/S SuB	-3.57	9.85	6.25×10^{-1}
	Del_3	SiA V/S SiB	-2.36	10.4	3.66×10^{-1}
		SiA V/S SuA	-16.4	-2.08	5.07×10^{-3}
		SiB V/S SuB	-11.9	-2.19×10^{-1}	3.85×10^{-2}
		SuA V/S SuB	5.51×10^{-1}	13.9	2.78×10^{-2}
	Pr_3	SiA V/S SiB	-1.48	21.0	1.15×10^{-1}
		SiA V/S SuA	-18.2	6.92	6.56×10^{-1}
		SiB V/S SuB	-19.8	6.98×10^{-1}	7.81×10^{-2}
		SuA V/S SuB	-5.86	17.5	5.74×10^{-1}
	$oDel_2$	SiA V/S SiB	-5.38	7.39	9.77×10^{-1}
		SiA V/S SuA	-16.4	-2.17	4.50×10^{-3}
		SiB V/S SuB	-11.8	-1.47×10^{-1}	4.20×10^{-2}
		SuA V/S SuB	-2.31	11.0	3.36×10^{-1}

Table J-3 Results from Tukey-Kramer Analysis for Exhaled CO_2 metrics in Nocturnal Apnea

		Exhaled CO_2			
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	P Value
Group 1	$ETCO_2$	Sleep V/S SuA	9.47×10^{-1}	5.03	1.74×10^{-3}
		Sleep V/S SuB	1.20×10^{-1}	4.62	3.62×10^{-2}
	Delta $ETCO_2$	Sleep V/S SuA	-9.59×10^{-2}	3.47	6.82×10^{-2}
		Sleep V/S SuB	5.25×10^{-1}	4.45	8.38×10^{-3}
Group 2	$ETCO_2$	Sleep V/S SuA	-5.36	7.24	5.84×10^{-2}
		Sleep V/S SuB	-7.08	-3.18	3.12×10^{-9}
	Delta $ETCO_2$	Sleep V/S SuA	-6.07	-9.46×10^{-1}	3.82×10^{-3}
		Sleep V/S SuB	-6.27	-2.58	5.41×10^{-8}

Table J-4 Results from Tukey-Kramer Analysis for CBFV metrics in Nocturnal Apnea

		CBFV			
Group	Metric	Comparison	Lower Confidence Limit	Upper Confidence Limit	P Value
Group 1	Del_1	Sleep V/S SuA	-24.2	-6.61	1.18×10^{-4}
		Sleep V/S SuB	-24.9	-5.60	6.30×10^{-4}
	PR_1	Sleep V/S SuA	-26.4	-5.37	1.16×10^{-3}

Table J-4: *Continued*

		Sleep V/S SuB	-26.8	-3.64	5.82×10^{-3}
	Del_2	Sleep V/S SuA	-19.9	-9.34	1.19×10^{-9}
		Sleep V/S SuB	-21.8	-10.2	1.25×10^{-9}
	Pr_2	Sleep V/S SuA	-14.9	7.63×10^{-2}	5.31×10^{-2}
		Sleep V/S SuB	-19.9	-3.31	2.95×10^{-3}
	Del_3	Sleep V/S SuA	-23.2	-12.4	9.56×10^{-10}
		Sleep V/S SuB	-23.3	-11.3	9.96×10^{-10}
	Pr_3	Sleep V/S SuA	-22.4	-8.83	2.05×10^{-7}
		Sleep V/S SuB	-24.1	-9.20	5.07×10^{-7}
	$oDel_2$	Sleep V/S SuA	-21.6	-10.5	9.86×10^{-10}
		Sleep V/S SuB	-23.9	-11.7	9.78×10^{-10}
	oPR_2	Sleep V/S SuA	-17.5	-1.99	9.06×10^{-3}
		Sleep V/S SuB	-23.6	-6.46	1.14×10^{-4}
	PRArea	Sleep V/S SuA	-32.6	-2.92	1.39×10^{-2}
		Sleep V/S SuB	-42.3	-9.65	5.64×10^{-4}
	Norm Area	Sleep V/S SuA	-1.14	-6.95×10^{-1}	9.56×10^{-10}
		Sleep V/S SuB	-1.18	-6.87×10^{-1}	9.56×10^{-10}
Group 2	Slope	Sleep V/S SuB	0.0057	0.52	4.37×10^{-2}*
	Norm Area	Sleep V/S SuA	-5.48×10^{-1}	-2.07×10^{-1}	6.05×10^{-7}
		Sleep V/S SuB	-4.02×10^{-1}	-1.57×10^{-1}	2.61×10^{-7}

Appendix K

MEANS OF THE CO_2 AND CBFV METRICS

Table K-1 Exhaled CO_2 Metric Means for Simulated Apnea study

	Group 1				Group 2			
	SiA	SiB	SuA	SuB	SiA	SiB	SuA	SuB
$ETCO_2$	4.10×10^{1}	4.01×10^{1}	4.02×10^{1}	4.09×10^{1}	4.59×10^{1}	4.80×10^{1}	4.59×10^{1}	4.84×10^{1}
Delta $ETCO_2$	5.68×10^{-3}	-5.54×10^{-1}	1.20×10^{-2}	-7.90×10^{-1}	8.2	6.43	5.21	6.12

Table K-2 CBFV Metric Means for Simulated Apnea study

	Group 1				Group 2			
	SiA	SiB	SuA	SuB	SiA	SiB	SuA	SuB
Slope	8.28×10^{-1}	8.95×10^{-1}	8.20×10^{-1}	8.84×10^{-1}	3.13×10^{-1}	4.17×10^{-1}	7.31×10^{-1}	6.11×10^{-1}
Del_1	2.91×10^{1}	3.18×10^{1}	3.31×10^{1}	3.30×10^{1}	1.26×10^{1}	1.34×10^{1}	2.33×10^{1}	1.72×10^{1}
PR_1	3.61×10^{1}	4.13×10^{1}	4.16×10^{1}	4.10×10^{1}	2.41×10^{1}	2.59×10^{1}	3.24×10^{1}	2.78×10^{1}
Del_2	3.10×10^{1}	3.33×10^{1}	3.38×10^{1}	3.53×10^{1}	1.56×10^{1}	1.46×10^{1}	2.26×10^{1}	1.95×10^{1}
PR_2	4.01×10^{1}	4.55×10^{1}	4.27×10^{1}	4.68×10^{1}	3.02×10^{1}	2.81×10^{1}	3.28×10^{1}	3.28×10^{1}

Table K-2: *Continued*

Del_3	3.25 x10^1	3.07 x10^1	3.57 x10^1	3.52 x10^1	1.48 x10^1	1.08 x10^1	2.40 x10^1	1.68 x10^1
PR_3	4.35 x10^1	3.93 x10^1	4.60 x10^1	4.70 x10^1	2.88 x10^1	1.90 x10^1	3.44 x10^1	2.86 x10^1
$oDel_2$	3.54 x10^1	3.66 x10^1	3.70 x10^1	3.87 x10^1	1.66 x10^1	1.56 x10^1	2.59 x10^1	2.16 x10^1
oPR_2	4.84 x10^1	5.20 x10^1	4.85 x10^1	5.38 x10^1	3.26 x10^1	3.06 x10^1	4.01 x10^1	3.79 x10^1
PRArea	5.47 x10^1	6.06 x10^1	5.32 x10^1	6.15 x10^1	4.24 x10^1	2.67 x10^1	4.44 x10^1	4.38 x10^1
Norm Area	1.10	1.09	1.44	1.45	9.95 x10^{-1}	7.59 x10^{-1}	8.98 x10^{-1}	8 x10^{-1}

Table K-3 Exhaled CO_2 Metric Means for Nocturnal Sleep Study

	Group 1			Group 2		
	Sleep	SuA	SuB	Sleep	SuA	SuB
$ETCO_2$	4.32 x10^1	4.02 x10^1	4.09 x10^1	4.32 x10^1	4.59 x10^1	4.84 x10^1
Delta $ETCO_2$	1.7	1.2 x10^{-2}	-7.9 x10^{-1}	1.7	5.21	6.12

Table K-4 CBFV Metric Means for Nocturnal Sleep Study

	Group 1			Group 2		
	Sleep	SuA	SuB	Sleep	SuA	SuB

Table K-4: *Continued*

Slope	8.74×10^{-1}	8.2×10^{-1}	8.84×10^{-1}	8.74×10^{-1}	7.31×10^{-1}	6.11×10^{-1}
Del_1	1.78×10^{1}	3.31×10^{1}	3.3×10^{1}	1.78×10^{1}	2.33×10^{1}	1.72×10^{1}
PR_1	2.57×10^{1}	4.16×10^{1}	4.1×10^{1}	2.57×10^{1}	3.24×10^{1}	2.78×10^{1}
Del_2	1.92×10^{1}	3.38×10^{1}	3.53×10^{1}	1.92×10^{1}	2.26×10^{1}	1.95×10^{1}
PR_2	3.53×10^{1}	4.27×10^{1}	4.68×10^{1}	3.53×10^{1}	3.28×10^{1}	3.28×10^{1}
Del_3	1.79×10^{1}	3.57×10^{1}	3.52×10^{1}	1.79×10^{1}	2.40×10^{1}	1.68×10^{1}
PR_3	3.04×10^{1}	4.60×10^{1}	4.70×10^{1}	3.04×10^{1}	3.44×10^{1}	2.86×10^{1}
$oDel_2$	2.09×10^{1}	3.70×10^{1}	3.87×10^{1}	2.09×10^{1}	2.59×10^{1}	2.16×10^{1}
oPR_2	3.88×10^{1}	4.85×10^{1}	5.38×10^{1}	3.88×10^{1}	4.01×10^{1}	3.79×10^{1}
PRArea	3.55×10^{1}	5.32×10^{1}	6.15×10^{1}	3.55×10^{1}	4.44×10^{1}	4.38×10^{1}
Norm Area	5.21×10^{-1}	1.44	1.45	5.21×10^{-1}	8.98×10^{-1}	8×10^{-1}

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