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Influences of cardiac and respiratory parameters on heart rate variability

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ABSTRACT

INFLUENCES OF CARDIAC AND RESPIRATORY PARAMETERS ON HEART RATE VARIABILITY

by
Melissa Leifer

Heart rate variability is a result of variation in the activity of the sympathetic and parasympathetic nervous systems. Methods have been developed to determine the level of parasympathetic activity by observing the heart rate variability spectrum. Most of the previously published research uses only level of parasympathetic activity and respiratory rate to draw conclusions about the interactions of the autonomic nervous system with physiological parameters. In order to gain a complete understanding of the autonomic nervous system and the mechanisms responsible for heart rate variability, respiratory volume, cardiac variables and pulmonary variables need to be considered. In addition, amount of sympathetic activity needs to be quantified.

The results of the present study demonstrate that many relationships and interactions exist between the physiological and autonomic parameters. The data indicate that heart rate and overall parasympathetic activity decreases as respiratory volume increases. Statistical analysis has demonstrated that parasympathetic activity, respiratory rate and volume are influenced by and related to respiratory variables such as $\dot{V}O_2$ l/min. and end tidal CO_2. Methods to relate and compare sympathetic influences when subjects change their level of activity are suggested and developed. It is demonstrated that changes in sympathetic influence can be qualitatively determined by comparing changes in HR and parasympathetic activity.

In this research, the experimental protocol was too lengthy to be executed in one day. Therefore, methods to compare data acquired on different days were developed.

INFLUENCES OF CARDIAC AND RESPIRATORY PARAMETERS ON HEART RATE VARIABILITY

by
Melissa Leifer

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APPROVAL PAGE

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This thesis is dedicated to my parents

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CHAPTER 1

BACKGROUND

1.1 Introduction

Understanding of experimental results is enhanced if certain fundamental principles are well understood. The aims of this chapter are to supply physiological background, introduce the concept of heart rate variability, and cite the objectives and goals of this thesis.

1.2 Physiology

1.2.1 The Cardiovascular System

The human cardiovascular system is essential for nutrient and waste transport, oxygen and carbon dioxide transport, temperature maintenance and hormone circulation [12]. The heart, blood vessels and blood are the components of the cardiovascular system.

The heart muscle is divided into right and left halves, each consisting of an atrium and ventricle. The blood in each atrium empties into the ventricle on the same side. Figure 1.2.1(A) [12] shows the general paths through which blood moves. In the systemic circulation, blood leaves the left side of the heart through the aorta and then diverges into a complex network of small diameter arteries, called arterioles. The blood then reaches all the organs and tissues (except the lungs) in the body via microscopic

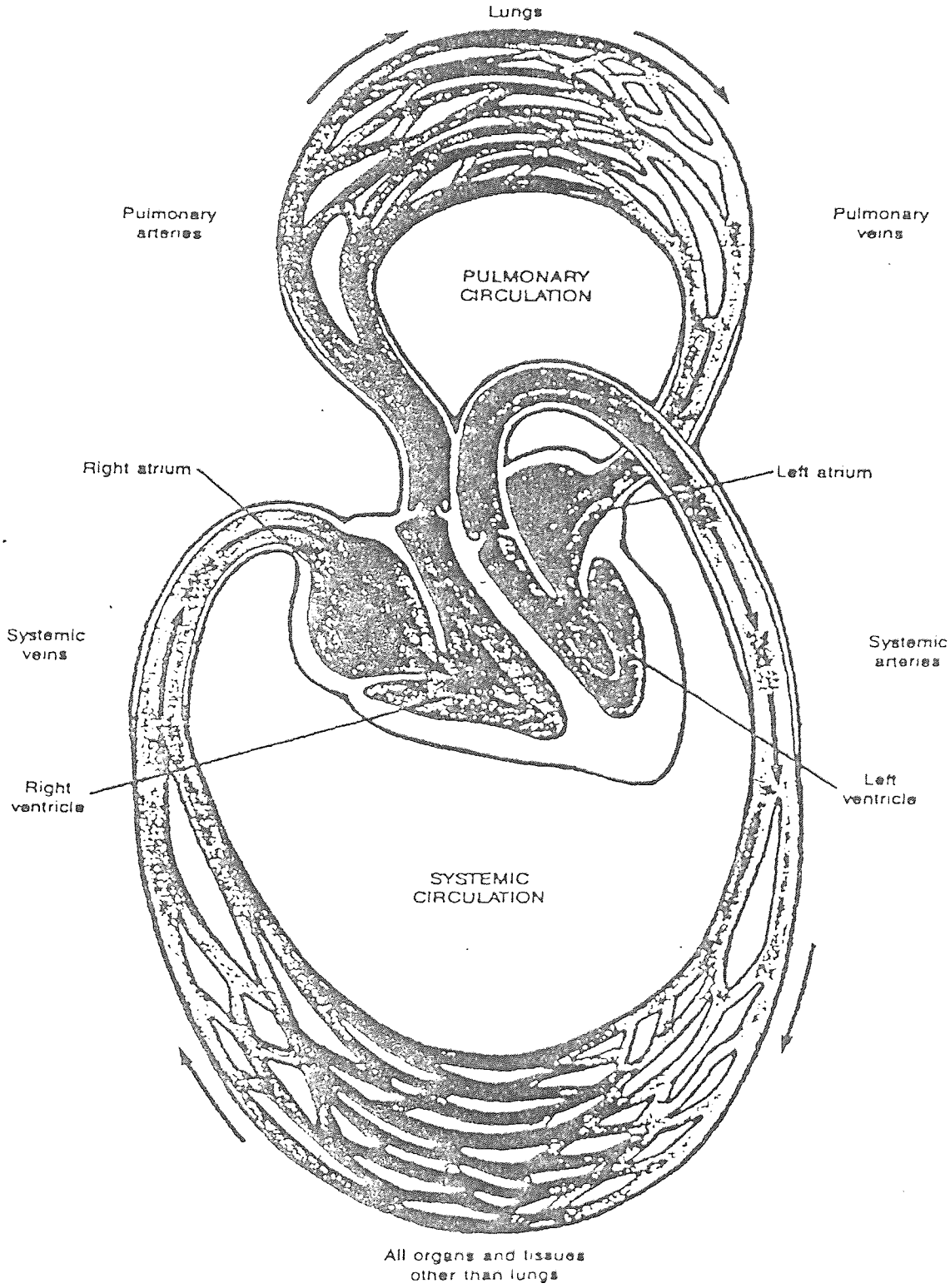

Figure 1.2.1(A) Cardiovascular Circulation (From A. J. Vander et al., *Human Physiology: The Mechanisms of Body Function*, McGraw-Hill, 1990)

tubes called capillaries. Oxygen and other substances are diffused from the blood into tissue through the capillaries. From the capillaries, blood travels into venules, or small veins. The deoxygenated blood eventually returns to the right atrium via the venacava.

From the right ventricle, deoxygenated blood circulates through the pulmonary artery, arterioles and into the capillary network that is associated with the lungs. The blood within these capillaries is reoxygenated and nutrients are replenished. The pulmonary circulation is then completed when the oxygenated blood enters the left atrium via the venules and pulmonary vein.

1.2.2 The Heart Beat

In order for blood to be pumped effectively, the cardiac muscle fibers of the heart must contract and relax in an organized manner. The contraction and relaxation of cardiac muscle constitutes a heart beat. The structure of cardiac muscle causes the heart beat to be coordinated.

The contraction of a cardiac muscle cell is initiated by a voltage change within the plasma membrane [12]. This voltage change or depolarization occurs from a sudden increase in membrane permeability to sodium. Since sodium is a positive ion, it causes the membrane potential in the cell interior to increase from -90 millivolts, which is resting membrane voltage, to +60 millivolts. Adjacent cardiac muscles are joined end to end and contain structures called gap junctions which cause the depolarization to spread to adjacent cells until all muscle cells are affected.

The origin of the depolarization is in a small group of conducting system cells, the sinoatrial node (SA node), which is located in the right atrium. The SA node is able to

initiate a depolarization since its resting potential is unstable. The resting potential automatically rises from -90 millivolts to +60 millivolts since membrane properties of the SA node induce a net increase of positive ions into the membrane. The change in membrane voltage, initiated by the SA node, subsequently spreads throughout the right atrium and then to the left atrium. The depolarization of the two atria occurs at approximately the same time; therefore, the contraction of the atria may be considered simultaneous. The atrioventricular node (AV node), which is located at the base of the right atrium, is also depolarized at this time. The AV node is the only path which will allow the depolarizations to reach the ventricles. The rise in atrial cardiac muscle membrane voltage is spread throughout the ventricle via conducting system fibers called the bundle of His and Purkinge fibers. The conducting system of the heart is shown in figure 1.2.2(A) [12].

Several cardiac parameters, which provide quantitative information about heart function are stroke volume, heart rate, and cardiac output. Stroke volume (SV) [L/beat] is defined as the total blood volume ejected by each ventricle with each beat. The depolarization rate of the SA node determines the heart rate (HR) [beats/min.]. HR is the number of heart beats per unit time. Without any external influences, the heart rate is approximately 100 beats per minute. Due to various influences, which are discussed in this chapter, the average resting heart rate is well below 100 beats per minute.

Cardiac output (CO) is defined as the volume of blood pumped by each ventricle in one minute and is related to SV and HR as shown in equation 1.1.

$$CO = SV*HR \text{ [Liters/Minute]}. \qquad (1.1)$$

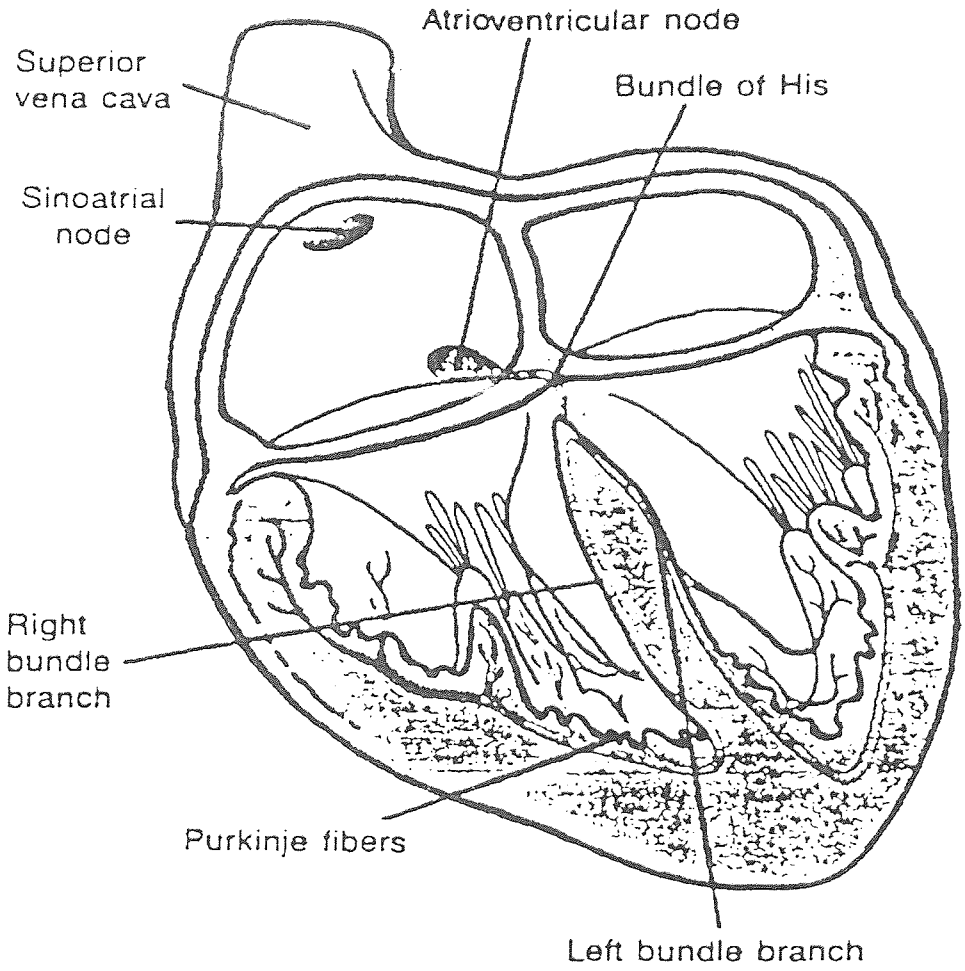

Figure 1.2.2(A) Conducting System of the Heart (From A. J. Vander et al., *Human Physiology: The Mechanisms of Body Function*, McGraw-Hill, 1990)

1.2.3 The Electrocardiogram (EKG)

Electrocardiogram (EKG) is utilized to evaluate and determine whether the heart is functioning correctly. Abnormalities can alter the characteristics of the EKG; therefore, the determination of heart pathology is facilitated. The EKG is a manifestation of the various phases in the heart beat that are described above. The EKG, however, cannot directly record the electrical phenomena in the heart since the measurements are taken

with electrodes that are located on the body surface [12]. Therefore, the EKG measures the currents generated in the extracellular fluid by these changes. Diagram 1.2.3(A) shows a typical EKG [12]. The P wave represents atrial depolarization. The QRS complex is due to ventricular depolarization, and occurs about 0.15 seconds after the P wave. The T wave results from ventricular repolarization. Repolarization refers to the restoration of the cardiac muscle membrane to its resting membrane potential. Atrial repolarization cannot be seen on the EKG, but is incorporated in the QRS complex.

Variations in the period of the EKG (time between each wave) are a manifestation of the external influences on the SA node. Due to these variations in period, a great deal of information can be extracted if the EKG is processed. In the next chapter, the methods used to process the EKG signal will be discussed in detail.

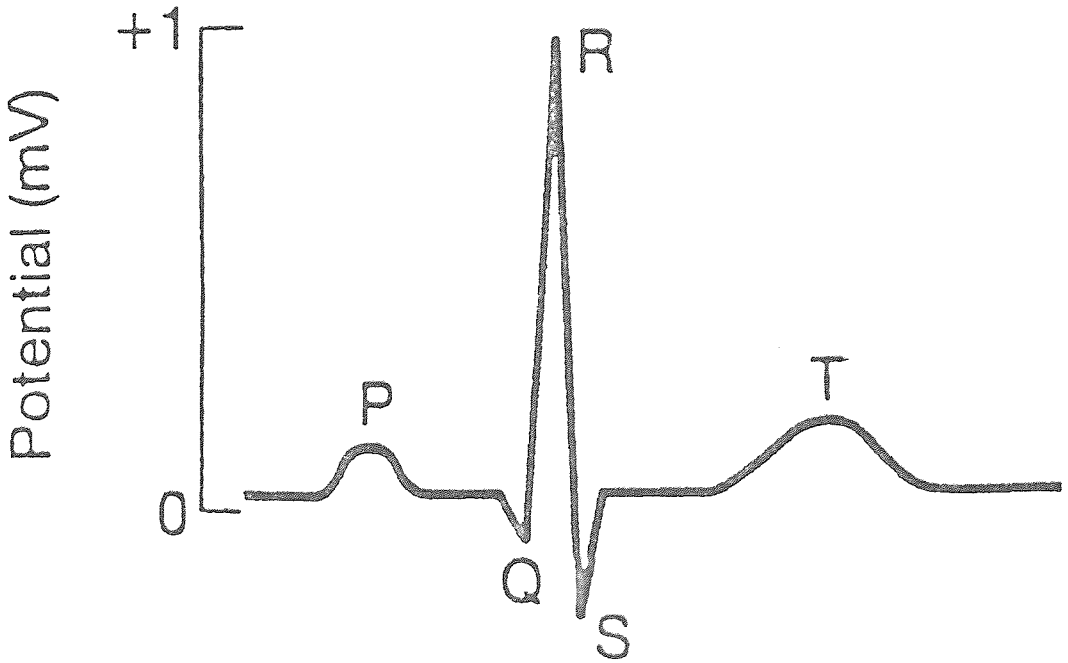

Figure 1.2.3(A) EKG (From A. J. Vander et al., *Human Physiology: The Mechanisms of Body Function*, McGraw-Hill, 1990)

1.2.4 Overview of Blood Pressure Function

The force that moves fluids through pipes is hydrostatic force. The hydrostatic force that blood exerts against the wall of a vessel is called blood pressure. Normally, some amount of blood is present in every blood vessel of the body, including all arteries, arterioles, capillaries, venules and veins.

Blood volume is greatest in the veins [12]. Venous blood pressure, however, is quite low because the vein walls are thin and compliant. Return of deoxygenated blood to the heart is facilitated by skeletal movement, mechanical movement from respiration and one-way valves.

Less than fifteen percent of the blood volume is present in the arteries. Mean arterial pressure, however, is approximately 100 mm Hg. Mean arterial pressure (MAP) depends upon overall arteriole resistance (TPR) and cardiac output (CO) . Specifically,

$$MAP = TPR * CO \text{ [mmHg]}. \qquad (1.2)$$

The resistance of a particular arteriole depends upon the associated organ's requirements. Under different conditions, an arteriole radius will be varied by control mechanisms to accommodate the need of the associated organ. If the overall radius of all arterioles decreases, then the TPR is increased, which may cause arterial blood pressure to increase, depending upon the CO value.

When blood flows into arteries and arterioles, stretching occurs due to the pressure that the blood exerts on the arterial walls. The maximum pressure, which is reached when the ventricles eject blood, is called the systolic pressure. The minimum arterial pressure occurs just before ventricular ejection begins and is called diastolic

pressure. Figure 1.2.4(A) [12] shows the blood pressure signal and figure 1.2.4(B) [12] demonstrates the effect of the blood pressure on the arterial walls.

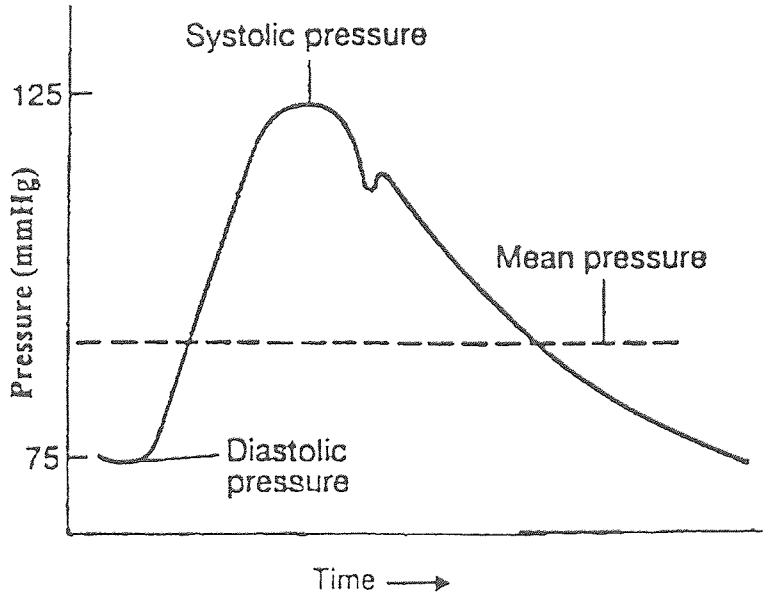

Figure 1.2.4(A) Blood Pressure Signal (From A. J. Vander et al., *Human Physiology: The Mechanisms of Body Function*, McGraw-Hill, 1990)

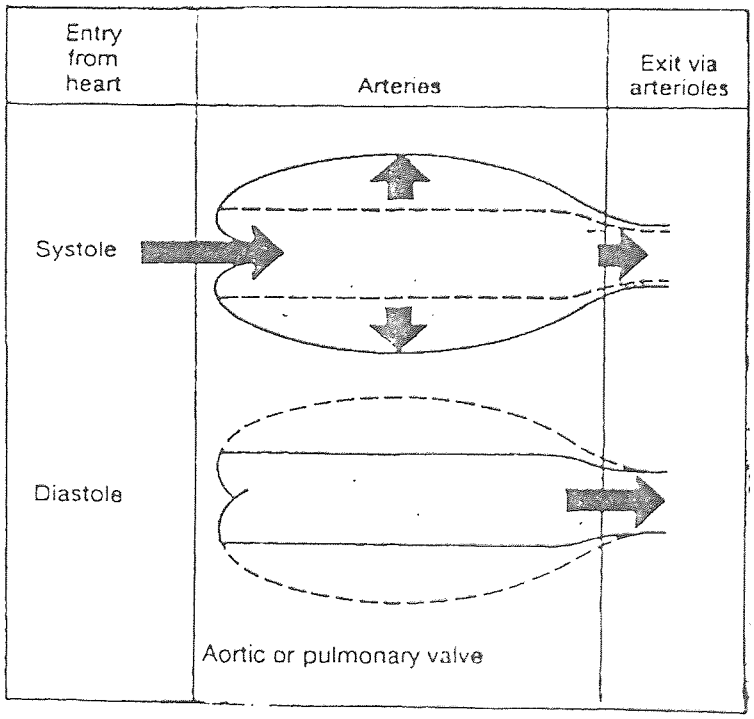

Figure 1.2.4(B) Effect of Blood Pressure on Arterial Wall (From A. J. Vander et al., *Human Physiology: The Mechanisms of Body Function*, McGraw-Hill, 1990)

1.2.5 Respiration

Respiration serves to provide cells with oxygen, eliminate carbon dioxide and regulate the hydrogen-ion concentration of blood (pH) [12]. In order to provide cells with oxygen, air from the environment needs to enter the body. This is accomplished during inhalation. Carbon dioxide and other unwanted substances are removed from the body to the environment by means of an exhalation. One inhalation plus one exhalation constitute a breath.

Figure 1.2.5(A) [12] and figure 1.2.5(B) [12] shows the basic components of the human respiratory system. Upon inhalation, air enters the body via the trachea, and then flows into the bronchi. The air then reaches the alveoli, which are clusters of hollow sacs with an extensive amount of surface area and thin membranes. The properties of the alveoli allow rapid and efficient exchange of gasses between the blood within the capillaries and the alveoli. During steady state, the volume of oxygen per unit time ($\dot{V}O_2$ [L/min.]) that is transported from the capillaries to the body cells is equal to volume of the inspired oxygen that is diffused from the alveoli into the blood at any given instant. Analogously, the volume of CO_2 produced by the body cells per unit time ($\dot{V}CO_2$ [L/min.]) is equal to the amount of CO_2 that diffuses from the blood to the alveoli . The ratio of CO_2 produced/O_2 consumed is called the respiratory quotient. The amount of CO_2 remaining in the pulmonary arteries following an exhalation is called end tidal CO_2 ($petCO_2$) [mL]. With the appropriate instrumentation, $\dot{V}O_2$ [L/min.] and $\dot{V}CO_2$ [L/min.] , RQ ratio and $petCO_2$ [mL] can all be determined noninvasively. These

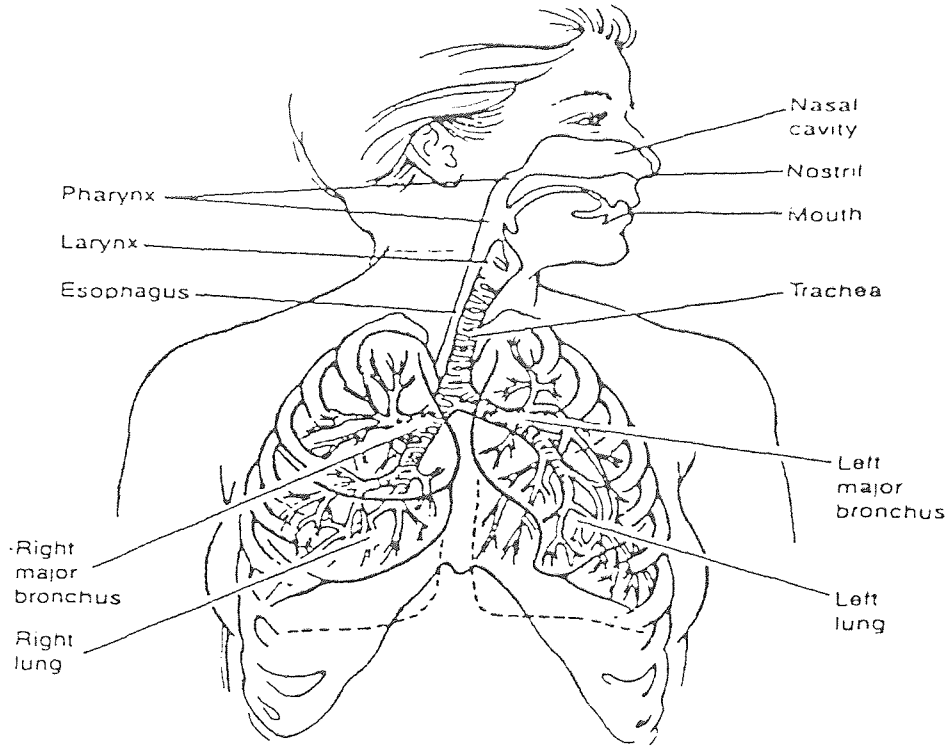

Figure 1.2.5(A) Respiratory System (From A. J. Vander et al., *Human Physiology: The Mechanisms of Body Function*, McGraw-Hill, 1990)

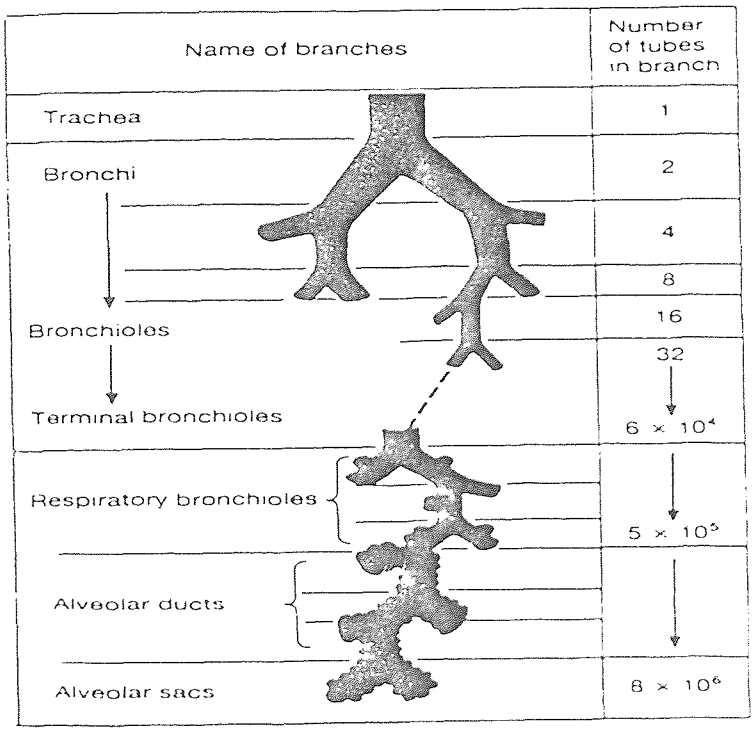

Figure 1.2.5(B) Airway Branching (From A. J. Vander et al., *Human Physiology: The Mechanisms of Body Function*, McGraw-Hill, 1990)

parameters are collected during the present study (see chapter 2), and contribute to the results of the research.

Tidal volume, which is measured by a spirometer, is defined as the volume of air that enters or exits the lungs during a normal breath. The total amount of air entering and leaving the body may be consciously controlled by changing the ventilation ($\dot{V}E$) [L/min.], which is the rate by which a volume of air is inhaled or exhaled.

$$\dot{V}E = TV*RR[Hz]*60 \ [L/min.] \qquad (1.3)$$

where TV is tidal volume and RR is respiratory rate. If ventilation is consciously adjusted to an extreme, fainting or light headedness may occur due to chemical and pH imbalances of the blood. Specifically, if an individual decreases ventilation without decreasing O2 consumption and CO2 production, then an increased arterial concentration of CO2 results. This is called hypoventilation. Due to chemical reactions in the blood, a rise in arterial CO2 precipitates a rise in hydrogen ions. This accumulation of hydrogen ions in the blood is termed respiratory acidosis. Analogously, hyperventilation occurs when ventilation increases without similar increase in O2 consumption or CO2 production. This causes blood concentrations of both CO2 and hydrogen ions to diminish, and is termed respiratory alkalosis.

$\dot{V}E$ [L/min.], HR [beats/min.], $\dot{V}O2$ [L/min.] and $\dot{V}CO2$ [L/min.] are used to derive other important respiratory and cardiac parameters. It is useful to know how efficiently the body consumes O2 and produces CO2. Efficiency of O2 consumption can

be calculated with the following equation:

$$\text{Eff O2} = \dot{V}E/\dot{V}O2 \ \% \qquad (1.4)$$

where $\dot{V}E$ [L/min.] is the ventilation. Eff O2 quantifies the amount of air that is taken in per amount of O2 that is consumed. For example, if an individual is out of breath after walking up a flight of stairs, then the Eff O2 will be low since a great deal of air is needed in order for the body to consume the amount of oxygen that is required. Efficiency of CO2 production can be calculated with the following equation:

$$\text{Eff CO2} = \dot{V}E/\dot{V}CO2 \ \% \qquad (1.5)$$

Eff CO2 quantifies the amount of exhaled air per amount of CO2 produced. The cardiac variable SV, which was discussed previously, can be derived by the equation:

$$SV = \dot{V}O2/HR \text{ [Liters/Breath]}. \qquad (1.6)$$

Respiratory volume and other respiratory parameters were measured and controlled in the experiments to be discussed in chapter 2. Only a small percentage of researchers have reported performing measurements on two of the above mentioned respiratory parameters: tidal volume and petCO2. In fact, Eckburg reports that only 11% of investigators have controlled respiratory volume [2]. Measurement of tidal volume occurred in only 22% of the studies. Two investigators, Eckburg and Selman, have done similar research to that of the present study. Eckburg and Selman both control tidal volume, but as explained in chapter 3, use different experimental protocols and have conflicting results. The results of the present study are compared to Eckburg's and Selman's study.

1.2.6 Nervous System

The general function of the nervous system is to transmit information between the brain and the body. The spinal cord and complex nerve networks are the necessary interfaces between the brain and body [12]. The nervous system has a wide range of functions ranging from motor function and coordination to breathing and endocrine secretion. The component of the nervous system which controls unconscious body functions is the autonomic nervous system. (The autonomic nervous system may be consciously controlled with techniques learned from undergoing biofeedback therapy.)

Depending upon the level of activity or stress, heart rate, blood pressure, and respiration may need to function at a higher or lower intensity. The autonomic nervous system contains networks of nerve fibers which provide information to the brain about the status of all the body systems. Therefore any imbalances which occur can be reversed or compensated.

The autonomic nervous system consists of two types of nerve pathways, the parasympathetic nerves and the sympathetic nerves. The sympathetic nerves contain pathways and chemicals that contribute to the increase in activity of particular bodily functions that will prepare an individual for a stressful or "fight or flight" situation. For example, the sympathetic nerve pathways prepare an individual for action by accelerating the heart, increasing metabolic rate, and performing related actions. In contrast, the parasympathetic nerve characteristics will result in the enhancement of activities that gain and conserve energy. For example, heart rates and blood pressure are decreased, and digestive function is increased. Later in this chapter, it will be explained how the level of parasympathetic and sympathetic activity can be inferred from the processed EKG signal.

Table 1.2.6(A) [12] is a summary of the effects that sympathetic and parasympathetic nerves have on different parts of the body.

Table 1.2.6(A) Some Effects of Autonomic System Activity (From A. J. Vander et al., *Human Physiology: The Mechanisms of Body Function*, McGraw-Hill, 1990)

EFFECTOR ORGAN	SYMPATHETIC EFFECT	PARASYMPATHETIC EFFECT
EYES		
Iris Muscle	Widens pupil	Makes pupil smaller
Ciliary Muscle	Flattens lens for far vision	Lens becomes convex
HEART		
S-A Node	Increases Heart Rate	Decreases Heart Rate
Atria	Increases Contractility	Decreases Contractility
A-V Node	Increases Conduction Vel.	Decreases Conduction Vel.
Ventricles	Increases Contractility	Decreases Contractility
ARTERIOLES		
Coronary	Constricts or Dilates	Dilates
Skin	Constricts	
Skeletal Muscle	Constricts or Dilates	
Veins	Constricts or Dilates	
LUNGS		
Brochial Muscle	Relaxes	Contracts
Bronchial Glands	Inhibits Secretion	Stimulates Secretion
Fat Cells	Increases Fat Breakdown	

1.3 Regulation and Control Mechanisms

1.3.1 Introduction

The physiological systems cited above do not function independently. The human body contains built-in regulatory mechanisms that control the function of the body systems so that homeostasis is maintained. Homeostasis is defined as the maintenance of normal conditions in the internal environment [12].

In many cases, homeostasis is maintained through feedback loops. In other words, if a change in system A alters system B, then the resulting change in system B will once again alter system A. See figure 1.3.1(A). Most control loops in the body are negative feedback loops. In a negative feedback control system, the system's response opposes a change initiated by the input; therefore stability is maintained [4]. For example, suppose the activity of system A increases. System B will then be altered. In negative feedback control, the change in system B will cause the activity of system A to decrease towards its original value. Consequently, the action of system B regulated and stabilized system A.

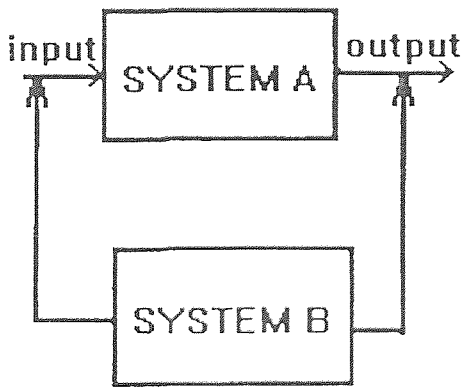

Figure 1.3.1(A) Feedback Loop

The study of physiological feedback loops is complex since it is often difficult to determine which system caused the original change. More research is needed to increase insight and knowledge about physiological control mechanisms. Regulation of heart rate, arterial blood pressure and respiration will now be discussed.

1.3.2 Control of Heart Rate

It was previously mentioned that the depolarization rate of the SA node, which determines the heart rate, is 100 beats\min. without any external influences. Heart rate, however, varies since the SA node is constantly under the influence of nerves. Activity of vagus nerves, which are parasympathetic nerves supplying the heart, cause heart rate to decrease [4]. Vagus nerve stimulation also decreases the SV and CO. In the resting state, there is more parasympathetic activity than sympathetic activity, which explains why the normal resting heart rate is below 100 beats/minute.

Activation of sympathetic nerves supplying the heart can cause the heart rate to increase to over 200 beats/minute. In addition, SV and CO can be increased as much as twofold to threefold. The abundance of nerves that supply the heart is illustrated in figure 1.3.2(A) [4].

1.3.3 Control of Blood Pressure

It was mentioned previously in equation 2.1 that the value of blood pressure depends upon CO and TPR. Therefore, in order to regulate blood pressure, peripheral resistance and cardiac output must be regulated.

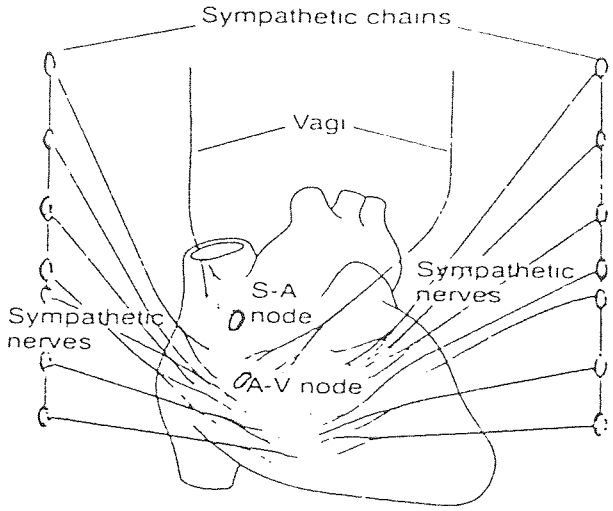

Figure 1.3.2(A) Nerves that Supply the Heart (From A. C. Guyton, *Textbook of Medical Physiology,* W. B. Saunders Company, 1991)

Peripheral resistance of a particular arteriole depends upon the amount of blood that the associated organ requires [12]. If the requirements of a particular organ change, then the resistance of the appropriate arterioles needs to change. Many sympathetic nerves are in contact with arterioles. When an organ needs less blood, associated sympathetic nerves are stimulated, which cause arterioles to constrict. If an organ needs more blood, then the arterioles dilate due to inhibition of the associated sympathetic nerves. There is no parasympathetic influence on TPR.

The value of cardiac output depends upon the excitation of the parasympathetic nerves and sympathetic nerves supplying the heart. Consequently, heart rate is a factor that influences blood pressure. In the next section, it is demonstrated that blood pressure also influences the heart function. Therefore, a feedback control mechanism exists.

1.3.4 Negative Feedback Control of Blood Pressure and Heart Rate (Baroreceptor Reflex)

A deviation in blood pressure causes a control mechanism, called the baroreceptor reflex, to be activated [12]. Baroreceptors or pressure receptors are nerves that are highly sensitive to stretch or distortion. Some baroreceptors are located in the carotid sinus which is at the bifurcation of the carotid arteries in the neck, the major arteries that convey blood to the head. Baroreceptors are also located at the arch of the aorta. These baroreceptors are called the aortic arch baroreceptors. Baroreceptors act to minimize deviations of the blood pressure by sensing changes in the radius of the blood vessels. Depolarizations that are initiated by the baroreceptor travel on nerve pathways to the cardiovascular control centers of the brain. The cardiovascular control center modulates the amount of vagal and sympathetic input into the heart. Resulting changes in heart function will then alter TPR and CO in a way that will cause blood pressure to return to its original value. (See equation 1.2.) For example, suppose there is a decrease in blood pressure. Stimulation of the baroreceptor's nerve endings decrease, which cause the cardiovascular center to increase sympathetic and decrease parasympathetic influences on the heart. Heart rate, SV, TPR and the contraction of the heart tissue increase due to the dominant sympathetic influence. The rise of SV and HR cause the CO to be increased. When CO and TPR increase, the blood pressure increases towards its original value.

Oscillations from the baroreceptor reflex at about 0.1 Hz can cause the arterial pressure to fluctuate as much as 30 mm Hg at the frequency of oscillation. These low frequency waves found in arterial blood pressure are called Mayer waves [4].

1.3.5 Control of Respiration

As discussed previously, the main function of respiration is to provide cells with oxygen, and dispose of waste. At different levels of activity, the amount of oxygen consumed and CO2 produced by the cells may vary. Therefore, breathing rate and volume need to be regulated in order to adapt to these changes in requirements. Breathing rate and volume are primarily regulated by chemoreceptors, which are most sensitive to CO2 variations in the blood [4]. An increase in arterial CO2 will cause volume and/or rate of breathing to increase so that the process of CO2 elimination is accelerated. Conversely, a decrease in arterial CO2 will cause breathing volume and/or rate to be decreased so that arterial CO2 levels can be restored.

Breathing rate and volume are also controlled by stretch receptors that are located in the walls of the bronchioles and throughout the lungs. When the alveoli sacs become overly inflated with air, depolarization of associated neurons activate a mechanism that stops further inhalation. This phenomenon is called the Hering -Breuer reflex.

Breathing rate and volume can be controlled voluntarily. Effects of consciously changing breathing patterns will be discussed in later sections.

1.3.6 Respiratory Influences on Heart Rate and Blood Pressure Function

During inhalation, heart rate increases since stretching of the lung walls and associated muscles constrict neighboring blood vessels. Conversely, exhalation decreases heart rate. Respiratory influence on blood pressure can be detected in the arterial blood pressure wave. With each respiratory cycle, the arterial pressure oscillates between 4 to 6 mmHg

at the respiratory frequency [4]. This occurs since signals sent by the respiratory center of the brain excite the vasomotor center of the brain. The vasomotor center controls the radius of blood vessels, therefore, blood pressure is affected.

1.4 Heart Rate Variability

It was discussed previously that the period of the heart beat varies. This is shown in figure 1.4(A). The periodic variations are easiest to detect by noting the differences in distance between respective R waves in the EKG. Such heart rate fluctuations are considered short term.

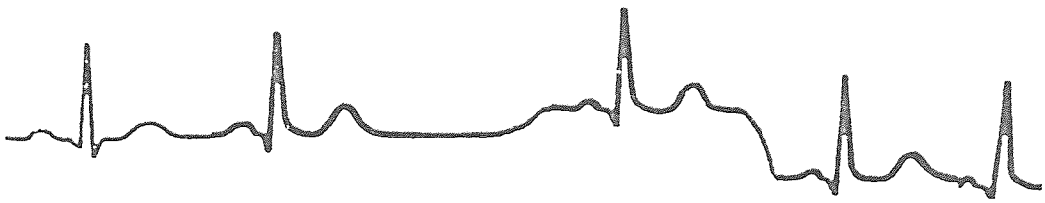

Figure 1.4(A) R-R Interval Variations in EKG

When heart rate information is extracted from the EKG and the result converted into the frequency domain, the resulting plot is called a heart rate variability spectrum. This is shown in figure 1.4(B) [7]. Experiments with pharmacological blockade of the parasympathetic and sympathetic nervous system were performed to determine the significance of the various frequency ranges [1,8]. Parasympathetic blockade abolished all frequency components above 0.15 Hz and substantially decreased the area of lower frequency components. Administration of sympathetic blockade removed residual low

frequency variations. Therefore, frequency components above .15 Hz are purely mediated by parasympathetic influences. Lower frequency fluctuations, however, are influenced and regulated by both the sympathetic and parasympathetic nervous systems. The significance of these results is that the heart rate variability spectrum permits the functioning of the parasympathetic nervous system to be assessed noninvasively via heart rate modulation. Knowledge about the parasympathetic influence on the heart can lead to insight into the function of regulatory mechanisms. Assessment of sympathetic activity, however, is more difficult since there is no frequency range that represents only sympathetic function.

Three peaks are usually found in the spectrum: a high frequency parasympathetic region between .15-.4 Hz, a low range between .05-.15 Hz and a very low frequency region between .02-.05 Hz. The frequency region below .05 Hz is associated with thermoregulatory activity and blood volume [5].

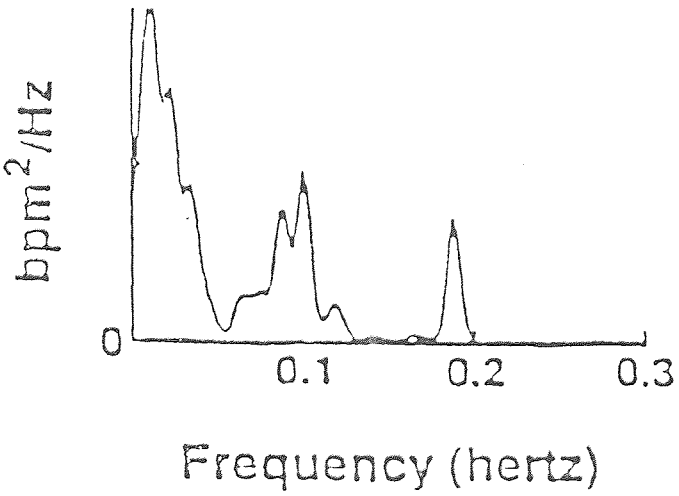

Figure 1.4(B) Heart Rate Variability Spectrum (From J. M. Mathias et al., "Heart Rate Variability: Principles and Measurement," ACC Current Journal Review, 1993)

The high frequency parasympathetic region is attributable to respiratory sinus arrhythmia (RSA), which is the variation in heart rate that occurs simultaneously with respiratory activity. When respiration rate is greater than approximately .15 Hz, the SA node's response to sympathetic activity is too slow to influence RSA; therefore, only parasympathetic control is present [1,8]. The peak of the high frequency parasympathetic region is usually coupled with the dominant respiratory frequency. For example, if an individual's respiratory frequency is .3 Hz (18 breaths per minute), then the spectral peak in the high frequency region will also occur at .3 Hz. If respiration is less than approximately .15 Hz (9 breaths/min.) , however, then RSA is influenced by both parasympathetic and sympathetic action since the respiratory peak will occur at a frequency that is less than .15 Hz. Phenomena which are explained next cause the low frequency and high frequency peaks to be nondiscernible in this case.

The low frequency peak (.05-.15 Hz) arises due to the feedback relationship between blood pressure and heart rate. When respiration of an individual is slow, then the high frequency and low frequency peak will be coalesced together [5]. On the average this coalescing will begin to occur at 9 breaths/min. The frequency of respiration where blending begins, however, may vary significantly with each individual. Therefore, the measurement of parasympathetic activity is not always accurate.

1.5 Blood Pressure Variability

When the arterial blood pressure wave is converted into the frequency domain, the resulting plot is called the blood pressure variability spectrum. The blood pressure plot typically contains a high frequency peak at the respiratory frequency, which shows the amount of respiratory influence on the blood pressure wave. Another frequency peak in the region .05-.13 Hz is representative of the Mayer waves, which arise due to the feedback relationship between blood pressure and heart rate [5].

As mentioned before, the individual spectral components derived from the heart rate variability spectra are not always well defined because there are dynamic interactions between the low frequency and high frequency components at certain respiratory frequencies. This problem also occurs within the blood pressure spectra. The origin of this problem is better understood if the low frequency and high frequency components of the variability plots are viewed as nonlinear coupled oscillators.

1.6 Oscillator Perspective

An oscillator is a system that is approximately periodic in nature and may be linear or nonlinear. The difference between these two types of oscillators can be observed when two oscillators of the same type interact with each other. When two linear oscillators that are operating at different frequencies are coupled, the output of the interacting oscillators will have spectral components only at frequencies of each individual oscillator. In the case of coupled nonlinear oscillators, frequency entrainment, modulation or frequency pulling can occur.

Frequency entrainment occurs if there is a small difference between the respective frequencies of the interacting oscillators [5]. If entrainment occurs, the corresponding spectrum of the coupled oscillators will contain a component at only one frequency. This frequency will correspond to that of the dominant oscillator. Frequency pulling occurs if the frequency difference in coupled oscillators is significant. In this case, the dominant oscillator displaces the spectral component of the weaker oscillator. Nonlinear modulation is another type of phenomenon that occurs in the unstable region prior to full entrainment. In nonlinear modulation, the peaks are partly coalesced, but are still discernible. In this situation, sidebands and harmonics are present in the spectrum.

As is discussed in later chapters, the low frequency peak and high frequency peak interactions are consistent with the properties of nonlinear oscillators. The frequency pulling and modulation phenomena may help explain the variation of the respiratory frequency at which coalescing occurs. Figure 1.6(A) shows a block diagram of the interaction between the heart rate and blood pressure oscillator.

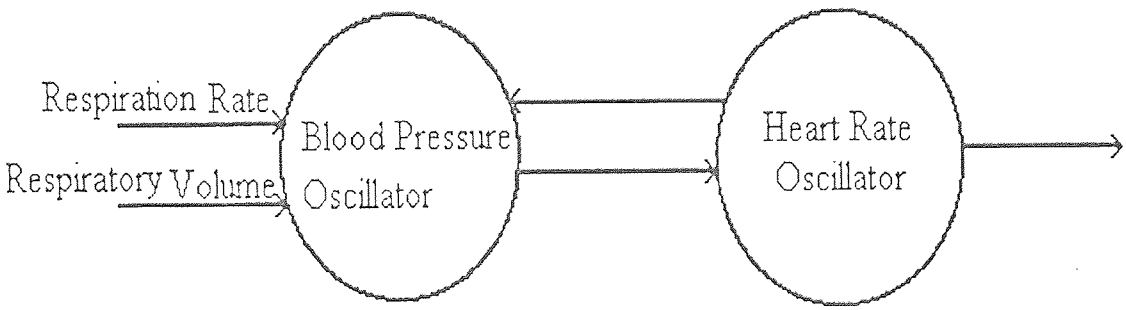

Figure 1.6(A) Interaction between Blood Pressure and Heart Rate Oscillator

Respiratory rate is considered as an input because it is voluntarily controlled in all associated experiments. It has been suggested by [5] that in order to fully describe the spectral components of nonlinear oscillators, the effect of tidal volume on heart rate variability needs to be investigated.

1.7 Statement of Objective

The original objective of this research was to determine whether or not the respiratory volume has a significant impact on parasympathetic activity. The scope of the research, however, was broadened since the complexity of the feedback loops in the body prevent the investigation of relationships of volume in terms of only one physiological parameter. Sympathetic activity, respiratory parameters and cardiac parameters all need to be considered.

An additional objective of this study is to explain and account for some of the complex interactions between physiological parameters. Development of some preliminary methods to determine sympathetic activity is another objective of this research. Knowledge acquired about the various physiological parameters, and methods developed to determine sympathetic activity can then be utilized to determine influences of tidal volume.

The present study required data acquisition of the same subject on different days. Preliminary analysis demonstrated that reproducibility of data acquired on different days was poor. Therefore, an additional objective, the development of methods to relate and compare data acquired at different times, became necessary.

CHAPTER 2

METHODS

2.1 Introduction

The objectives of this chapter are to discuss the laboratory setup, instrumentation, the data acquisition methods, processing methods and the experimental protocol used to collect the data presented in this document. Acquired data consists of EKG, respiration, volume of respiration, blood pressure and metabolic information. In addition, statistical methods utilized to facilitate interpretation of data are discussed.

2.2 Laboratory Setup

Beat to beat arterial finger blood pressure is measured by an Ohmeda 2300 Finapres blood pressure monitor. Figure 2.2(A)[13] is a diagram of this apparatus. The arterial blood pressure of the finger is measured noninvasively by utilizing a finger cuff which is wrapped around the subject's middle finger. The finger cuff contains photoelectric components that measure the amount of blood passing through the finger by plethysmography, and an inflatable bladder for applying pressure to the finger [13]. The finger cuff is connected to the patient interface module which contains a pressure transducer, microprocessor, amplifiers and other necessary electronics. The patient interface connects to the display which shows the systolic, diastolic and mean blood pressure along with the pulse rate. The Finapres is able to noninvasively measure the complete arterial wave form by using the Penaz technique, as explained in [13].

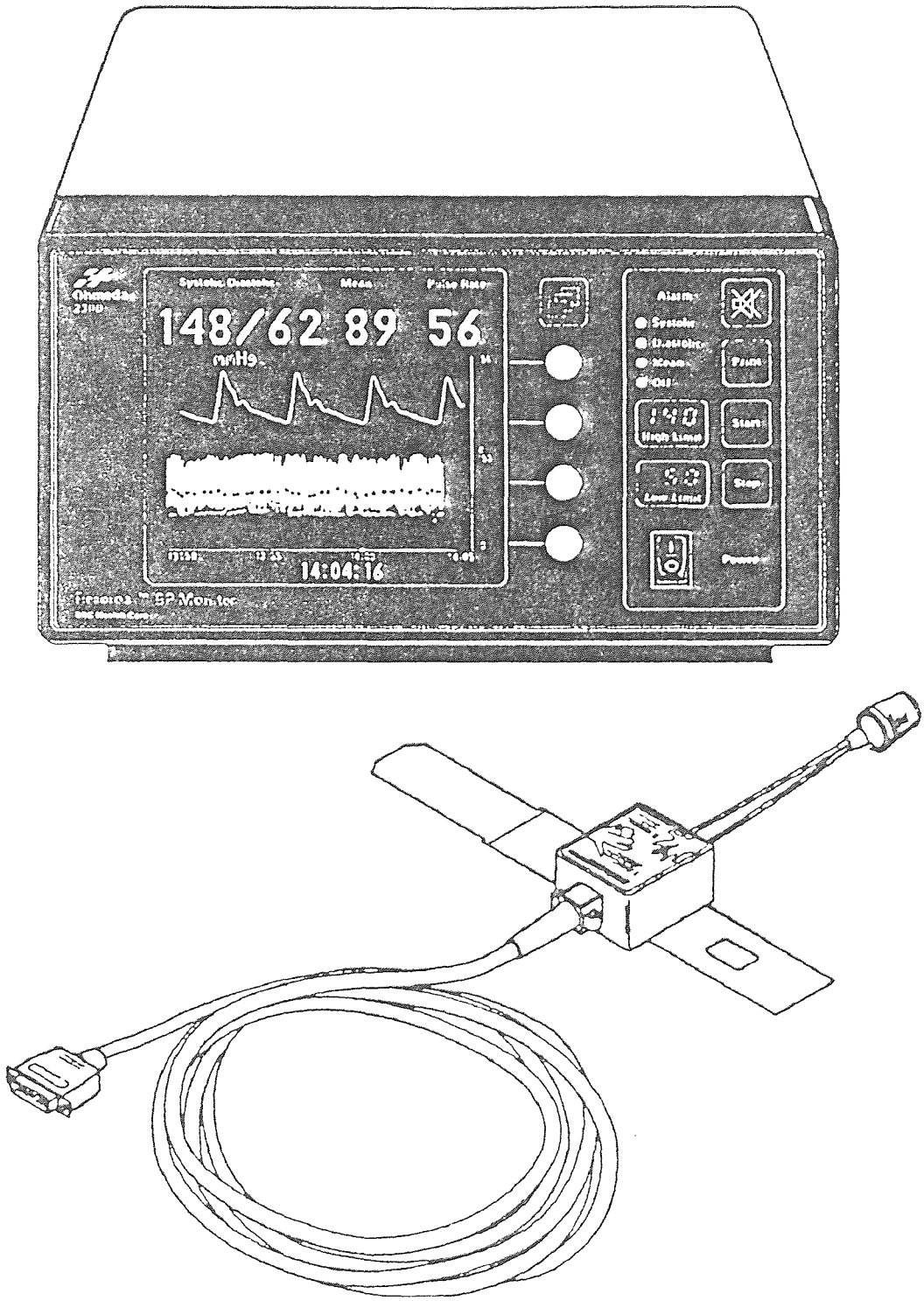

Figure 2.2(A) Ohmeda 2300 Finapres Blood Pressure Monitor (From *2300 Finapres Blood Pressure Monitor Service Manual*, BOC Health Care INC., 1992)

The respiratory rate is determined by impedance pneumography. The subject is connected to the impedance pneumograph with two signal electrodes and one ground electrode. One of the signal electrodes is applied to the right clavicle, and the other is applied to the left upper rib. The resistance between the signal electrodes is measured. As the subject inhales and exhales, the impedance between the two electrodes changes due to the variations in the dimensions of the chest and rib area that result from breathing. This change in resistance is explained by the equation:

$$R \alpha (L/A) \qquad (2.1)$$

where L = length of chest cavity and A = area of chest cavity. A respiration plot that is derived from impedance pneumography is shown in Figure 2.2(B).

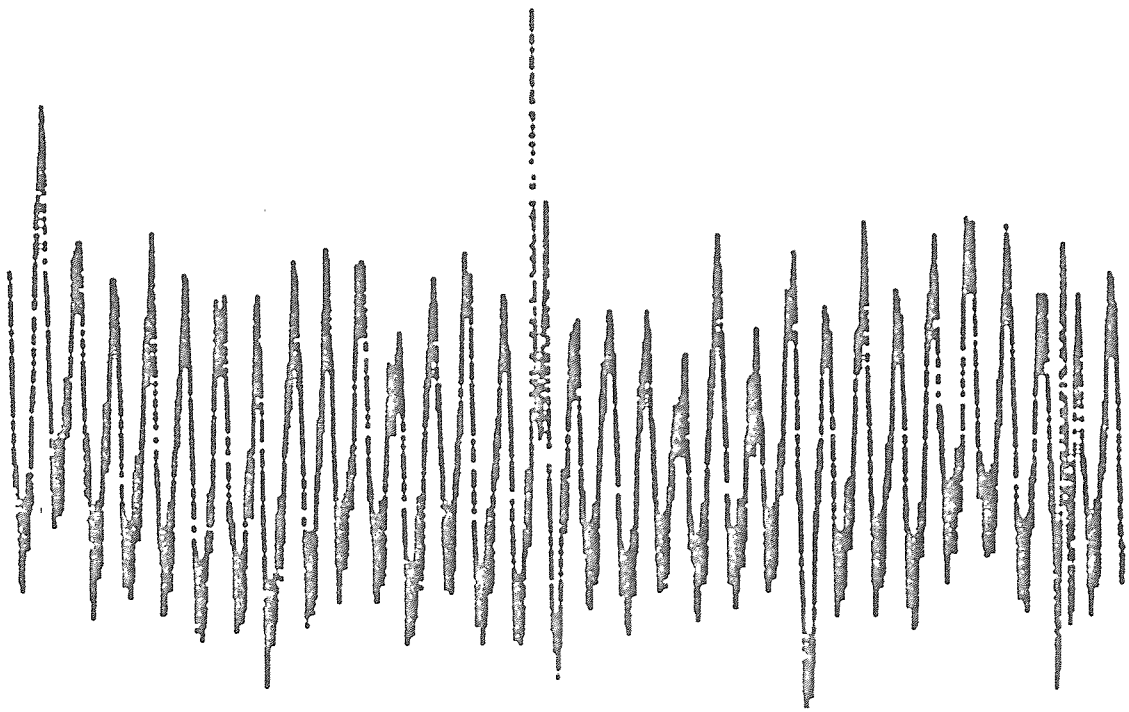

Figure 2.2(B) Respiratory Signal Derived from Impedance Pneumography

Respiration volume is measured with a spirometer. In order to utilize the spirometer, the subject needs to wear a mask which contains valves that allow the subject to inhale room air. Exhaled air is driven into a tube, which connects the mask to the input of the spirometer. The total volume of the exhaled air is automatically displayed on a digital readout. In order to determine and preserve information about volume per breath, mean volume of several breaths and total volume, the output signal from the spirometer is processed as described in section 2.4.

EKG is collected from a Quinton Q4000 stress test monitor as shown in figure 2.2(C) [14]. The patient is connected to the machine via leads that terminate at the patient cable connection. The Q4000 stress test monitor acquires EKG signals of various lead configurations and generates a pulse train which is synchronized with the detection of the QRS complexes.

A Quinton Q-PLEX cardio-pulmonary exercise system, shown in figure 2.2(D) [15], is used to collect petCO2 [mL], RQ ratio, $\dot{V}O2$ [mL/Kg/min.], $\dot{V}CO2$ [L/min.], and $\dot{V}O2$ [L/min.]. Additional measures of respiratory rate and tidal volume are also collected, but only used to verify the accuracy of the impedance pneumograph and spirometer. A mask is used to interface the Q-PLEX to the patient. The spirometer and the Q-PLEX are connected in series; consequently, exhaled gases will enter the Q-PLEX after traveling through the spirometer.

Respiration rate, Lead I and Lead III EKG, synchronous pulse train, blood pressure, and respiratory volume signal outputs are all interfaced to the computer in order to facilitate subsequent analysis. The signals are connected, via an interface box, to a

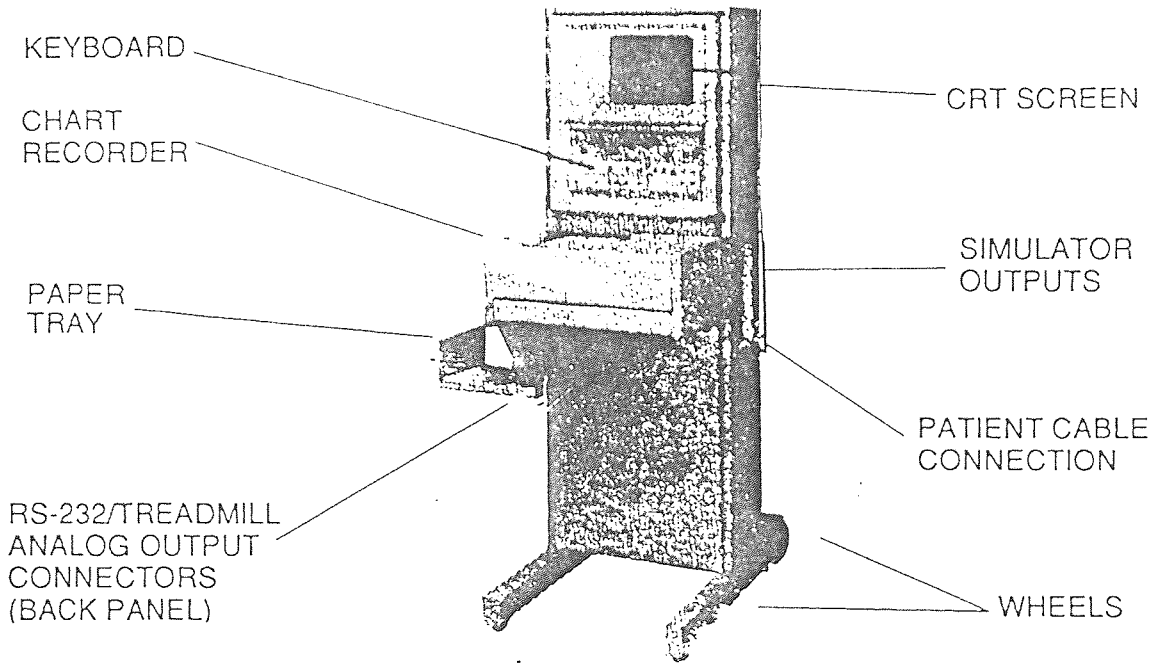

Figure 2.2(C) Quinton Q4000 Sress Test Monitor (From *Q4000 Monitor Operator Manual*, Quinton Instrument Co., 1992)

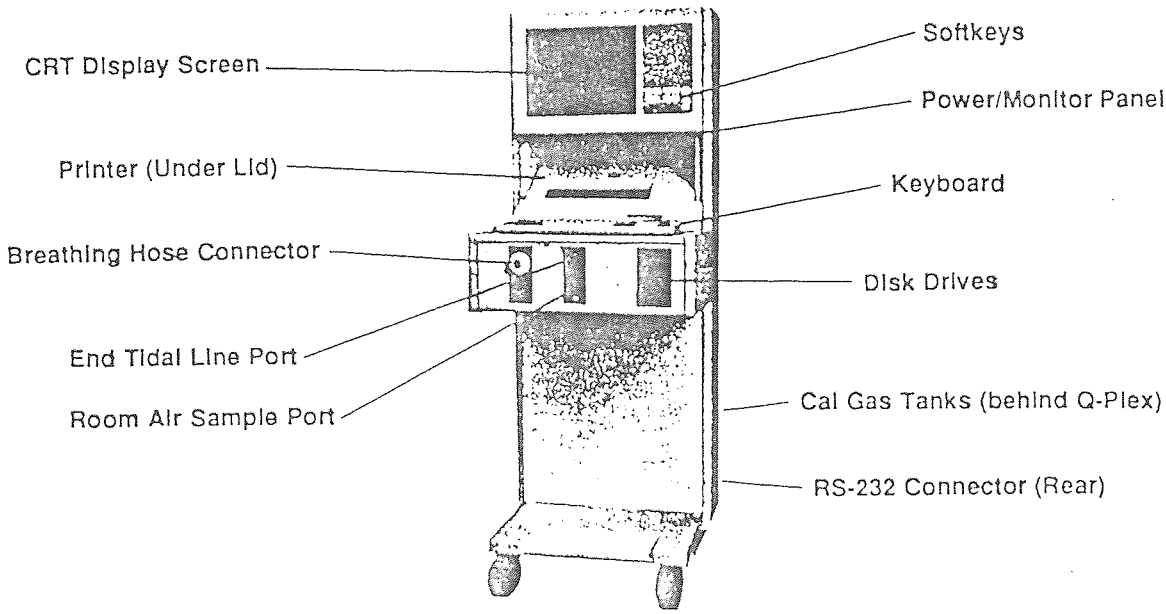

Figure 2.2(D) Quinton Q-PLEX Cardio-Pulmonary Exercise System (From *Q-PLEX Cardio-Pulmonary Exercise System Operator Manual, Quinton Instrument Co., 1992)*

KEITHLEY- Metrabyte DAS-16 board, which is a 16 channel A-D converter. The analog signal outputs are interfaced to channels 0 through 5 of the DAS-16 in the following order: respiration, synchronous pulse train, blood pressure, lead I EKG, respiratory volume, and lead III EKG. An overall block diagram of the experimental set up is shown in figure 2.2(E).

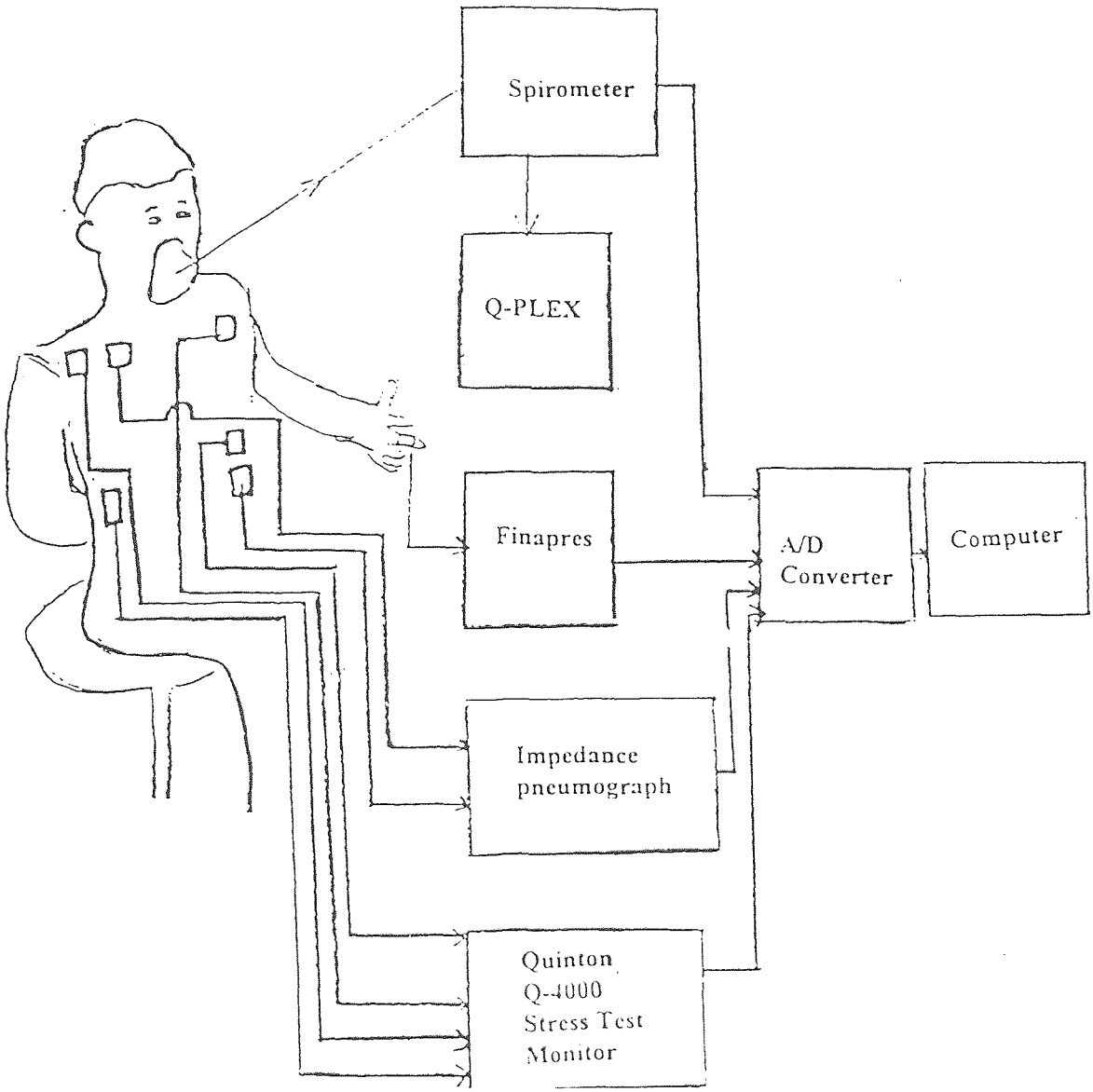

Figure 2.2(E) Overall Experimental Set-up

Before commencing an experiment, it is essential to check that the inputs to the DAS-16 channels are interfaced correctly. This is done using software called Primplot which was developed in our laboratory. Primplot allows the input of a selected channel to be displayed in real-time, so that the presence and gain of each signal can be checked. In order to actually collect data, a high speed data acquisition software program called KEITHLEY-Metrabyte Streamer is utilized. Upon activating Streamer, data are collected and stored in files. Before using Streamer, files must be created with a MKFILE command and file size must be specified. File size is determined by the following equation:

2*data collection time(sec)*number of channels*sampling rate per channel. (2.2)

For the experiment described in section 2.3: number of channels=6, collection time = 120 seconds, and sampling rate = 0.2 KHz per channel. Each section of the protocol is performed for two minutes. Therefore, it facilitates analysis if each two minute portion of data is collected and stored into a separate file. Data are stored in binary form.

Data from the Q-PLEX are not interfaced to the acquisition computer. Instead, data for an entire experiment are stored in one ASCII file in the computer present in the Q-PLEX. Once the Q-PLEX is activated, data are continuously collected into the file. Event markers are used to note the beginnings of the two minute data collection intervals. Therefore, the Q-PLEX data that is associated to a particular 6 channel, two minute file can be identified.

2.3 Experimental Protocol

Ten normal subjects, 6 male and 4 female, whose ages range from 20 to 42, participated in the study. The experiment consisted of three separate sections that were performed on different days at approximately the same time of day.

In section one of the experiment, 5 two minute intervals of data were acquired while the subject rested in a seated position. From this data, the normal resting respiration rate of each individual subject was determined preceding section two.

In section two, seven two minute intervals of data were acquired. In the first interval, the subject was requested to rest. Paced breathing at the predetermined normal rate of respiration without respiratory volume control was collected in the second interval. In the remaining five intervals, the subject performed paced breathing at his predetermined respiration rate while maintaining a specified volume of respiration for the duration of a particular interval. The five respiratory volumes used were either .4, .7, 1, 1.2 and 1.4 liters or .5, .8, 1, 1.3, and 1.5 liters. The set of volumes utilized depended upon the subject's normal tidal volume. If, for example, the subject's average tidal volume per breath was .4 liters or less, then the first set of volumes was used.

Fifteen two minute intervals of data were acquired in section three of the experiment. The subject was requested to rest in the first interval. The next two intervals of data duplicated the protocols of two intervals from section two of the experiment. In the fourth interval, paced breathing was performed at 3/2 of the predetermined rate of respiration without volume control. In the next five intervals, the subject performed paced breathing at this rate while maintaining a specified volume of respiration for the

duration of the interval. In the remaining intervals, the protocol was repeated at 2/3 of the predetermined resting respiration rate. As in section two, the five respiratory volumes used were either .4, .7, 1, 1.2 and 1.4 liters or .5, .8, 1, 1.3, and 1.5 liters.

The subjects used visual feedback to control breathing rate. The control was designed such that the subject could choose a comfortable ratio between inhalation time and exhalation time. Respiratory volume was also controlled visually via a digital display. Before section 2 of the experiment commenced, each subject was requested to practice controlling respiratory rate and volume simultaneously.

Deviations from the above experimental protocol occurred. If the subject experienced extreme discomfort at certain rates and volumes, the associated two minute intervals were skipped. In addition, the sequence of the protocol within section two and section three of the experiment were varied to avoid an ordering effect.

2.4 Data Processing

As previously mentioned, all acquired data, except Q-PLEX data, was in binary form. In order to begin data processing, the data was converted into ASCII form and scanned into a software package called S-Plus for Windows. The scanned S-Plus file consisted of a matrix with six columns, where each column contained the sampled and digitized data from the corresponding channel on the DAS-16. All data, with the exception of the data generated by the Q-PLEX, was processed in S-Plus.

The concepts of heart rate variability were described in chapter 1. In order to measure vagal (parasympathetic) tone and sympathetic tone, S-Plus data was processed as follows: As previously mentioned, the synchronous pulse, which is unevenly spaced

due to respiratory arrhythmia, was generated upon detection of an R wave. An S-Plus program, "pslwsu," was utilized to derive heart rate variability from the synchronous pulse. In the first step of the program, interbeat intervals (IBIs) were derived from the synchronous pulse. An IBI plot consisted of a series of points, whose height signified the amount of time between two consecutive heart beats. A subroutine, called "lsbpu", was then called, which computes the Fourier spectrum of the IBI signal as follows[10]. First, the sequence of IBIs was interpolated to provide a continuous data stream at the same sampling rate as respiration. In this interpolation scheme, which is called backward step function interpolation, the IBI signal was given the value for the IBI for as long as the IBI lasts. For instance, if a beat occurs at time 2 seconds and the next beat occurs at time 2.9 seconds, the interpolated values between time 2 sec and time 2.9 sec are all .9 seconds. If the sampling rate is 200 Hz, then there are 180 interpolated points with a value of .9 seconds. The interpolated IBI (IIBI) resembles a sequence of steps. In figure 2.4(A) [10], the steps needed to convert EKG into interpolated IBIs are shown.

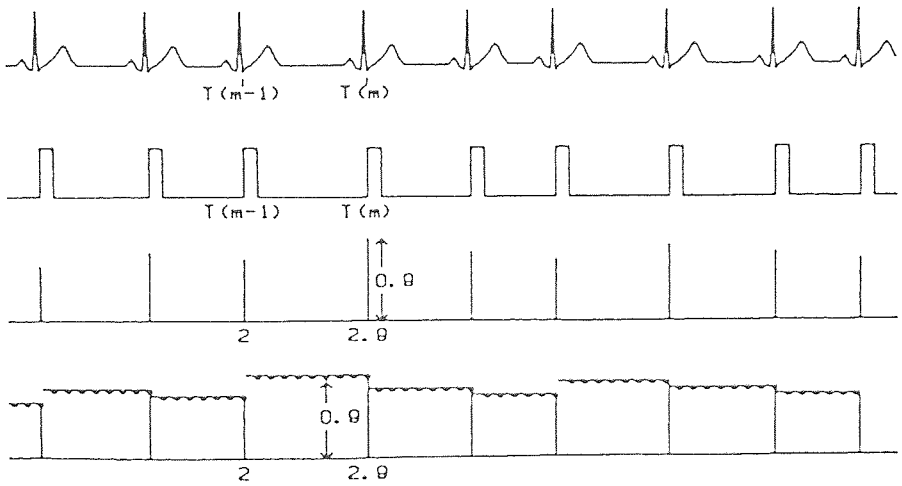

Figure 2.4(A) Steps to convert EKG into IIBI (From S. Shin et al., "Assessment of Autonomic Regulation by the Method of Complex Demodulation," IEEE Trans. Biomedical Engineering, 1989)

The resulting data set contained an excess of data points due to the interpolation. Therefore, the sampling rate was decimated by ten producing a function sampled at 20 Hz. Consequently, the data was reduced to 18 interpolated points with a value of .9 seconds. Decimation is important so that unnecessary redundancy is avoided. In the next step, the resulting IIBI data was detrended using a robust locally weighted regression procedure. This procedure removes very low frequency trends which can distort the spectrum. The resulting data were split into 4096 point sections. Each section was tapered using a split-bell cosine window. Finally, the data were transformed into frequency spectra using Fast Fourier Transform (FFT) algorithms and smoothed across blocks of frequencies to produce a spectrum.

The spectrum and IIBI were utilized to derive autonomic activity levels and HR. In chapter 1 it was explained that a high frequency parasympathetic region occurs in the range of .15-.4 Hz and that a low frequency range, which results from both sympathetic and parasympathetic influences, occurs in the range between .05-0.15 Hz. These autonomic influences were quantified by calculating the area under the low frequency and high frequency peaks. This was done by utilizing an S-Plus program called "spect1," which is shown in appendix A. The frequency ranges used to calculate high frequency areas are shown in table 2.4(A). The reasons for using the ranges in table 2.4(A) will be explained in the next chapter.

The mean heart rate value was derived from the IBI for each two minute sequence of data. This was done by first deriving the mean IBI of the two minute sequence. The

mean heart rate was then calculated by the following equation:

$$HR\ [beats/min.] = SR/MIBI*60 \qquad (2.2).$$

where SR is the sampling rate (200 Hz). The mean IBI value is denoted as MIBI.

Table 2.4(A) Ranges used to Calculate the Area of the High Frequency Peak

Respiration Rate	Range of Area
< 9.1 breaths/min	.1-.4 Hz
9.1-19.1	.15-.4 Hz
> 19.1	.15-.6 Hz

The "lsbpu" program also processes the beat to beat blood pressure data that is present in column three of the S-Plus file. Blood pressure spectra, however, were derived differently from the heart rate variability spectra. The main difference was that detrending, windowing and the FFT algorithms were applied to the original blood pressure signal rather than to a processed version of the original signal. A flowchart of "lsbpu" and "pslwsu" are shown in figure 2.4(B) and 2.4(C). The actual programs can be found in Appendix A.

The Splus program utilized to display the heart rate variability spectra is called "stdgraf." The program utilizes "splus" functions such as "par," which provides control over the action of the graphics device. "Stdbp," which is a revised version of "stdgraf," plots the blood pressure spectra. "Mgraph" is utilized to plot the data in a more condensed form. All programs are found in Appendix A. Graphs generated by these programs are used to derive vagal tone, which will be discussed in chapter 3.

In order to obtain information about volume of respiration, the output signal from the spirometer, which is found in column 5 of the S-Plus data, was processed with an S-

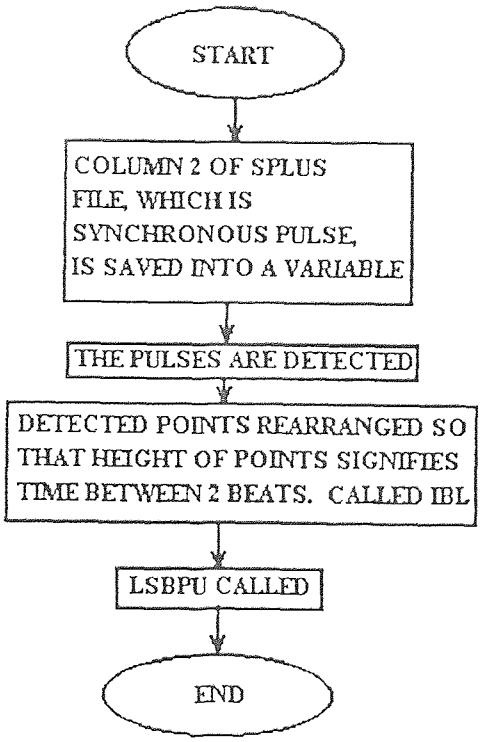

Figure 2.4(B) Flowchart of "Pslwsu"

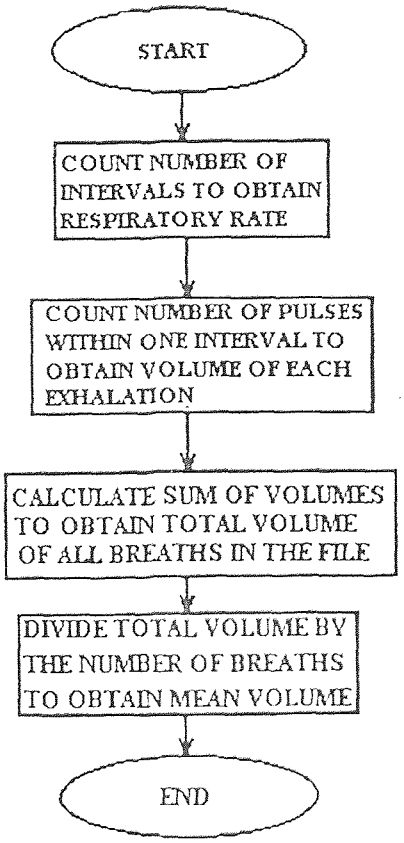

Figure 2.4(C) Flowchart of "Lsbpu"

Plus program called "Spir." In order to understand "spir," the format of the spirometer output must first be explained. The output of the spirometer was in the form of pulse trains that occur at intervals, as shown in figure 2.4(D). Each interval of pulses corresponded to one exhalation. Each individual pulse represented a displacement of 0.1 liters of air. The flat area between each interval of pulses corresponded to an inhalation.

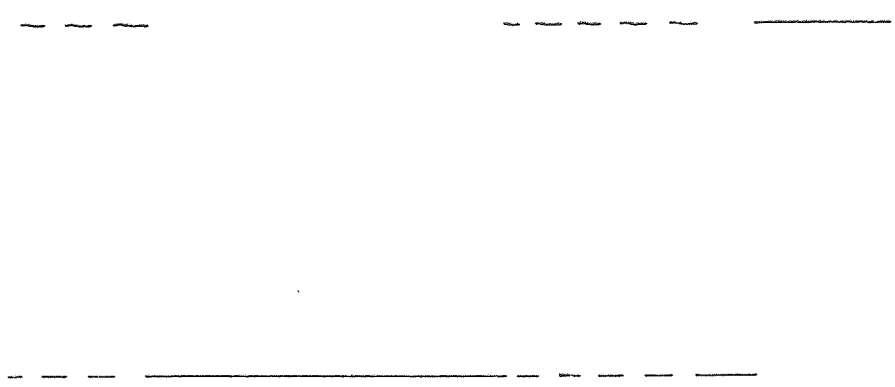

Figure 2.4(D) Output of the Spirometer

This area of inactivity occurred since no input signal was entering the spirometer during inhalation. The "spir" program derives the mean volume, total volume, volume per breath and respiratory rate. A flowchart of this program is shown in figure 2.4(E). The actual program is in Appendix A. The respiration rate was determined by counting the number of flat areas, or inhalations. The next portion of the program evaluated the respiratory volume of each breath by counting up the number of pulses in each interval and multiplying by 0.1. To obtain the total volume, the respiratory volumes obtained for each breath were added together. Mean volume was computed by dividing the total volume by the number of breaths.

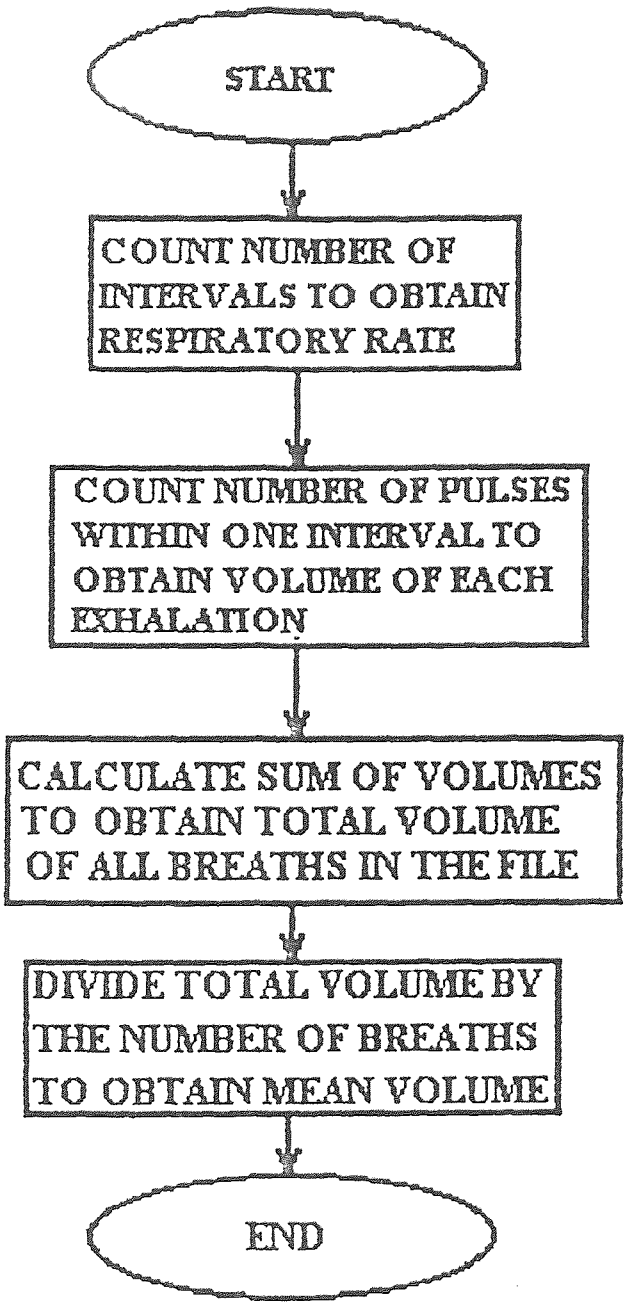

Figure 2.4(E) Flowchart of "Spir"

Data from the Q-PLEX was not processed with S-Plus software. Instead, the entire ASCII file, which contains the Q-PLEX data for an entire experimental section, was printed and processed manually. The printout contained several columns of metabolic data including petCO2 [mL], RQ ratio, $\dot{V}O2$ [L/min.], $\dot{V}O2$ [mL/Kg/min.], and $\dot{V}CO2$ [L/min.]. Figure 2.4(E), which is found in Appendix B, shows a portion of this print out. Multiple values of each metabolic parameter occurred within a two minute interval since Q-PLEX readings occurred for every breath. As mentioned previously, event markers were inserted at the beginning of two minute data collection intervals. At the time that an event marker was entered, however, the output from the Q-PLEX still applied to previous data for petCO2 [mL], RQ ratio, $\dot{V}O2$ [L/min.], $\dot{V}O2$ [mL/Kg/min.] and $\dot{V}CO2$ [L/min.] since it took time for the exhaled gases to traverse through the spirometer and the tubes that were between the mask and the Q-PLEX. Therefore, the readout that truly corresponded to the beginning of the two minute data collection interval actually occurred some time after the event marker . The procedure used to calculate this delay time is shown in Appendix B. Although the calculated delay time is just an approximation, it does improve the accuracy of the results. Since the test time is indicated in the first column of the printout, the delay time and event marker provided enough information so that the beginning and ending times of the two minute intervals could be estimated. Within the appropriate two minute intervals, averages of petCO2 [mL], RQ ratio, $\dot{V}CO2$ [L/min.], $\dot{V}O2$ [L/min.], and $\dot{V}O2$ [mL/Kg/min.] are calculated and entered into an EXCEL spreadsheet which is referenced in the next chapter.

EXCEL software features facilitate derivation of metabolic parameters from the Q-PLEX data. The following quantities were calculated using EXCEL: eff O2, eff CO2, SV[L/beat] and CO [L/min.].

2.5 Statistical Methods

In this research, statistical methods were utilized to facilitate the detection of important relationships between the variables and to support interpretations, projections and conclusions. Several statistical methods were utilized in the present study. In this section, the statistical methods will be explained, and the results of the statistical analyses will be presented. All statistical analysis was performed with a software package called SYSTAT [11].

Analysis of variance (ANOVA) is a statistical technique that was utilized in the present research. This technique is used to detect patterns between independent and dependent variables. The first step of using an ANOVA is to declare a particular hypothesis, which states that fluctuations in the dependent variable are not associated with the changes in the independent variable. This is called the null hypothesis. A probability (P), ranging from zero to one, is computed in order to prove or disprove the hypothesis. If P=.800, for example, then the data fail to provide sufficient evidence to doubt the validity of the null hypothesis [3]. In general, if P<.050, the hypothesis is disproved since there exists a significant relationship between the associated dependent and independent variables. If P<.100, then the relationship between the independent and

dependent variables approaches significance. Table 2.5(A) summarizes the definition and concept of significance.

Table 2.5(A) Definition of Significance (From T. Colton, *Statistics in Medicine*, Little, Brown and Company, 1974)

Statistically significant	= Reject null hypothesis	= Sample value not compatible with null hypothesis value	= Sampling variation is an unlikely explanation of discrepancy between null hypothesis and sample values
Not statistically significant	= Do not reject null hypothesis	= Sample value compatible with null hypothesis value	= Sampling variation is a likely explanation of discrepancy between null hypothesis and sample values

Many different types of ANOVA techniques exist. The ANOVA techniques used in this research were 3x5 ANOVA with POSTHOC, MANOVA, and repeated MANOVA. The three respiratory rates and the five tidal volumes that were maintained by each subject during the experiment were treated as the independent variables in the 3x5 ANOVA method. A 3x5 ANOVA was calculated for the following dependent variables: HR [beats/min.], RQ ratio, petCO2 [mL], parasympathetic activity [V^2], VE [L/min.], VO2 [mL/Kg/min.], VO2 [L/min.], eff O2, eff CO2, VCO2 [L/min.], sn/pn, and low freq. area [V^2]. Twelve separate 3x5 ANOVA calculations were required since there were twelve dependent variables. The resulting P values are shown in table 2.5(B). For each dependent variable, two P values result from the 3x5 ANOVA calculation. P Rate is the probability that variations in a dependent variable resulting from a change in

respiratory rate are arbitrary. P Volume is the probability that respiratory volume and the associated dependent variable are not related. For example, it is shown that a pattern exists between rate and vagal tone since P=0.00.

A POSTHOC is a statistical method used after an ANOVA calculation which provides more detailed information about the variable relationships. In this work, the Tukey method with Bonferonni adjustment was used. The Bonferonni adjustment applies strict conditions which result in higher P values.

The Tukey method determines under which circumstances the significant differences between the variables occur. In table 2.5(B) the 3x5 ANOVA shows that rate vs. vagal tone is significant. Specific information about these variable relationships, however, are not provided by the ANOVA itself. Results of the Tukey method with Bonferonni adjustment for rate vs. parasympathetic activity provide much more information, as shown in table 2.5(C) which is found in Appendix C. Rate 1 is the value of the slowest rate, rate 2 corresponds to the middle rate, and rate three is the fastest respiratory rate. In table 2.5(C) ,for example, it can be observed that significant patterns in the parasympathetic activity associated with rates 1 and 2 occur since p=.001. When the significance of variables between rates 2 and 3 are compared, however, p=.311. Therefore, the null hypothesis cannot be rejected in this case. Since p>.05, the dependent variables are not significant. In table 2.5(C), the same type of analysis was done for respiratory volume vs. parasympathetic activity.

The multiple ANOVA (MANOVA) and repeated MANOVA are similar to the 3x5 ANOVA. The main difference is that only one MANOVA calculation is needed to

Table 2.5(B) 3X5 ANOVA Results

	P Rate	P Volume
Low freq. area[V^2]	0.135	0.069
Vagal Tone [V^2]	0	0.425
sn/pn	0	0.114
HR [beats/min]	0.003	0.003
VE [L/min]	0	0
PetCO2 [mL]	0	0
VO2 L/min	0.027	0.037
VO2 ml/kg/min	0	0
VCO2 L/min	0	0
RQ ratio	0.97	0.081
eff CO2	0	0
eff O2	0	0

Table 2.5(D) MANOVA Results

	P Rate	P Volume	P rate*vol
Low freq. area[V^2]	0.389	0.079	0.986
Vagal Tone [V^2]	0.001	0.853	0.748
sn/pn	0	0.153	0.456
HR [beats/min]	0.025	0.053	0.835
VE [L/min]	0	0	0.002
RQ ratio	0.991	0.095	0.725
VO2 L/min	0.004	0.038	0.589
VCO2 L/min	0.001	0	0.246

Table 2.5(E) Repeated MANOVA Results

	P Rate	P Volume	P rate*vol
Vagal Tone [V^2]	0.001	0.973	0.989
Low freq. area[V^2]	0.224	0.105	0.902
sn/pn	0	0.681	0.364
VE [L/min]	0	0	0.003
PetCO2 [mL]	0	0	0.993
RQ ratio	0.909	0.467	0.92
eff O2	0	0	0
eff CO2	0	0	0.002
VO2 L/min	0	0	0.444
VCO2 L/min	0	0	0.029

provide the P values of multiple dependent variables. In the MANOVA and Repeated MANOVA, the dependent variables are: parasympathetic activity[V^2], sympathetic activity[V^2], VE [L/min.], VO2 [L/min.], VCO2 [L/min.], HR [beats/min.], RQ ratio, sn/pn and petCO2 [mL]. The MANOVA methods only accept one independent variable. In this research, three MANOVA and Repeated MANOVA calculations were done. The first calculation, as shown in table 2.5(D) and 2.5(E), determines P values of the rate vs. the dependent values. The second MANOVA calculation was done with volume as the independent variable. The third MANOVA calculation used rate * volume as the independent variable. In this case, the probability that a pattern exists between the dependent variables at given rates and volumes is evaluated.

The P values obtained from the three ANOVA techniques are similar in all cases. For example, the P values obtained for rate vs. parasympathetic activity are all less than .001. The similarity in the results of the various ANOVA calculations adds credibility to the statistical results.

Multiple regression is another type of statistical technique used. As in the ANOVA calculation, P values were determined. The multiple regression techniques, however, allow interrelationships between the dependent physiological parameters to be evaluated. Two types of multiple regression techniques were utilized in this study: stepwise multiple regression, and linear multiple regression. Although these techniques differ algorithmically, the respective results produced by the different methods were consistent with each other.

Multiple regressions that determine significance between parasympathetic activity and other dependent variables were calculated. The associated dependent variables are HR [beats/min.], SV [L/beat], eff O2, eff CO2, VO2 [L/min.], VO2 [mL/Kg/min.], and VCO2 [L/min.]. The P values are shown in Table 2.5(F). The multiple regression techniques also provided an indication of how each of the dependent variables related to each other by supplying a matrix of correlation coefficients, as seen in table 2.5(G). The correlation coefficients range between -1 and 1. The dependent variables which were more related to each other have correlations closer to -1 or 1; where 1 corresponds to a direct relationship and -1 corresponds to an inverse relationship. Dependent variables that were not related have correlation coefficients closer to 0. Since the maximum correlation coefficient equals 0.745, no strong correlation exists between the dependent variables.

Although the above statistical techniques detect trends in data, the nature of the relationships are not evident until graphs are generated from the data tables. Relationships between variables, and the relevant statistics are discussed in the next chapter. Not all statistical results mentioned in this chapter are utilized in the next chapter. Every statistical result, however, is documented since they may be useful for future work.

Table 2.5(F) Multiple Regression Results

	Vagal Tone [V^2]
HR [beats/min]	P = 0
SV [L/beat]	P = 0.001
eff O2	P = 0.013
eff CO2	P = 0.18
VO2 L/min	P = 0.076
VO2 mL/Kg/min	P = 0
VCO2 L/min	P = 0.209

Table 2.5(G) Matrix of Correlation Coefficients

	eff O2	eff CO2	VO2 L/min	VO2 mL/Kg/min	VCO2 L/min
eff O2	1				
eff CO2	-0.831	1			
VO2 L/min	0.056	0.03	1		
VO2 mL/Kg/min	0.238	-0.456	-0.745	1	
VCO2 L/min	-0.664	0.512	0.026	-0.526	1
	HR [beats/min]	SV [L/beat]			
HR [beats/min]	1				
SV [L/beat]	0.617	1			

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Introduction

Many cardiac, respiratory and autonomic parameters are collected and derived in this work. The processed S-Plus data consists of heart rate variability spectra, high-frequency-peak area [V^2], low-frequency-peak area [V^2], blood pressure variability spectra, respiratory rate [breaths/min.], tidal volume [L], HR [beats/min.], VE [L/min.], SV [L/beat], and CO [L/min.] for each two minute interval of data acquired from the subjects. Processed data from the Q-PLEX provides RQ ratio, VO2 [L/min.], VO2 [mL/Kg/min.], VCO2 [L/min.] , end tidal CO2 [mL], eff CO2, and eff O2 for every two minute interval of data acquired from the subjects. In addition, subjects indicate subjective difficulty level for every two minute interval. The levels used are C, L, M, and V which denote comfortable, lightly difficult, moderately difficult and very difficult.

All of the results for subjects 1 through 10 are shown in tables 3.1(A) through 3.1(J). 3.1(B) through 3.1(J) are in Appendix D. Each individual table contains the results for a particular subject. As various relationships and patterns are explained, the associated data will be referenced.

The original objective of this research was to determine whether or not the respiratory volume has an important impact on heart rate variability. Therefore, at the

Table 3.1(A) Results for Subject 1

Section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[Hz]	[L]	[L]	[mL]	
2a	16	17.5	0.2916667	0.4	0.49	35.7	0.798
2b	16	17.5	0.2916667	0.7	0.7	30.74	0.902
2c	16	17.25	0.2875	1	0.98	25.5	1.09
2d	16	17.25	0.2875	1.2	1.19	20.3	1.095
2e	16	17.25	0.2875	1.4	1.36	18.4	1.04
3a	24	25	0.4166667	0.4	0.44	29.9	0.73
3b	24	25.5	0.425	0.7	0.73	22.3	0.978
3c	24	25.75	0.4291667	1	0.99	18.5	1.02
3d	24	25.2	0.42	1.2	1.19	16.03	0.938
3e	24	26.5	0.4416667	1.4	1.33	14.5	0.914
3f	11	12	0.2	0.4	0.364	32	0.357
3g	11	11.75	0.1958333	0.7	0.7	28	0.526
3h	11	12	0.2	1	0.96	24.4	0.713
3i	11	12	0.2	1.2	1.15	21.6	0.755
3j	11	12.5	0.2083333	1.4	1.3	20.1	0.817

Section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2a	m	70.9	16.72	43.2	8.6	55	5.77
2b	c	39.8	11.05	35.1	12.3	57	8.03
2c	c	23.5	8.03	27.6	16.9	67	6.99
2d	l	15.04	4.8	22	20.5	69	7.49
2e	l	17.3	3.52	22.1	23.5	73	7.82
3a	l	23.6	10.42	34.6	11	62	5.07
3b	c	6.45	5.25	18.9	18.6	71	6.06
3c	l	1.73	3.42	4.8	25.5	80	7.1
3d	l	4.82	7.53	12.2	30	82	7.6
3e	m	10.7	7.21	18.1	35.2	77	8.92
3f	c	131.4	14.71	51.1	4.4	68	8.87
3g	c	55.04	9.42	37.9	8.2	59	8.27
3h	c	43.12	9.56	33	11.5	62	6.42
3i	l	84.9	8.09	37.4	13.8	63	6.85
3j	l	31.4	4.59	27.7	16.3	69	6.72

Section	vco2	vo2	eff o2	eff co2	sv	sn/pn	co
	[L/min]	[L/min]			[L/beat]		[L/min]
2a	0.3	0.37	23.4	28.5	0.0066	0.236	0.366
2b	0.46	0.51	24.1	26.7	0.0089	0.277	0.509
2c	0.48	0.44	38.2	34.6	0.0066	0.341	0.443
2d	0.52	0.48	43.1	39.3	0.0069	0.319	0.476
2e	0.51	0.49	47.3	45.7	0.0068	0.203	0.496
3a	0.24	0.32	34.1	46.4	0.0052	0.441	0.323
3b	0.38	0.39	48.2	49	0.0054	0.814	0.386
3c	0.46	0.45	56.5	55	0.0056	1.98	0.451
3d	0.45	0.48	62.2	66.2	0.0059	1.56	0.482
3e	0.52	0.57	62.2	68.1	0.0074	0.67	0.567
3f	0.21	0.56	7.75	21.2	0.0082	0.11	0.563
3g	0.27	0.53	15.7	30.1	0.0089	0.171	0.526
3h	0.29	0.41	28.3	39.6	0.0066	0.221	0.407
3i	0.33	0.44	31.6	41.9	0.0069	0.095	0.437
3j	0.35	0.43	38	46.5	0.0062	0.146	0.427

beginning of the study, the effect of regulating respiratory volume at a given respiratory rate on heart rate variability was the only phenomenon investigated. It soon became evident that, for three reasons, the scope of the research needed to be broadened.

Many cardiac, respiratory and autonomic nervous system parameters influence heart rate variability. Therefore, it is difficult to investigate the effect of just one factor. Increased complexity also occurs since all factors that influence heart rate variability also interact, influence and regulate each other. An objective of this study is to explain and account for some of the complex interactions that occur in the body. This is done in sections 3.5 -3.8.

The process of acquiring and measuring data will both change and corrupt physiological parameters. Inaccuracies of results that occur due to data acquisition and analysis are cited in section 3.4.

In present data analysis techniques, there is no method to quantify sympathetic activity. An objective of this study is to propose methods of acquiring a measure of sympathetic activity. This is done is sections 3.1-3.5.

3.2 The Autonomic Nervous System Measurement

As mentioned previously, areas under the high frequency and low frequency peaks of the heart rate variability spectra were calculated in order to quantify the autonomic influences that produce heart rate variability. The area of the high frequency peak contributes a great deal to the research results since it indicates the level of parasympathetic activity. The area of the low frequency peak, however, represents a mixture of both sympathetic and parasympathetic influences; therefore, it is less useful since not as much information

can be elicited. Since many of the results from this study are based on these area measurements, it is important to discuss the advantages and disadvantages of the techniques used to obtain this information. The methods utilized in our laboratory vary from the common procedure which is explained by [6]. [6] determines vagal tone by calculating the area in the range of 0.15-0.4 Hz because the high frequency peak is typically within this range. In the present research vagal tone was usually determined by calculating the area in the range of 0.15-0.4 Hz . In some cases, however, different frequency ranges were used since heart rate variability spectra derived experimentally were not always typical. Specifically, if respiratory rate was below 9 breaths/minute or above 19 breaths per minute, then the range of .15-.4 Hz will be incorrect since the parasympathetic peak is shifted either below 0.15 Hz or above 0.4 Hz, as in figure 3.2(A).

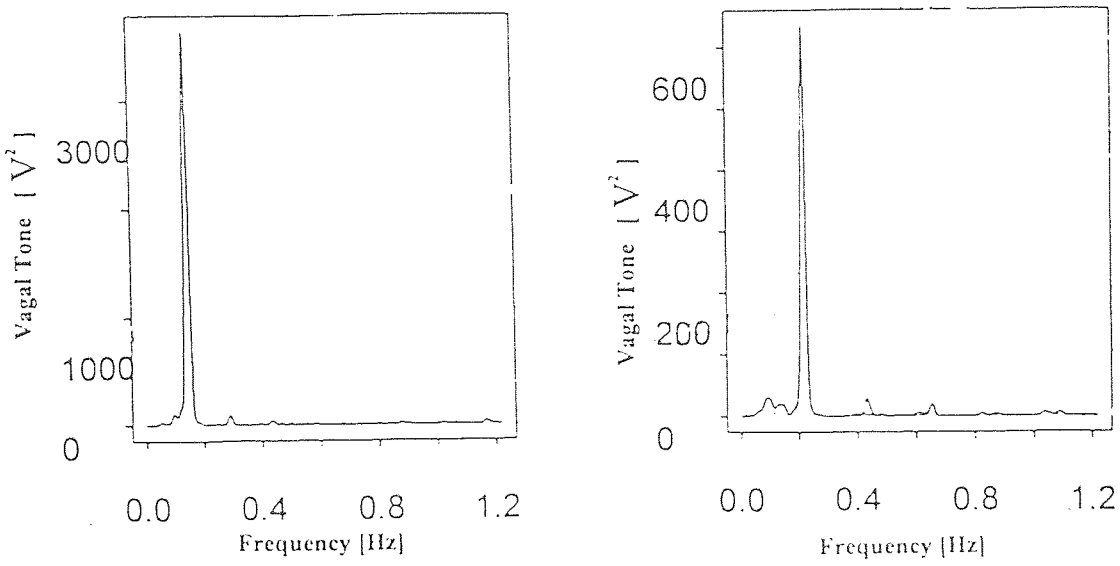

Figure 3.2(A) High Frequency Peak in the Left Plot is at a Lower Frequency than the Right Plot since the Respiratory Rate is Slower in this Case.

Therefore, in this research, the ranges used to calculate the area were dependent upon the respiratory rate. Table 2.4(A) shows the frequency ranges used to calculate areas of the high frequency peak. The resulting vagal tones of all the subjects are listed in the middle section of column 3 of tables 3.1(A) through 3.1(J).

Areas under the low frequency peaks are shown in the middle section of column 4 of tables 3.1(A) through 3.1(J). The ranges used to calculate these areas are from .05 Hz to the frequency where the parasympathetic peak begins. Therefore, in the typical case, the range is from .05-.15 Hz.

It is important to mention the assumption that is made when the areas are calculated: the low frequency and high frequency peaks are treated as independent entities. These peaks, however, may actually be coalesced, either partially or completely. Coalescing occurs due to the oscillatory properties of the peaks which are explained in chapter one. No method, however, has been developed to take this phenomenon into account.

It is speculated that the relationships between the BP spectrum peak areas and heart rate variability peak areas will add insight on the extent of coalescing and quantify the extent of sympathetic influence. In addition, oscillatory phenomena, that are discussed in chapter 1, are most apparent in the blood pressure spectrum. Hence, investigation and identification of entrainment, frequency pulling and nonlinear modulation of the high and low frequency blood pressure peaks may also add insight to the degree of coalescing and amount of sympathetic influence in the heart rate variability plot.

Comparison of heart rate variability and blood pressure variability plots were touched upon in this research. It was discovered, however, that the method used to derive the blood pressure variability plot made it impossible to detect any relationships. Specifically, the frequency component of the entire BP signal was calculated. Since the blood pressure signal is dependent on the heart rate, the blood pressure spectrum contains artifact components due to heart rate variability. In order to prevent the occurrence of heart rate variability components in the blood pressure, the FFT of interpolated systolic blood pressure values needs to be determined. This will be developed in the future.

3.3 HR and Vagal Tone

It was discussed in chapter 1 that heart rate changes are due to the parasympathetic and sympathetic nerves enervating the heart. There are four possible mechanisms that lead to a change in heart rate. A decrease in parasympathetic influence or increase in sympathetic influence will result in an increase in heart rate. Conversely, an increase in parasympathetic influence or a decrease in sympathetic influence will result in a decrease in heart rate. Only parasympathetic influence, however, can be directly measured by using the heart rate variability spectrum. It is conjectured in the present research that using HR along with vagal tone is a powerful method to determine sympathetic influence. This theory can be applied by generating a parasympathetic activity vs. HR plot as shown in figure 3.3(A). Each point corresponds to a particular two minute data sequence. Therefore, when two points are compared, the relative changes in heart rate and parasympathetic activity are apparent. The relative changes in sympathetic activity can be inferred by observing the direction in which both HR and vagal tone change. If HR

and parasympathetic activity both decrease, then it implies that sympathetic activity decreased. This conclusion can be reached since, as mentioned before, a decrease in heart rate results from either an increase in vagal tone or a decrease in sympathetic influence. If it is known that parasympathetic activity increased then, by the process of elimination, sympathetic activity decreased. Consider for example, the two points in figure 3.3(A) which are labeled X and Y. Point X shows HR and vagal tone of subject 1 while breathing at 12 breaths/minute and .4 liters/breath. After finishing sequence X, the subject breathed at 12 breaths/minute and .7 liters/breath. As shown by point Y, both HR and vagal tone decreased. Therefore, it is conjectured that subject 1's sympathetic activity decreased at this time. Conversely, if HR and parasympathetic activity both increase, it implies that sympathetic activity increased. In the cases that HR and parasympathetic activity change in the same direction, the sympathetic influence overrides the parasympathetic component. If HR and parasympathetic activity change in opposite directions, however, it is difficult to infer the influences of sympathetic activity. For example, if HR increases and vagal tone decreases, then sympathetic influence either remains stable, increases or insignificantly decreases. In most cases, HR and parasympathetic activity change in opposite directions. This is evident in figure 3.3(A) when the overall trend is observed. If a linear regression is done, a line with a negative slope would result. Statistical analysis confirms that vagal tone and HR are related. Multiple regression analysis yields a P value of 0.00. In the future, determination of sympathetic influence by using HR and vagal tone needs to be investigated further. For example, research is needed to quantify the level of

sympathetic activity by investigating the proportion or relative rate of change of vagal tone compared to HR. In addition, if blood pressure values are acquired, vagal tone vs. BP may contribute additional information since, as mentioned in chapter 1, there is significant sympathetic influence on BP.

In the future, investigation and comparison of methods proposed in the final paragraph of section 3.2 and in this section may both be used together to quantify sympathetic activity and coalescing of peaks.

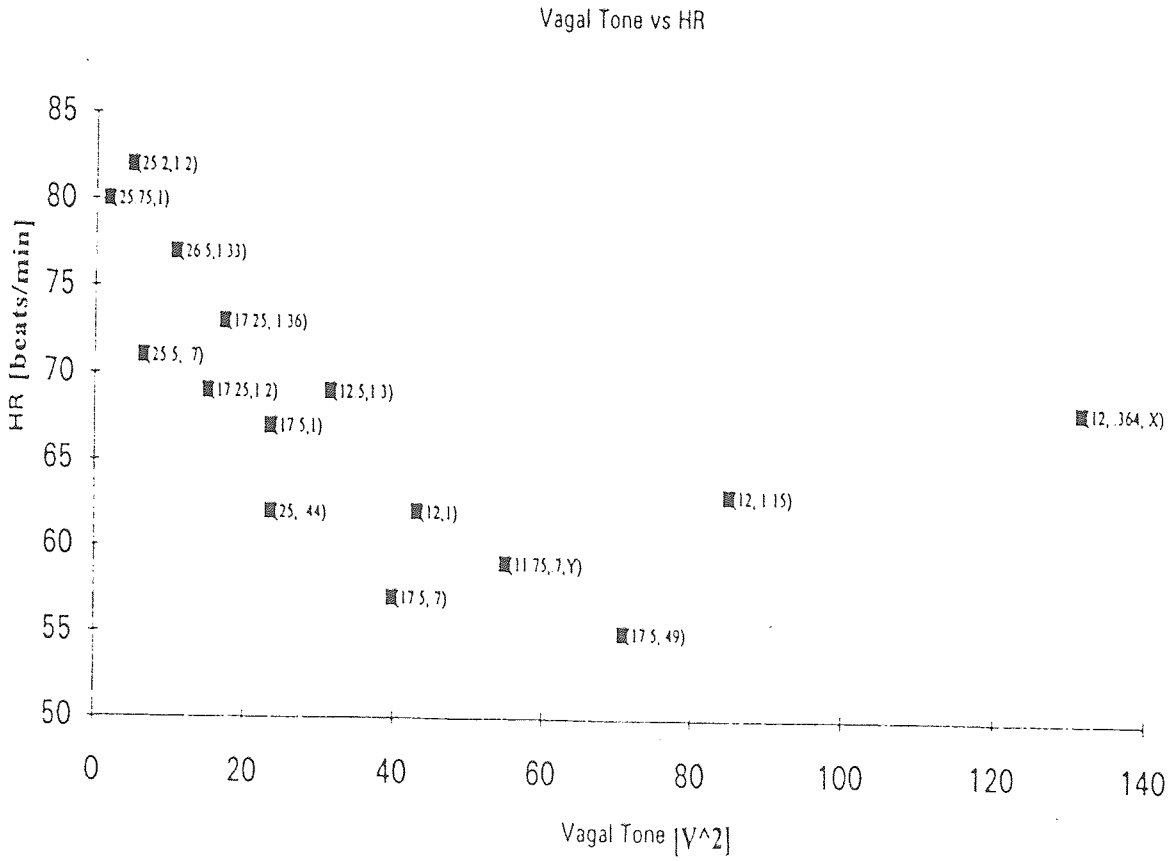

Figure 3.3(A) Vagal Tone vs. Heart Rate

3.4 Reproducibility of Data

Data is reproducible if comparable results occur when an experiment is repeated or continued on a different day. In this study, experimentation occurs on three separate days because the experimental protocol was too lengthy to do in one or two sessions. In order to maintain the same conditions, subjects were tested at the same time of day for all sections and requested to abstain from alcoholic and caffeine beverages for 24 hours prior to each experiment. In 5 out of 10 subjects, however, reproducibility of parasympathetic activity between the second and third experimental sessions were poor. The subjects' respiratory rates were above and below the normal rate during the third experimental section, and at normal respiratory rates during the second section (The first section is not included in the determination of vagal tone reproducibility since none of the associated data is used in the results.)

Reproducibility of vagal tone is difficult since overall parasympathetic activity continuously fluctuates. Emotional state of the subject, weather, amount of sleep, interactions with people and many other factors will alter overall parasympathetic level. Such environmental factors can even influence the nervous system from one minute to the next. For example, the level of a subject's autonomic nervous system is effected by the investigator's instructions and/or if the subject knows that the experiment is almost finished. Most of these factors are difficult or impossible to control. Therefore, reproducibility in experiments that measure vagal tone are likely to be poor. In the future, a method needs to be devised so that acquired vagal tone can be normalized.

In the present study, methods are developed to determine the relative differences of overall vagal tone in the experimental sections. Two methods are utilized to

determine the relative differences in overall vagal tone. The first method uses the established relationship between respiratory rate and vagal tone. It has been shown by [2] that vagal tone and respiratory rate have an inverse relationship. The statistical results in this study support the established relationship since the 3 x 5 ANOVA shows that respiratory rate vs. vagal tone has a P=0.000, and repeated MANOVA and MANOVA calculate P to be 0.001. If only the two respiration rates from the third experimental section are considered, then 100% of the data from the present study follows the expected trend. When data from both the second and third section are considered there are a total of three respiratory rates. Since one of these rates was acquired on a different day, it is possible that the established relationship will not be affirmed due to poor reproducibility. As expected, only 6 out of 9 subjects' data are consistent with the established relationship due to poor reproducibility. Table 3.4(A) indicates a conjecture about the difference in overall vagal tone between the different days for all subjects.

Table 3.4(A) Conjecture of Differences in Overall Vagal Tone Using Method 1

Subject	Overall vagal tone of subject on day 2 relative to day 3
1	same
2	same
3	same
4	lower
5	higher
6	same
7	same
8	same
9	lower

Figure 3.4(A), for example, shows respiratory rate vs. vagal tone for subject 1. It is conjectured that the subject had the same overall parasympathetic activity on both test days since the expected inverse relationship between respiration rate and vagal tone occurs at all volumes. Hence, the reproducibility of the vagal tone data is good for subject 1. The respiration rate vs. vagal tone plot for subject 5 is shown in figure 3.4(B). In this case, the trend is opposite to the expected result for 3 out of 5 volumes since the middle rate has a higher vagal tone than the slow respiratory rate. Therefore, it is theorized that subject 5 had an overall higher vagal tone during the second experimental section. In figure 3.4(C), respiratory rate vs. vagal tone is shown for subject 9. In this case, the vagal tones associated with the faster respiratory rate are higher than for the middle rate. Hence, it is conjectured that subject 9's overall vagal tone is low during the second experimental section as compared to the third experimental section. Perhaps the subject was nervous during this phase of experimentation.

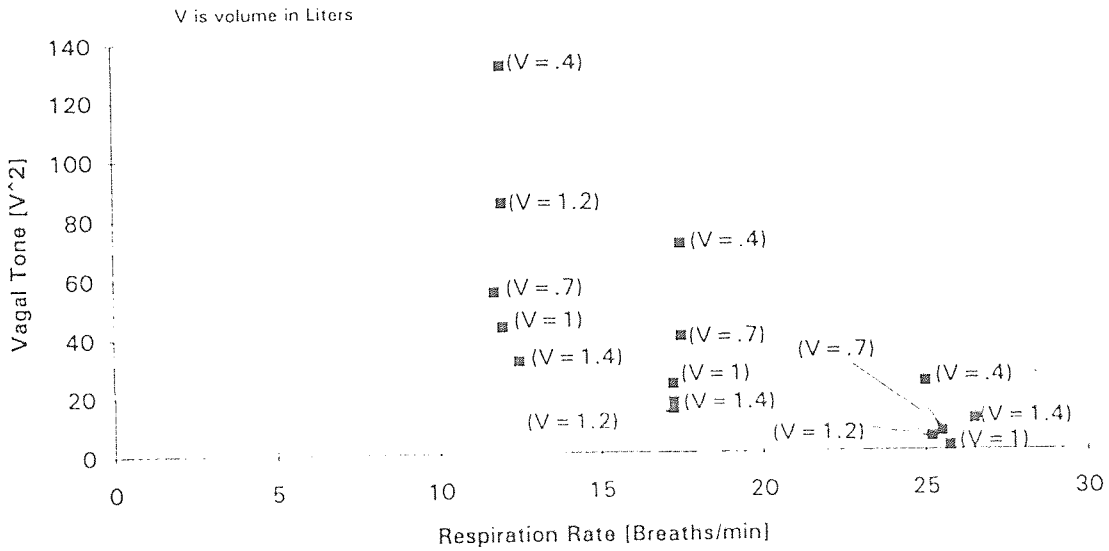

Figure 3.4(A) Respiratory Rate vs. Vagal Tone for Subject 1

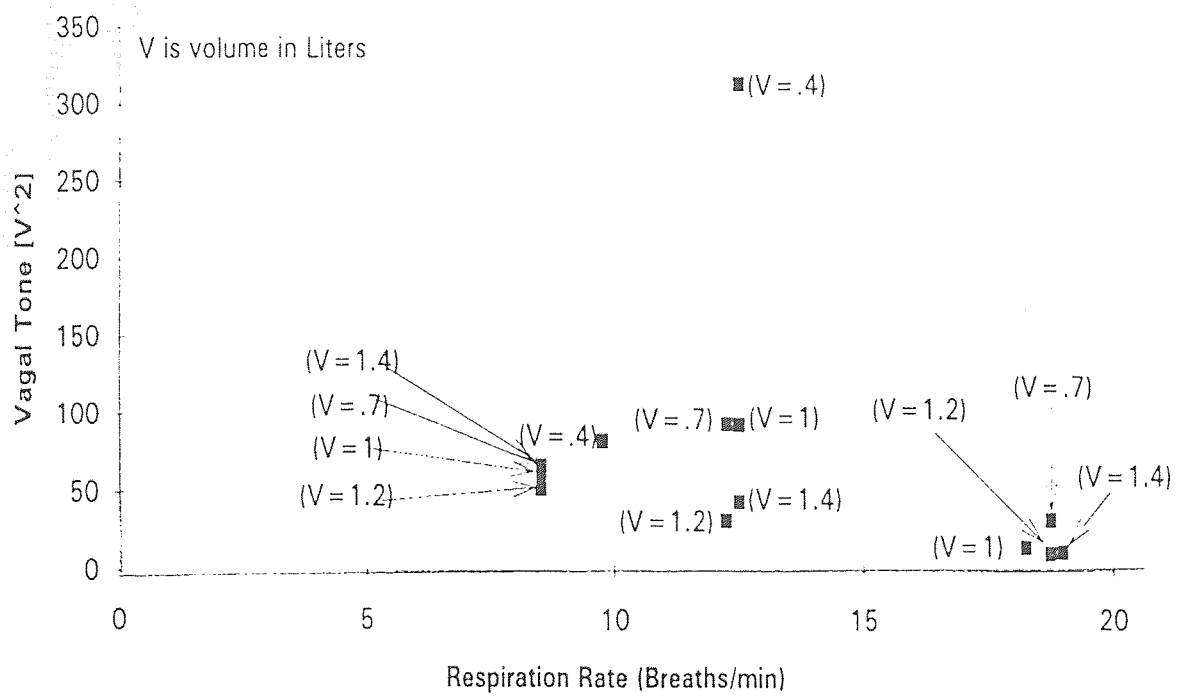

Figure 3.4(B) Respiratory Rate vs. Vagal Tone for Subject 5

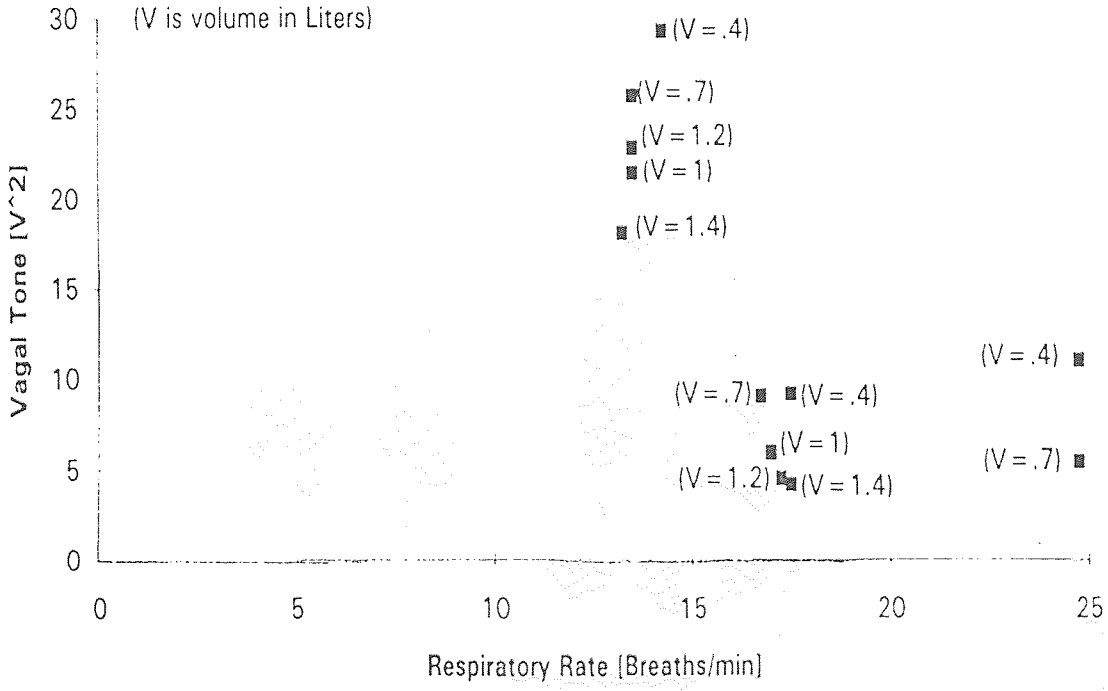

Figure 3.4(C) Respiratory Rate vs. Vagal Tone for Subject 9

The second method determines relative differences in overall vagal tone by using data that was acquired for this purpose. In both experimental sections, two minute intervals of data are acquired while the subject is resting in a seated position and while the subject is performing paced breathing at his/her normal respiratory rate. The resulting vagal tones of the rest and paced breathing data from the different sections are then compared, and conclusions are made about differences in overall parasympathetic activity. The resulting vagal tones are shown for nine out of the ten subjects in table 3.4(B).

Table 3.4(B) Differences in Overall Vagal Tone Using Method 2

	vagal tone	resp rate	vagal tone	resp rate
SUBJECT	Rest Sec. 2	Rest Sec. 2	Rest Sec. 3	Rest Sec. 3
1	91	12.5	58.9	13.25
2	5.22	18.5	5.02	19.25
3	24.6	13.25	30.5	13.5
4	14.41	16	99.1	14.25
5	156.15	15	49.1	14.5
6	12.1	12.5	13.1	22
7	17.9	14.25	32.1	18.25
8	12.4	16.5	19.5	15.5
9	9.83	15	13	16.5

	vagal tone	resp rate	vagal tone	resp rate
subject	pace sec. 2	pace sec. 2	pace sec. 3	pace sec. 3
1	30.6	17	35.8	17
2	6.7	18.25	7.91	18.5
3	17.74	13.75	18.4	14
4	16.1	14.75	37.2	14.5
5	142.35	12.5	27.6	13.5
6	12.7	18.75	25.8	19
7	10.9	18	2.38	18.25
8	5.19	18.5	9.8	15
9	8.66	17.25	15.8	18.5

SUBJECT	Overall Vagal Tone on Day2 Relative to Day 3
1	Inconclusive
2	Same
3	Same
4	Lower
5	Higher
6	Lower
7	Inconclusive
8	Same
9	Lower

Conjectures are indicated about the difference in overall vagal tone between the different days. For example, subject 6 has a resting vagal tone of 12.1 V^2 at an average respiratory rate of 12.5 breaths/min. in the second section, and a resting vagal tone of 13.1 V^2 at an average respiratory rate of 22 breaths/min. in the third section. Vagal tone is at about the same level for both sections. Average respiratory rate, however, is significantly higher in the second experimental section. Therefore, the rest data sequences indicate that overall vagal tone is lower in the second experimental section. During 19 breaths/minute paced breathing, subject 6 has vagal tones of 12.7 V^2 and 25.8 V^2 for section 2 and section 3 respectively. Therefore, the paced breathing data sequences also indicate that overall vagal tone is lower in the second experimental section. Since the rest and paced sequences evoke the same result, it can be concluded that overall vagal tone is lower during the second experimental section. In two subjects, the rest and paced breathing data sequences indicate opposite results. In these cases, the relative overall vagal tone is considered inconclusive.

The two methods of determining overall parasympathetic activity produce consistent results for 6 out of 9 subjects. Two out of the three results are inconsistent since method two yields inconclusive results. The information acquired from implementing the two methods is utilized in later sections. The methods developed are a first step to the long process of developing a process of normalizing data acquired at different times.

3.5 Volume vs. Vagal Tone, HR and Gain

As mentioned previously, it has been established that respiratory rate and vagal tone have an inverse relationship. It has been suggested that in addition to respiratory rate, volume is a significant factor in the level of parasympathetic activity. Experiments that control or measure volume, however, are rarely encountered. Eckburg cited [2] prominent researchers in the field of R-R interval power spectrum research. Only 11% of these investigators controlled volume along with the respiration rate. In this section, the relationship of both volume vs. vagal tone, volume vs. HR, volume vs. gain are investigated. The resulting trends are then compared with the results of other investigators.

The relationships between volume and vagal tone are examined by plotting both volume vs. vagal tone and respiration rate vs. vagal tone. In figure 3.5(A), volume vs. vagal tone is shown.

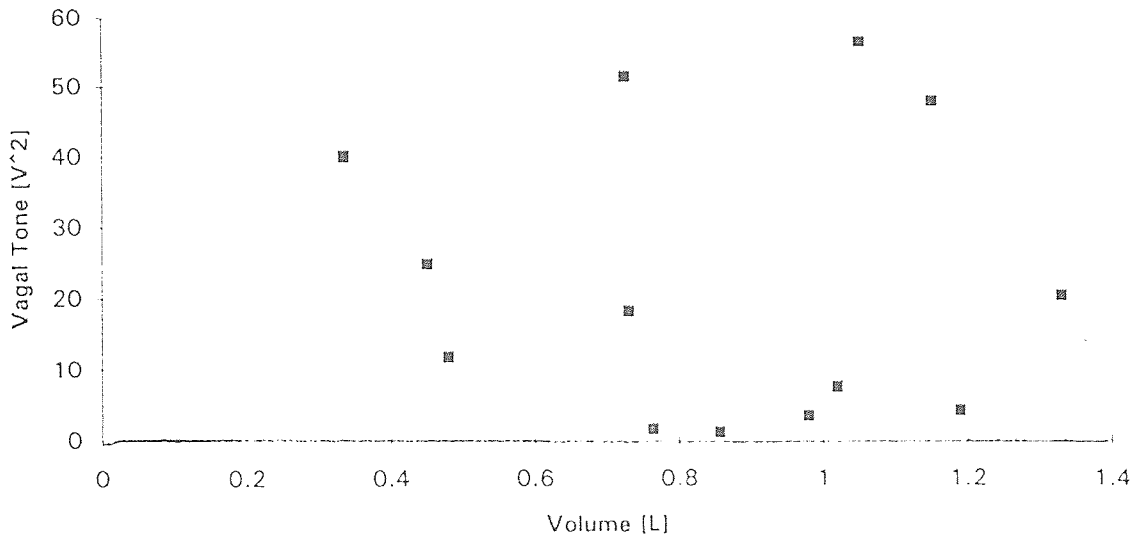

Figure 3.5(A) Volume vs. Vagal Tone

No apparent relationship between volume and vagal tone are observed. In addition, statistical analysis supports this observation since P values are high. Specifically, a 3x5 ANOVA analysis results in a P value of .425. The MANOVA analysis yields a P value of 0.853. A P value of 0.973 results from a repeated MANOVA calculation.

In figure 3.5(B) a respiration rate vs. vagal tone plot is shown. At each data point, the average tidal volume that is maintained for the two minute data sequence is indicated. A weak relationship between volume and parasympathetic activity is detectable when a respiration vs. vagal tone plot is utilized. The weak relationship observed is that as the volume maintained at a given respiratory rate increases, parasympathetic activity decreases. Table 3.5(A) indicates for which subjects and associated respiratory rates that the relationship applies. In three subjects, volume and vagal tone have an inverse relationship for 2 out of 3 respiratory rates. In three of the subjects, the volume and vagal tone are inversely proportional for 1 out of three respiratory rates. In three subjects, no relationship is seen at any rate. There are a total of 27 respiratory rates for 9 subjects. In 18 out of 29 rates, no relationship between volume and vagal tone is observed. As shown in table 3.5(A), the relationship between volume and vagal tone is strengthened if only the extreme values of volume are considered. Such an improvement in the trend may occur since weak patterns in data may become more obvious when differences in the independent variable are larger. If all volumes in subject 1 are considered, for example, no relationship is observed in any case. If only the minimum and maximum volumes of subject 1 are considered, however, the relationship is quite strong. Specifically, at all respiratory rates, the maximum value of vagal tone corresponds to the

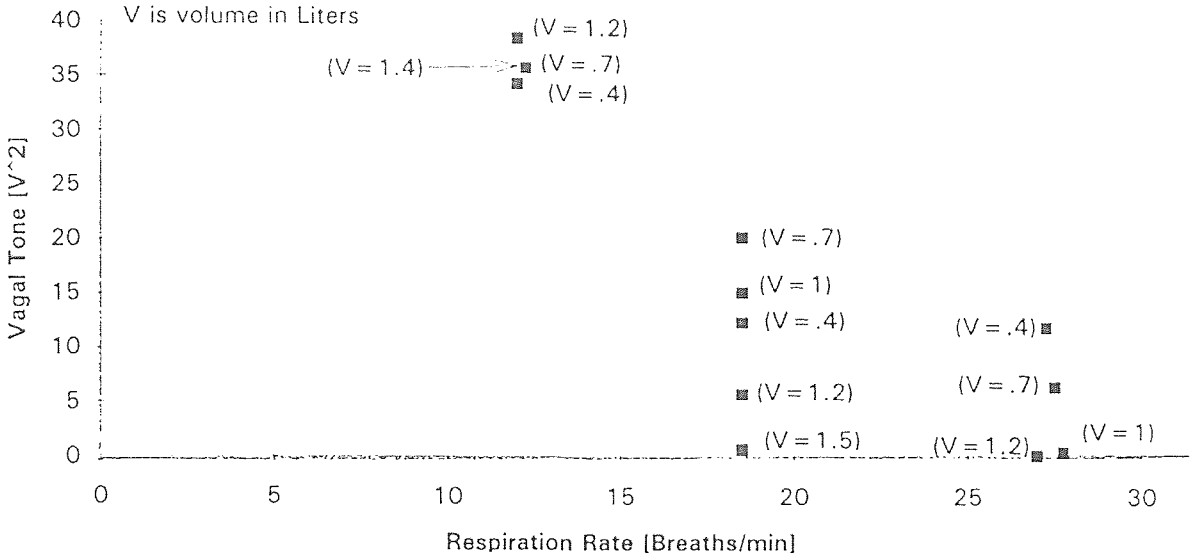

Figure 3.5(B) Respiration Rate vs. Vagal Tone

Table 3.5(A) Results Pertaining to Volume vs. Vagal Tone Relationship

	****All volumes considered****				Min and Max values of volume only	
				Tot rates that		tot rates that
subject	slow rate 1	mid rate 2	fast rate 3	follow trend		follow trend
1	no	no	no	0		2
2	no	no	yes	1		1
3	no	yes	no	1		1
4	no	no	yes	1		2
5	no	no	no	0		2
6	no	no	no	0		0
7	no	yes	yes	2		2
8	no	yes	yes	2		2
9	no	yes	yes	2		3
			TOTAL:	9	TOTAL:	15
	yes = followed trend					
	no = didn't follow trend					

minimum volume. Minimum vagal tone corresponds to maximum volume for 2 out of three respiratory rates.

The extent of the inverse relationship between volume and parasympathetic activity depends upon the respiratory rate. This observation can be verified by identifying the relative respiration rates of the 18 cases that do not show a relationship between vagal tone and volume. 9 out of the 18 rates that don't show a relationship correspond to the minimum rate of the associated subject. Therefore, in all subjects considered, the minimum respiratory rate does not follow the trend. 5 out of the 18 rates that don't follow the trend correspond to the normal rates of the associated subject. 4 out of the 18 rates that do not follow the trend correspond to faster than normal rates for the associated subjects. The above information suggests that volume and parasympathetic activity are more closely correlated at higher respiratory rates than at low respiratory rates.

The relationships between volume and HR are examined by plotting both volume vs. HR and respiration vs. HR. In figure 3.5(C), vol. vs. HR is shown. For all ten subjects, a linear regression would result in a positive slope. Therefore, it is conjectured that as volume increases, HR increases. Statistical analysis indicates a strong relationship between volume and heart rate. Specifically, a 3x5 ANOVA analysis results in a P value of .003. The MANOVA analysis yields a P value of .053.

In figure 3.5(D), a respiration rate vs. HR plot is shown. At each data point, the average tidal volume that is maintained for the two minute data sequence is indicated. The direct relationship between volume and HR detected in figure 3.5(C) is even more visible in the respiration rate vs. HR plot.

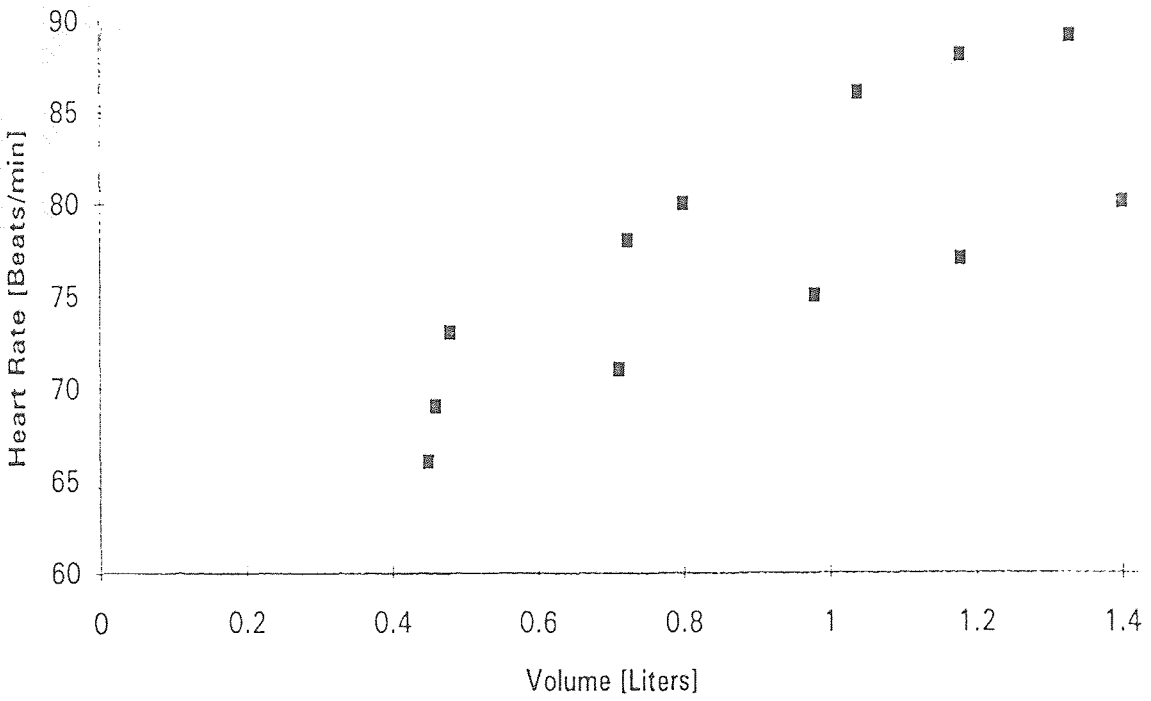

Figure 3.5(C) Volume vs. Heart Rate

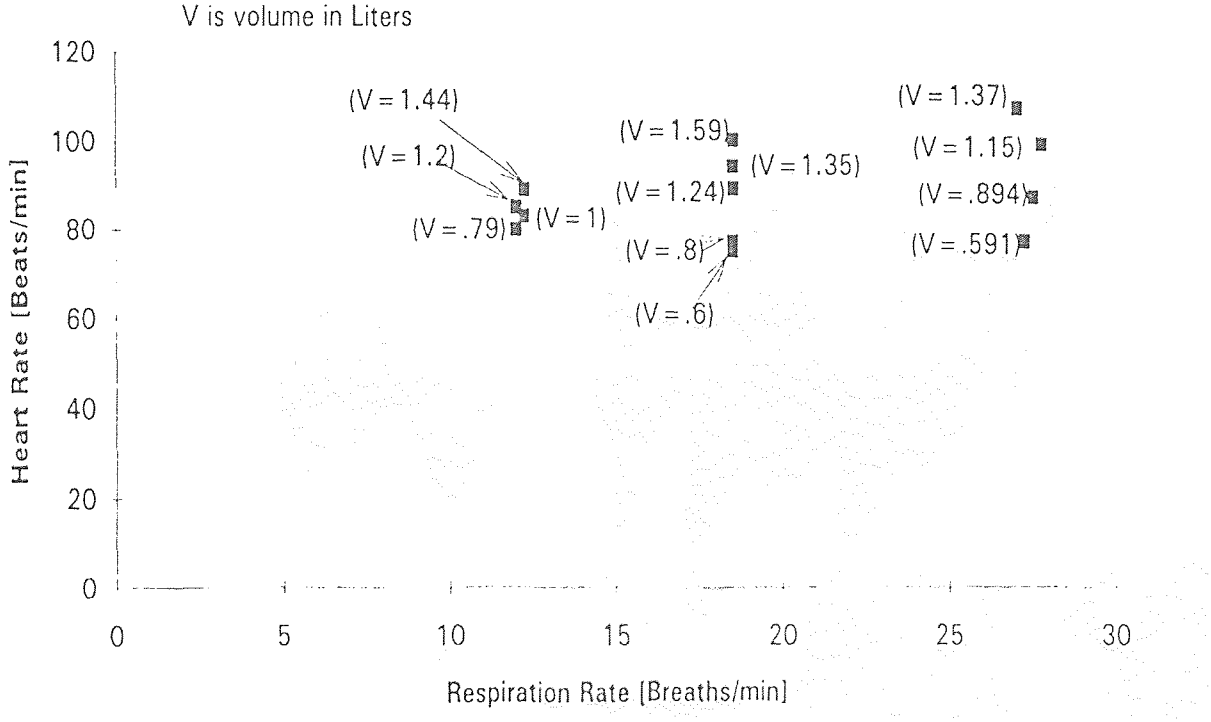

Figure 3.5(D) Respiration Rate vs. Heart Rate

Table 3.5(B) indicates for which subjects and associated respiratory rates that the direct relationship applies. In 5 subjects, volume and HR have a direct relationship for all respiratory rates. In 2 subjects, volume and vagal tone are directly proportional for 2 out of three respiratory rates. In one subject, a direct relationship applies to one out of the three respiratory rates. In one subject, no relationship is seen at any rate. There are a total of 27 respiratory rates for 9 subjects. In 7 out of 29 rates, no relationship between volume and HR is observed. As shown in table 3.5(B), the relationship between volume and vagal tone is strengthened if only the extreme values of volume are considered.

Recall, in the above explanation, that it was suggested that volume and parasympathetic activity are more correlated at high respiratory rates. This theory is supported by an additional trend observed in the volume vs. HR plots. Specifically, it is observed in all subjects that HR is more sensitive to changes in volumes at high respiratory rates. As shown in figure 3.5(D), at low rates, all the data points are concentrated in one area. As respiratory rate increases, however, the points become more spread out.

Table 3.5(B) Results Pertaining to Volume vs. HR Relationship

	****All volumes considered****				Min and Max values of volume only	
				Tot rates that	tot rates that	
subject	slow rate 1	mid rate 2	fast rate 3	follow trend	follow trend	
1	no	yes	no	1	2	
2	yes	yes	yes	3	3	
3	no	yes	yes	2	2	
4	yes	no	yes	2	2	
5	no	no	no	0	0	
6	yes	yes	yes	3	3	
7	yes	yes	yes	3	3	
8	yes	yes	yes	3	3	
9	yes	yes	yes	3	3	
			TOTAL:	20	TOTAL: 21	
	yes = followed trend					
	no = didn't follow trend					

It has been demonstrated both statistically and descriptively that the relationship between volume vs. HR is significant and volume vs. parasympathetic activity is insignificant. In the last section, it was discussed that HR varies due to both sympathetic and parasympathetic influences. Therefore, since HR is more correlated to volume than vagal tone then, by the process of elimination, an increase of volume significantly increases sympathetic activity. Statistical analysis supports this conjecture since the P value obtained in a 3x5 ANOVA technique for volume vs. low frequency area is .069. Using MANOVA and repeated MANOVA techniques, the P values obtained are .079 and .105 respectively. Although the P values indicate that volume and low frequency area are not related, it is conjectured that P becomes > .05 due to the vagal influence that is present in the low frequency peak. As mentioned previously, the P values obtained for volume vs. vagal tone are all statistically insignificant. Therefore, it can be inferred that the sympathetic influence present in the low frequency peak causes its P value to approach significance.

It is often useful to view the relationships between physiological parameters with an engineering systems point of view by defining a transfer function. In general,

H=output/input or H=20LOG(output/input) [dB]. (3.1).

In this research, H represents the complex feedback system involving the brain, nervous system, heart, and lungs. In order to investigate the relationship between vagal tone and tidal volume in this partially known system, the input and output are assigned tidal volume and vagal tone respectively. In this case, H=20LOG(vagal tone/tidal vol.) [dB]. H [dB] is shown in the middle section of column 5 of the tables 3.1(A) through 3.1(J). When this engineering perspective is used, an assumption is being made that the system

is linear. Although the system being investigated is nonlinear, an assumption of linearity is an acceptable way to acquire initial information about an unknown system.

In figure 3.5(E), a Bode plot with respiration rate vs. H is shown. At each data point, the average tidal volume that is maintained for the two minute sequence is indicated. An inverse relationship between volume and system gain is observed.

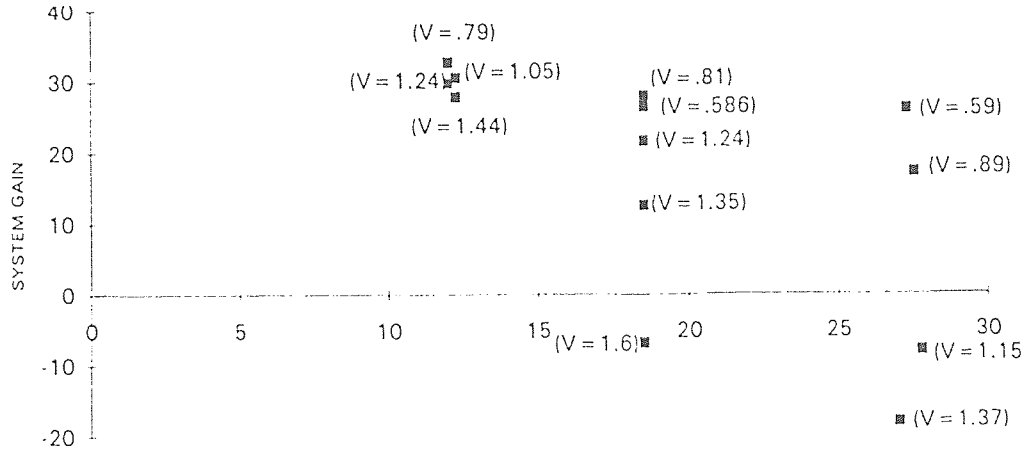

Figure 3.5(E) Respiration Rate [breaths/min] vs. Gain [dB]

Eckburg and Selman [2,9] have investigated the effect of respiratory volume on heart rate variability. The experimental protocol of Eckburg and Selman differ from the present study in several respects. The number of fixed volumes used in Eckburg's, Selman's and this study are 2, 7, and 5 respectively. The number of fixed rates used in each study are 5, 7, and 3 respectively. The subjects in this research and Selman's study were seated. The subject's in Eckburg's study, however, were supine. In addition, petCO2 was held constant in Eckburg's study. Eckburg and Selman both investigate the

role of volume using a systems perspective. In Eckburg's research, volume is the input, and vagal tone is the output of the system. In Eckburg's results, the gain and respiratory volume have a direct relationship, which is inconsistent with the result obtained in the present study. It is conjectured that this inconsistency occurs since Eckburg's subjects are supine. Further investigation is needed to determine the impact of the subject's position on the relationship between volume and vagal tone.

In Selman's research, volume is also considered the input. The output, however, is the overall autonomic nervous system power; which includes both the sympathetic and parasympathetic components. In Selman's results, there is an increase in gain as volume decreases, which is consistent with the result obtained in the present study.

3.6 Respiration Rate vs. Gain

As previously mentioned, it was established that RR interval vs. vagal tone has an inverse relationship. However, the relationship of RR interval and gain, where gain is defined in equation 3.1, however, was not established. In Eckburg's results, gain decreases linearly as respiratory rate increases. It has been conjectured that the linear result occurs since petCO2 is kept constant in this study. In Selman's research [9], petCO2 is not regulated. His results show that with increasing RR interval, the changes in gain are markedly nonlinear, increasing and decreasing in an M shape pattern. In the present study, it was expected that the results would also be nonlinear since petCO2 was not regulated. It was also conjectured that, at a given respiratory volume, the maximum gain will correspond to the normal respiratory rate of a particular subject. The results of the present study, however, turned out to be inconclusive due to the reproducibility problem that was

discussed in section 3.4. For example, figure 3.6(A) shows a RR interval vs. gain plot for subject 9 from the present study. Upon inspection of this plot, it appears as if a nonlinear relationship exists between RR interval and gain. As previously mentioned, however, the normal respiration rate data was acquired on a different day. At this time, subject 9 had a lower overall vagal tone. To normalize these points to the other days, the gain would need to be increased. It is not known, however, exactly how much these points need to be increased since no normalization method exists; therefore, no conclusion can be reached. Inconclusive results also occur in subjects that had good reproducibility between the experimental sections. Therefore, additional subjects, with good reproducibility, are needed to further investigate the relationship between RR and gain.

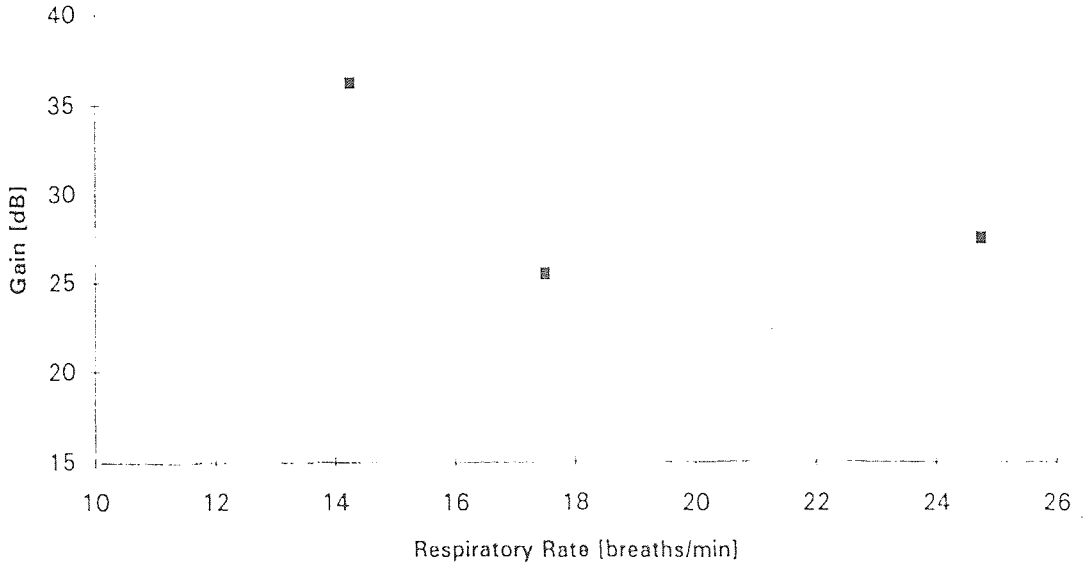

Figure 3.6(A) Respiratory Rate vs. Gain at a tidal volume of 0.4 Liters

3.7 The Level of Difficulty

As mentioned previously, all subjects indicated the level of difficulty that was experienced at different respiratory rates and volumes. Specifically, the subject indicated comfortable (C), lightly difficult (L), moderately difficult (M) and very difficult (V) at the completion of each 2 minute data sequence.

It was expected that as vagal tone decreased, the comfort level would also decrease. This, however, did not occur. Instead, a strong relationship between petCO2 and comfort level was observed in all subjects. In figure 3.7(A), petCO2 is plotted as a function of vagal tone. Extremely low levels of petCO2, which correspond to deep, fast breathing, is consistently perceived as very difficult. As petCO2 increases, the subject perceives less difficulty. If petCO2 reaches a level above normal, however, maximum difficulty is perceived since the subject's respiration is both slow and shallow.

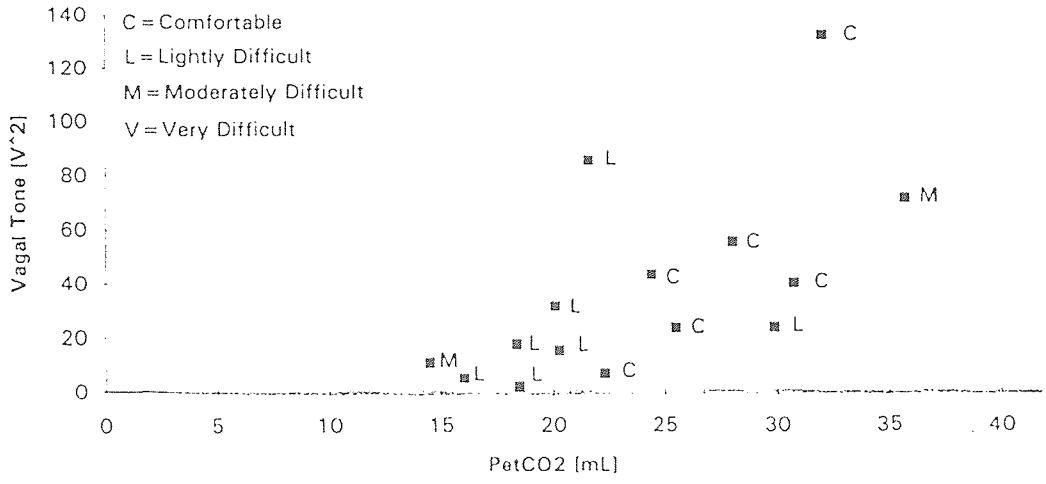

Figure 3.7(A) Petco2 vs. Vagal Tone

More information may have been elicited from perceived difficulty information if an established scale had been used. In the future, the Borg scale of exertion may be utilized to determine the subjective level of difficulty.

3.8 Role of Other Physiological Parameters

One cardiac variable, six metabolic parameters and one autonomic parameter, which are listed in the s-tables, have not as yet been discussed or used in the results. The autonomic parameter not yet considered is sn/pn. sn/pn is defined by the following equation:

$$(sn/pn) = \text{low freq. area/high freq. area} \quad (3.2).$$

sn/pn is used by some investigators to indicate the relative amount of sympathetic activity between two data sequences. For example, if sn/pn increases and the high frequency area decreases between 2 consecutive data sequences, it can be inferred that sympathetic activity increased. If, however, sn/pn increases and the high frequency area increases, the level of sympathetic activity is difficult to determine. In the future, sn/pn and vagal tone vs. HR should be used together to help quantify the level of sympathetic activity.

The respiratory parameters not yet considered are $\dot{V}O2$ [L/min.], $\dot{V}CO2$ [L/min.], eff O2, eff CO2, RQ and $\dot{V}E$. $\dot{V}E$ is derived from rate and volume by equation 1.3. Therefore, as expected, rate and volume are highly related to $\dot{V}E$. In the future, $\dot{V}E$ vs. autonomic parameters and $\dot{V}E$ vs. cardiac parameters should be investigated. A great deal

could be learned by investigating these relationships since $\dot{V}E$ encompasses both rate and volume.

It is shown in the statistics using the 3x5 ANOVA that volume vs. RQ ratio approaches significance since P=.081. Rate vs. RQ ratio, however, has no relationship since P=.970. For all other respiratory variables, if rate has a P>.05, then volume also has a P>.05. Conversely, if P<.05 when rate is compared to a particular respiratory variable then volume vs. the particular respiratory variable also has a P<.05. Therefore, in the future, relationships involving the RQ ratio are especially important to investigate since associated trends involve respiratory volume only. As a consequence, if RQ ratio is found to influence heart rate variability, then an autonomic regulatory mechanism that involves only respiratory volume without respiratory rate exists.

As shown in equation 1.4 and 1.5, eff CO2 and eff O2 are derived from $\dot{V}CO2$ [L/min.] and $\dot{V}O2$ [L/min.] respectively. It has been shown, using multiple regression, that high frequency area vs. eff O2 is significant since P=.013. In addition, high freq. area vs. eff CO2 approaches significance since P=.18. Preliminary investigation shows that vagal tone decreases as eff O2 increases, as shown by figure 3.8(A). In the future, more investigation is needed to determine the effects of $\dot{V}CO2$ [L/min.], $\dot{V}O2$ [L/min.], eff O2 and eff CO2 on vagal tone, respiratory rate ,volume and HR. Further study of these parameters will reveal information about how the pulmonary system is regulated by autonomic and cardiac variables.

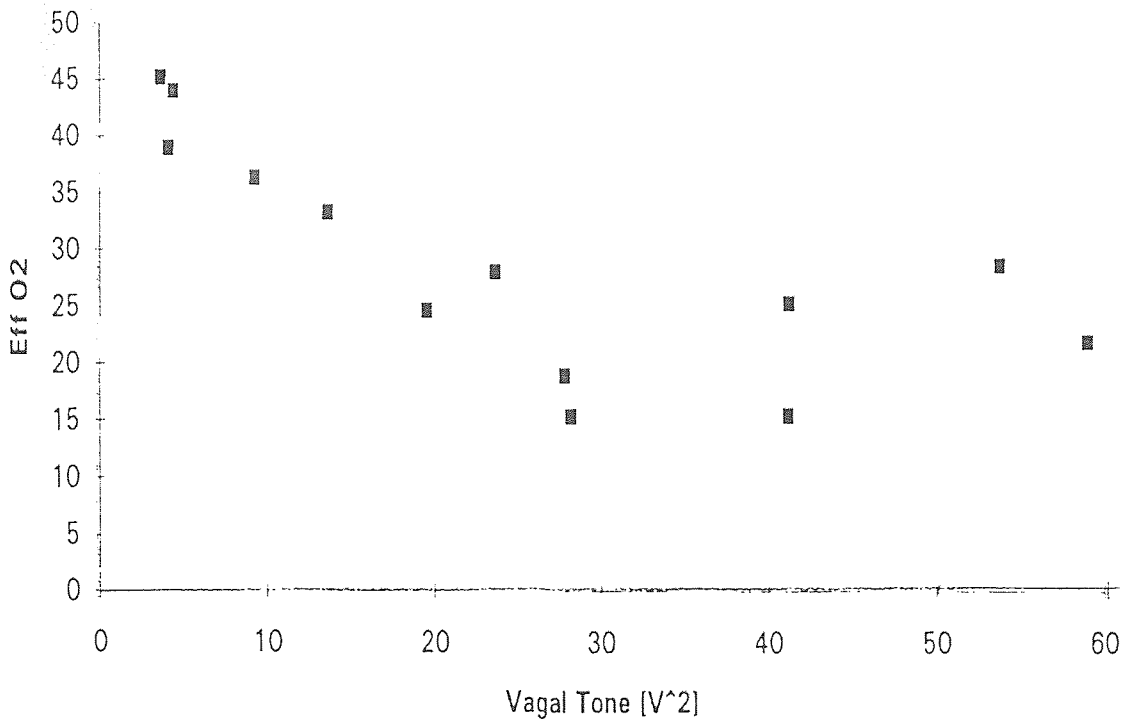

Figure 3.8(A) Vagal Tone vs. Eff O2

CHAPTER 4

CONCLUSIONS

4.1 Introduction

In this chapter, the results derived by the author and suggestions for future work are summarized.

4.2 Summary of Results

It has been shown that reproducibility of autonomic parameters are almost impossible if multiple tests are performed since levels of parasympathetic and sympathetic influence are continuously changing. Therefore, methods were developed to compare outcomes of experiments performed on a subject at different times. These methods were used to indicate the relative difference in overall vagal tone between the different test sections. Conversion of data from one test section in terms of another test section, however, is not yet possible.

A method to determine relative changes of sympathetic activity in sequences of data has been theorized. It is conjectured that if relative changes of HR and vagal tone between two data sequences either both increase or decrease, then relative change of sympathetic activity between two data sequences can be determined.

Experiments have shown that respiratory volume and vagal tone have an inverse relationship, which was most pronounced at fast respiratory rates. In addition, as tidal volume increased, HR increased. Using statistical analysis, it was concluded that changes in volume affect sympathetic activity more than parasympathetic activity.

An inverse relationship between respiratory volume and system gain was observed in this study. These results were compared to those of two other investigators; Eckburg and Selman. Selman's results were consistent with the results of this study. Specifically, an inverse relationship between volume and gain was observed. Eckburg, however, observed a direct relationship between volume and gain.

The relationship between respiratory rate and gain was investigated in this research. The results in this study, however, were inconclusive due to the reproducibility problem between different experimental sections. Eckburg observed a linear decrease in gain as respiratory rate increased. Selman, however, observed nonlinear fluctuations in gain as rate varied.

During experimentation, the subjects indicated level of difficulty for each 2 minute data sequence. It was observed that the indicated level of difficulty was related to the amount of petCO2. Specifically, extremely low or high levels of petCO2 were associated with indications that the required respiratory rate and volume were very difficult to maintain.

4.3 Summary of Future Work

In the discussion, it was mentioned that reproducibility of data acquired on different days was poor since overall vagal tone at different times varies. In the future, a normalization procedure needs to be developed so that comparison of data acquired at different times can be facilitated. Perhaps experiments that require subjects to perform mental exercises may be used to investigate effects of overall vagal tone since mental exercise may be an effective method of lowering overall parasympathetic function. In addition, if interactions between investigator and subject are standardized, and the subject does not know when the experiment will end, reproducibility may improve.

In this research, methods to determine relative changes in sympathetic activity have been suggested. A technique needs to be developed to quantify the levels of sympathetic activity. This may be accomplished by investigating three different alternatives: evaluation of sympathetic activity via the FFT of the systolic blood pressure peaks, sympathetic activity determination with the vagal tone vs. HR plot, and determination of sympathetic activity with sn/pn.

The role of respiratory parameters, such as eff O2 and RQ ratio, on heart rate variability needs to be determined. Differences between interactions of respiratory, autonomic and cardiac parameters of subjects in different positions (supine instead of sitting) need to be investigated in order to determine the reasons that Eckburg and Selman elicit conflicting conclusions.

An established scale of difficulty needs to be utilized in future studies. Although the scale used in this study contributed interesting results, subjectivity may be decreased if established scales are used.

It may seem that quantification of sympathetic activity, normalization of experiments done at different times and further determination of relationships between physiological parameters are not related. This, however is not true since achievement of one goal will facilitate the other goals. In addition, to achieve significant understanding about the complex feedback systems involving the brain, nervous system, heart and lungs, it is essential to pursue all of the future topics that are suggested above. Each topic is a piece of the puzzle that will lead to complete understanding .

APPENDIX A

S-PLUS PROGRAMS

Spect1

```
function(x, low.freq = 0.15, high.freq = 0.4, srate = 200)
{
        isp <- x
        low.no <- round((2 * length(isp) * low.freq * 10)/srate)
        high.no <- round((2 * length(isp) * high.freq * 10)/srate)
        isp.new <- isp[low.no:(high.no - 1)]
        isp.dif <- diff(isp[low.no:high.no])
        area.tmp <- sum(isp.new + isp.dif/2) * (srate/(2 * length(
                isp) * 10))  return(area.tmp)
```

Lsbpu

```
function(x, x.pk, nt = 8192, ns = 6, decimate = 10,
        tooruff = 0.8, f = 0.1, ld = 10, sd = 10){
        mruff <- max(abs(ruff(diff(x.pk))))
        if(mruff >= tooruff)
                print(paste("ibi's may be too ruff",
                        tooruff, sep = ""))
        x.ecg <- x[, 2]
        x.iu <- iibi(diff(x.pk))
        x.i <- x.iu[seq(1, len(x.iu), decimate)]
        x.sq <- sqdt(x.i, f = f, ld, sd)
        x.isp <- spect(x.i - x.sq, nt = nt, ns = ns)
        x.rbp <- x[seq(1, len(x[, 3]), 10), 3]
        x.dbp <- lowess(1:len(x.rbp), x.rbp, f = 0.3, iter
                = 2, delta = ceiling((length(x.rbp) * 0.3)/8))$y
                x.bp <- spect(x.rbp - x.dbp, nt = nt, ns = ns)
        x.rpd <- x[seq(1, len(x[, 1]), 10), 1]
        x.rlw <- lowess(1:len(x.rpd), x.rpd, f = 0.3, iter
                = 2, delta = ceiling((length(x.rpd) * 0.3
                )/8))$y
        x.rsp <- spect(x.rpd - x.rlw, nt = nt, ns = ns)
        z <- list(pk = x.pk, ibi = x.i, ibiu = x.iu, sq =
                x.sq, rpd = x.rpd, rlw = x.rlw, isp =
                x.isp, rsp = x.rsp, ecg = x.ecg, rbp =
                x.rbp, dbp = x.dbp, bp = x.bp)
```

```
        z
}
}
```

Pslwsu

```
function(x)
{
        jks <- x[, 2]
        aa <- grep(T, diff(jks) > 1000)
        ljs <- lsbpu(x, aa)
        ljs
}
```

Stdgraf

```
function(x, title = " ", wait = T, sr = 20, sr2 = sr * 10
        )
{
#z <- attributes(x)
#if(length(z$names) < 7)
#       stop("Wrong structure -- check attributes")
        nt <- (length(x$isp) - 1) * 2
        par(mfrow = c(3, 1), mar = c(6.1, 6.1, 4.1, 3.1))
        if(missing(sr)) {
                plot(diff(x$pk), xlab = "Beat Number",
                        ylab = "IBI", main = paste(title,
                        "Interbeat Intervals"))
                plot(x$ibi, type = "l", xlab = "Time",
                        ylab = "IIBI", main = paste(title,
                        " - IIBI", sep = ""))
                lines(x$sq)
                plot(x$rpd, type = "l", xlab = "Time",
                        ylab = "Resp", main = paste(title,
                        " - Resp", sep = ""))
                lines(x$rlw)
                if(wait)
                        scan()
                par(mfrow = c(1, 1), mar = c(6.1, 6.1, 4.1,
                        4.5))
                plot(x$isp[1:500], type = "l", xlab =
                        "Frequency Number", ylab = "Power",
                        main = title)
```

```
                par(new = T)
                plot(x$rsp[1:500], type = "l", lty = 3,
                        axes = F, xlab = "", ylab = "")
                axis(4)
                mtext("Resp Power - - ", side = 4, line =
                        3)
        }
        else {
                par(mfrow = c(3, 1), mar = c(6.1, 6.1, 4.1,
                        3.1))
                plot(diff(x$pk)/sr2, xlab = "Beat Number",
                        ylab = "IBI", main = paste(title,
                        " - IBI", sep = ""))
                plot(x$ibi/sr2, type = "l", xlab = "Time",
                        ylab = "IIBI", main = paste(title,
                        " - IIBI", sep = ""))
                lines(x$sq/sr2)
                plot(x$rpd, type = "l", xlab = "Time",
                        ylab = "Resp", main = paste(title,
                        " - Resp", sep = ""))
                lines(x$rlw)
                if(wait)
                        scan()
                xf <- ((1:500) - 1)/nt * sr
                par(mfrow = c(1, 1), mar = c(6.1, 6.1, 4.1,
                        4.5))
                plot(xf, x$isp[1:500], type = "l", xlab =
                        "Frequency", ylab = "Power", main
                         = title)
                par(new = T)
                plot(xf, x$rsp[1:500], type = "l", lty = 3,
                        axes = F, xlab = "", ylab = "")
                axis(4)
                mtext("Resp Power - - ", side = 4, line =
                        3)
        }
}
```

Mgraph

```
function(w, x, y, z, title = " ", wait = T, sr = 20, sr2
         = sr * 10)
{
        nt <- (length(x$isp) - 1) * 2
        {
```

```
                xf <- ((1:500) - 1)/nt * sr
                par(mfrow = c(1, 1), mai = c(4.9, 1.5, 0.3,
                        6.5))
                plot(xf, w$isp[1:500], type = "l")
                par(new = T)
                plot(xf, w$rsp[1:500], type = "l", lty = 3,
                        axes = F, xlab = "", ylab = "")
                axis(4)
                par(mai = c(4.9, 6.5, 0.3, 1.5), new = T)
                plot(xf, x$isp[1:500], type = "l")
                par(new = T)
                plot(xf, x$rsp[1:500], type = "l", lty = 3,
                        axes = F, xlab = "", ylab = "")
                axis(4)
                par(mai = c(0.9, 1.5, 4.3, 6.5), new = T)
                plot(xf, y$isp[1:500], type = "l")
                par(new = T)
                plot(xf, y$rsp[1:500], type = "l", lty = 3,
                        axes = F, xlab = "", ylab = "")
                axis(4)
                par(mai = c(0.9, 6.5, 4.3, 1.5), new = T)
                plot(xf, z$isp[1:500], type = "l")
                par(new = T)
                plot(xf, z$rsp[1:500], type = "l", lty = 3,
                        axes = F, xlab = "", ylab = "")
                axis(4)
        }
}
```

Stdbp

```
function(x, title = " ", wait = T, sr = 20, sr2 = sr * 10
        )
{
#z <- attributes(x)
#if(length(z$names) < 7)
#       stop("Wrong structure -- check attributes")
        nt <- (length(x$isp) - 1) * 2
        par(mfrow = c(3, 1), mar = c(6.1, 6.1, 4.1, 3.1))
        if(missing(sr)) {
                plot(diff(x$pk), xlab = "Beat Number",
                        ylab = "IBI", main = paste(title,
                        "Interbeat Intervals"))
                plot(x$ibi, type = "l", xlab = "Time",
```

```
                ylab = "IIBI", main = paste(title,
                " - IIBI", sep = ""))
        lines(x$sq)
        plot(x$rbp, type = "l", xlab = "Time",
                ylab = "Resp", main = paste(title,
                " - BP", sep = ""))
        lines(x$dbp)
        if(wait)
                scan()
        par(mfrow = c(1, 1), mar = c(6.1, 6.1, 4.1,
                4.5))
        plot(x$isp[1:400], type = "l", xlab =
                "Frequency Number", ylab = "Power",
                main = title)
        par(new = T)
        plot(x$bp[1:400], type = "l", lty = 3,
                axes = F, xlab = "", ylab = "")
        axis(4)
        mtext("BP Power - - ", side = 4, line = 3)
}
else {
        par(mfrow = c(3, 1), mar = c(6.1, 6.1, 4.1,
                3.1))
        plot(diff(x$pk)/sr2, xlab = "Beat Number",
                ylab = "IBI", main = paste(title,
                " - IBI", sep = ""))
        plot(x$ibi/sr2, type = "l", xlab = "Time",
                ylab = "IIBI", main = paste(title,
                " - IIBI", sep = ""))
        lines(x$sq/sr2)
        plot(x$rbp, type = "l", xlab = "Time",
                ylab = "Resp", main = paste(title,
                " - BP", sep = ""))
        lines(x$dbp)
        if(wait)
                scan()
        xf <- ((1:400) - 1)/nt * sr
        par(mfrow = c(1, 1), mar = c(6.1, 6.1, 4.1,
                4.5))
        plot(xf, x$isp[1:400], type = "l", xlab =
                "Frequency", ylab = "Power", main
                 = title)
        par(new = T)
        plot(xf, x$bp[1:400], type = "l", lty = 3,
                axes = F, xlab = "", ylab = "")
```

```
        axis(4)
        mtext("BP Power - - ", side = 4, line = 3)
    }
}
```

Spir

```
function(x)
{
    x[x > 1000] <- 2000
    x[x < 1000] <- 0
    rlength <- rle(x)$length
    rval <- rle(x)$value
    # print(paste(rlength,rval))  #counts packets
    n <- length(rlength)
    packet <- 0
    for(k in 1:n) {
        if(rlength[k] > 200) {
            packet <- packet + 1
        }
    }
    print(paste("the number of inhales is", packet))
    #counts pulses
    rlength[rlength < 200] <- 0
    rlength[rlength > 200] <- 1
    rpulse <- rle(rlength)$length
    print(paste(rpulse))
    vol <- ((rpulse + 1) * 0.05)
    vol[vol == (0.1)] <- 0
    print(paste(vol))
    t <- length(vol)
    count <- 0
    for(k in 1:t) {
        if(vol[k] > 0) {
            count <- count + 1
        }
    }
    print(paste("The count is", count))
    svol <- sum(vol)
    print(paste("the sum is", svol))
    mvol <- svol/count
    print(paste("the mean is", mvol))
    inf <- list(vol = vol, mvol = mvol)
}
```

APPENDIX B

Q-PLEX DATA

Calculation of Delay Time

Diameter of tube = 1.5 in. Area of Tube = pi(.75)^2 = 1.766 in^2
Conversion: 58.4 in^3/1 Liter
58.4 in^3/Liter * 1/1.766 in^2 = 33 in/Liter Therefore, if breath one liter of air, it travels through 33 in of tubing. Total of 158 in of tubing, 158/33= 4.7 breaths

Example: Suppose respiratory rate = 8 Breaths/min. then 4.7/8 = .6 min. = 36 seconds
Add 30 sec to account for time air takes to go through spirometer and actual Q-PLEX.
Therefore, 36 + 30 = 66 seconds delay time.

Printout From Q-PLEX

Test Time	% CO2 exp	% O2 exp	VBR /min	Heart Rate	VO2 /KG	VCO2 STPD	VO2 STPD	R	Fat CO2	METS	VT	ST Level	ST Slope
0:06	2.45	17.33	19		5.3	0.22	0.36	0.61		1.66	0.55		
0:09	2.45	17.33	22		4.5	0.17	0.28	0.61		1.29	0.40		
0:12	2.45	17.29	20		5.0	0.19	0.30	0.62		1.42	0.41		
0:15	2.45	17.33	17		4.9	0.18	0.30	0.61	71.4	1.39	0.50		
0:18	2.46	17.22	19		5.5	0.20	0.34	0.59		1.58	0.52		
0:21	2.46	17.22	19		4.6	0.17	0.28	0.59		1.33	0.45		
0:25	2.46	17.22	16		4.8	0.17	0.29	0.59		1.36	0.54		
0:28	2.45	17.17	19		4.2	0.15	0.26	0.58	71.0	1.20	0.40		
0:31	2.45	17.17	25		7.4	0.27	0.46	0.58		2.12	0.65		
0:34	2.45	17.17	16		4.5	0.16	0.28	0.58		1.28	0.52		
0:38	2.45	17.17	17		4.5	0.16	0.28	0.58		1.29	0.49		
0:42	2.44	17.16	17		5.2	0.18	0.32	0.58	71.6	1.48	0.51		
0:45	2.44	17.16	17		4.9	0.17	0.30	0.58		1.40	0.52		
0:48	2.44	17.18	17		5.3	0.19	0.33	0.58		1.52	0.55		
0:52	2.44	17.18	19		4.5	0.16	0.27	0.58		1.27	0.45		
0:55	2.44	17.17	16		5.1	0.18	0.31	0.58	71.9	1.46	0.60		
start Event Marker													
0:58	2.44	17.17	21		4.5	0.16	0.28	0.58		1.28	0.41		
1:01	2.44	17.18	21		5.1	0.18	0.31	0.58		1.45	0.45		
1:05	2.44	17.18	17		4.2	0.15	0.26	0.58		1.20	0.49		
1:09	2.44	17.18	17		4.2	0.15	0.26	0.58	71.8	1.20	0.48		
1:12	2.44	17.18	17		4.0	0.14	0.24	0.58		1.14	0.45		
1:16	2.44	17.17	18		4.0	0.14	0.24	0.58		1.15	0.43		
1:19	2.44	17.17	18		4.3	0.15	0.26	0.58		1.23	0.48		
1:23	2.44	17.17	19		4.2	0.15	0.25	0.58	72.1	1.21	0.43		

One Minute

Delay Time

APPENDIX C

BONFERONNI ADJUSTMENT

Table 2.5(C) Bonferonni Adjustment

low freq peak	Rate1	Rate 2	Rate 3		
Rate 1	1				
Rate 2	1	1			
Rate 3	0.145	0.456	1		
low freq peak	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5
Vol 1	1				
Vol 2	1	1			
Vol 3	0.759	1	1		
Vol 4	0.062	1	1	1	
Vol 5	0.432	1	1	1	1
vagal tone	Rate 1	Rate 2	Rate 3		
Rate 1	1				
Rate 2	0.001	1			
Rate 3	0	0.311	0		
vagal tone	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5
Vol 1	1				
Vol 2	1	1			
Vol 3	1	1	1		
Vol 4	0.811	1	1	1	
Vol 5					
VO2 l/min	Rate 1	Rate 2	Rate 3		
Rate 1	1				
Rate 2	0.078	1			
Rate 3	0.056	1	1		
VO2 l/min	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5
Vol 1	1				
Vol 2	0.135	1			
Vol 3	0.433	1	1		
Vol 4	0.1	1	1	1	
Vol 5	0.099	1	1	1	1
VCO2 l/min	Rate 1	Rate 2	Rate 3		
Rate 1	1				
Rate 2	0	1			
Rate 3	0	0.42	1		
VCO2 l/min	Vol 1	Vol 2	Vol 3	Vol 4	
Vol 1	1				
Vol 2	0	1			
Vol 3	0	0.077	1		
Vol 4	0	0.005	1	1	

RQ	Rate 1	Rate 2	Rate 3		
Rate 1	1				
Rate 2	1	1			
Rate 3	1	1	1		
RQ	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5
Vol 1	1				
Vol 2	1	1			
Vol 3	0.078	0.267	1		
Vol 4	1	1	1	1	
Vol 5					
sn/pn	Rate 1	Rate 2	Rate 3		
Rate 1	1				
Rate 2	0.032	1			
Rate 3	0	0.002	1		
sn/pn	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5
Vol 1	1				
Vol 2	1	1			
Vol 3	0.373	0.535	1		
Vol 4	0.638	0.876	1	1	
Vol 5	1	1	1	1	1
eff CO2	Rate 1	Rate 2	Rate 3		
Rate 1	1				
Rate 2	0.015	1			
Rate 3	0	0	1		
eff CO2	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5
Vol 1	1				
Vol 2	0.918	1			
Vol 3	0.035	1	1		
Vol 4	0	0.002	0.135	1	
Vol 5					
eff O2	Rate 1	Rate 2	Rate 3		
Rate 1	1				
Rate 2	0	1			
Rate 3	0	0	1		
eff O2	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5
Vol 1	1				
Vol 2	0.001	1			
Vol 3	0	0	1		
Vol 4	0	0	0.502	1	
Vol 5					

PetCO2	Rate 1	Rate 2	Rate 3			
Rate 1	1					
Rate 2	0.053	1				
Rate 3	0	0.003	1			
PetCO2	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5	
Vol 1	1					
Vol 2	0.015	1				
Vol 3	0	0.136	1			
Vol 4	0	0	0.372	1		
Vol 5	0	0	0.053	1	1	
VE	Rate 1	Rate 2	Rate 3			
Rate 1	1					
Rate 2	0	1				
Rate 3	0	0	1			
VE	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5	
Vol 1	1					
Vol 2	0	1				
Vol 3	0	0	1			
Vol 4	0	0	0.02	1		
Vol 5						
HR	Rate 1	Rate 2	Rate 3			
Rate 1	1					
Rate 2	0.011	1				
Rate 3	0.011	1	1			
HR	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5	
Vol 1	1					
Vol 2	1	1				
Vol 3	0.017	1	1			
Vol 4	0.006	0.485	1	1		
Vol 5						
SV	Rate 1	Rate 2	Rate 3			
Rate 1	1					
Rate 2	1	1				
Rate 3	1	1	1			
SV	Vol 1	Vol 2	Vol 3	Vol 4	Vol 5	
Vol 1	1					
Vol 2	1	1				
Vol 3	1	1	1			
Vol 4	1	1	1	1		
Vol 5	1	1	1	1	1	

APPENDIX D

RESULTS FOR SUBJECTS 2 THROUGH 10

Table 3.1(B) Results for Subject 2

Section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[Hz]	[L]	[L]	[mL]	
2c	18	18.5	0.3083333	0.4	0.586	26.32	0.742
2d	18	18.5	0.3083333	0.7	0.808	24.19	0.853
2e	18	18.5	0.3083333	1	1.24	22.88	1.16
2f	18	18.5	0.3083333	1.2	1.35	18.44	1.08
2g	18	18.5	0.3083333	1.4	1.59	15.5	1.07
3e	27	27.25	0.4541667	0.4	0.591	22.1	0.821
3f	27	27.5	0.4583333	0.7	0.894	19.54	0.964
3g	27	27.75	0.4625	1	1.15	16.66	1.02
3h	27	27	0.45	1.2	1.37	15.38	0.977
3l	12	12	0.2	0.7	0.789	20.7	0.596
3m	12	12.25	0.2041667	1	1.05	19.28	0.685
3n	12	12	0.2	1.2	1.24	18.63	0.737
3o	12	12.25	0.2041667	1.4	1.44	17.02	0.827

Section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2c	l	12.4	3.1	26.5	10.8	75	5.71
2d	c	20.22	7.87	27.9	14.9	77	6.98
2e	l	15.17	6.05	21.8	22.9	89	6.85
2f	c	5.77	3.24	12.6	24.9	94	7.27
2g	l	0.722	0.876	-6.86	29.4	100	7.75
3e	c	11.95	4.72	26.11	16.1	77	6.15
3f	l	6.49	3.79	17.2	24.6	87	7.39
3g	l	0.462	1.89	-7.9	31.9	99	7.78
3h	m	0.172	0.637	-18	36.9	107	8.95
3l	c	34.28	10.39	32.7	9.5	80	5.34
3m	l	35.8	7.95	30.7	12.9	83	6.43
3n	c	38.51	7.07	29.8	14.9	85	6.74
3o	c	35.78	2.17	27.9	17.6	89	6.75

Section	vco2	vo2	eff o2	eff co2	SV	sn/pn	CO
	[L/min]	[L/min]			[L/beat]		[L/min]
2c	0.268	0.363	29.8	40.4	0.0048	0.25	0.363
2d	0.377	0.444	33.7	39.6	0.0058	0.389	0.444
2e	0.515	0.436	52.6	44.5	0.00489	0.398	0.436
2f	0.504	0.463	53.9	49.6	0.004925	0.562	0.463
2g	0.527	0.493	59.7	55.8	0.004931	1.21	0.493
3e	0.325	0.391	41.2	49.6	0.0051	0.395	0.391
3f	0.452	0.469	52.5	54.4	0.0054	0.584	0.469
3g	0.51	0.494	64.6	62.9	0.0049	4.09	0.494
3h	0.564	0.57	64.9	65.6	0.0053	3.7	0.57
3l	0.204	0.339	27.9	46.4	0.0042	0.303	0.339
3m	0.281	0.408	31.5	45.7	0.0049	0.222	0.408
3n	0.314	0.4288	34.7	47.3	0.0051	0.184	0.4289
3o	0.355	0.4293	41.1	49.7	0.0048	0.061	0.4293

Table 3.1(C) Results for Subject 3

Section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	(br/min)	(br/min)	(Hz)	(L)	(L)	(mL)	
2c	13	14	0.2333333	0.4	0.54		0.65
2d	13	14	0.2333333	0.7	0.7		0.763
2e	13	14.25	0.2375	1	0.89		0.861
2f	13	13.75	0.2291667	1.2	1.07		0.882
2g	13	14	0.2333333	1.4	1.3		0.9
3e	8.5	9	0.15	0.4	0.58	34.58	0.676
3f	8.5	8.5	0.1416667	0.7	0.75	32.16	0.698
3g	8.5	8.25	0.1375	1	1.14	29.35	0.805
3h	8.5	8.25	0.1375	1.2	1.18	25.6	0.853
3i	8.5	8.5	0.1416667	1.4	1.3	25.1	0.849
3k	19.5	22.25	0.3708333	0.4	0.43	23.2	0.741
3l	19.5	22	0.3666667	0.7	0.67	20.4	0.876
3m	19.5	20	0.3333333	1	0.85	18.56	0.91

Section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		(V^2)	(V^2)	(dB)	(L/min)	(beats/min)	(mL/Kg/min)
2c	m	27.85	4.71	34.25	7.56	69	5.817
2d	l	19.53	4.42	28.91	9.8	75	5.824
2e	m	13.6	14.2	23.68	12.68	77	5.6
2f	m	9.26	3.94	18.74	14.71	83	5.94
2g	v	4.39	3.27	10.57	18.2	87	6.06
3e	v	28.2	8.8	33.74	5.22	62	4.93
3f	l	41.2	5.45	34.79	6.38	65	6.03
3g	m	59.02	2.12	34.28	9.41	63	6.27
3h	l	41.24	2.1	30.87	9.74	71	5.61
3i	m	53.8	4.28	32.34	11.05	69	5.63
3k	c	23.62	4.36	34.79	9.57	63	4.99
3l	m	4.1	1.95	15.73	14.74	76	5.54
3m	v	3.63	2.18	12.61	17	78	5.503

Section	vco2	vo2	eff o2	eff co2	SV	sn/pn	CO
	(L/min)	(L/min)			(L/beat)		(L/min)
2c	0.258	0.396	19.1	29.3	0.0057	0.169	0.396
2d	0.304	0.397	24.7	32.3	0.0053	0.226	0.397
2e	0.329	0.38	33.3	38.6	0.0049	1.044	0.38
2f	0.355	0.405	36.4	41.4	0.0048	0.425	0.405
2g	0.371	0.414	44	49.1	0.00475	0.745	0.414
3e	0.228	0.338	15.47	22.9	0.00544	0.312	0.338
3f	0.289	0.412	15.52	22.1	0.00632	0.132	0.411
3g	0.344	0.428	21.98	27.4	0.00679	0.036	0.428
3h	0.325	0.382	25.5	29.9	0.00538	0.051	0.382
3i	0.329	0.384	28.8	33.6	0.0056	0.079	0.384
3k	0.252	0.34	28.1	38	0.0054	0.185	0.34
3l	0.329	0.378	38.9	44.8	0.0049	0.476	0.378
3m	0.342	0.376	45.2	49.6	0.0048	0.601	0.376

Table 3.1(D) Results for Subject 4

Section	Tgt RR	Act RR	Act rr	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[Hz]	[L]	[L]	[mL]	
2c	14	14.5	0.2416667	0.5	0.517	25.44	0.802
2d	14	14.75	0.2458333	0.7	0.717	22.76	0.926
2e	14	14.5	0.2416667	1	1.04	19.77	0.959
2f	14	13.75	0.2291667	1.3	1.38	16.82	0.926
2g	14	14.5	0.2416667	1.5	1.49	15.62	0.894
3e	21	21.25	0.3541667	0.5	0.586	20.37	0.751
3f	21	21	0.35	0.7	0.727	18.08	0.845
3g	21	21	0.35	1	1.08	14.59	0.891
3h	21	21.25	0.3541667	1.3	1.19	13.85	0.832
3k	9	8.75	0.1458333	0.5	0.564		
3l	9	8.75	0.1458333	0.7	0.714	18.93	0.605
3m	9	8	0.1333333	1	1.06	16.6	0.654
3n	9	9.25	0.1541667	1.3	1.09	17.22	0.678
3o	9	8.75	0.1458333	1.5	1.44	17.83	0.734

Section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2c	c	24.98	8.14	33.68	7.49	94	5.7
2d	c	22.84	5.63	30.07	10.58	92	5.73
2e	l	12.49	3.54	21.59	15.08	100	7.02
2f	l	17.94	10.98	22.28	18.98	104	7.25
2g	m	9.64	1.47	16.22	21.61	102	7.5
3e	c	20.99	18.1	31.08	12.45	72	6.08
3f	l	13.66	8.69	25.48	15.27	80	6.15
3g	m	8.02	4.49	17.42	22.68	86	7.21
3h	v	5.21	6.18	12.83	25.29	85	7.37
3k	l	338.8	7.84	55.57	4.94	63	
3l	l	265.1	14.97	51.39	6.25	67	5.2
3m	l	256.7	22.15	47.68	8.48	69	5.45
3n	m	194.4	8.89	45.03	10.08	69	5.87
3o	m	261.78	12.3	45.19	12.6	71	6.37

Section	vco2	vo2	eff o2	eff co2	SV	sn/pn	CO
	[L/min]	[L/min]			[L/beat]		[L/min]
2c	0.239	0.298	25.1	31.39	0.00316	0.326	0.298
2d	0.275	0.299	35.35	38.46	0.00325	0.246	0.299
2e	0.3514	0.368	41.02	42.91	0.00368	0.283	0.368
2f	0.3515	0.379	50.13	53.98	0.00364	0.612	0.379
2g	0.349	0.391	55.32	61.93	0.00383	0.152	0.391
3e	0.237	0.317	39.17	52.46	0.00442	0.862	0.317
3f	0.272	0.321	47.61	56.13	0.004	0.636	0.321
3g	0.335	0.373	60.89	67.63	0.0043	0.559	0.373
3h	0.32	0.385	65.63	78.94	0.0045	1.19	0.385
3k					0	0.023	0
3l	0.164	0.273	22.88	38.13	0.00407	0.056	0.273
3m	0.1875	0.286	29.62	45.23	0.00415	0.086	0.286
3n	0.209	0.307	32.88	48.27	0.00444	0.046	0.307
3o	0.239	0.333	37.87	52.69	0.00469	0.047	0.333

Table 3.1(E) Results for Subject 5

Section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[Hz]	[L]	[L]	[mL]	
2e	12	12.5	0.2083333	0.5	0.51		0.62
2g	12	12.25	0.2041667	0.7	0.706		0.608
2d	12	12.5	0.2083333	1	0.99		0.86
2c	12	12.25	0.2041667	1.3	1.316		1.03
2f	12	12.5	0.2083333	1.5	1.45		0.929
3e	8	9.75	0.1625	0.5	0.526	38.8	0.636
3f	8	8.5	0.1416667	0.7	0.67	35.8	0.712
3g	8	8.5	0.1416667	1	0.95	32.7	0.834
3h	8	8.5	0.1416667	1.3	1.23	29.1	0.9
3i	8	8.5	0.1416667	1.5	1.52	26.7	0.907
3k	18	18.75	0.3125	0.5	0.51	27.5	0.718
3l	18	18.75	0.3125	0.7	0.74	24.83	0.825
3m	18	18.25	0.3041667	1	1.11	21.6	0.969
3n	18	19	0.3166667	1.3	1.4	18.8	0.98

Section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2e	l	314.4	47.8	55.8	6.38	67	5.08
2g		94.5	30.1	42.5	8.65	66	5.5
2d	l	93.9	12.55	39.5	12.38	67	5.21
2c	m	32.62	5.15	27.9	16.12	71	5.67
2f	v	44.82	10.5	29.8	18.13	69	6.25
3e	v	83.52	18.25	44	5.13	71	5.02
3f	l	57.4	2.1	38.7	5.7	67	5.32
3g	l	53.9	2.23	35.1	8.1	67	6.09
3h	l	52.4	2.05	32.6	10.5	69	6.13
3i	m	67.14	8.51	32.9	12.9	71	5.82
3k	l	11.4	6.8	26.9	9.56	68	5.83
3l	m	32.8	19.64	32.9	13.9	67	6.13
3m	m	15.2	7.76	22.7	20.3	74	6.62
3n	v	12.3	1.59	18.9	26.6	75	7.65

Section	vco2	vo2	eff o2	eff co2	SV	sn/pn	co
	[L/min]	[L/min]			[L/beat]		[L/min]
2e	0.213	0.345	18.46	29.88	0.00515	0.152	0.345
2g	0.228	0.375	23.04	37.98	0.00569	0.318	0.375
2d	0.308	0.354	34.92	40.17	0.00529	0.134	0.354
2c	0.404	0.386	41.81	39.91	0.0054	0.158	0.386
2f	0.398	0.427	42.47	45.47	0.00619	0.234	0.427
3e	0.221	0.342	14.97	23.22	0.0048	0.219	0.342
3f	0.257	0.361	15.76	22.15	0.0054	0.037	0.361
3g	0.347	0.415	19.45	23.29	0.0062	0.041	0.415
3h	0.377	0.418	25	27.74	0.0061	0.039	0.418
3i	0.362	0.398	32.49	35.74	0.0056	0.127	0.398
3k	0.285	0.397	24.08	33.53	0.0058	0.596	0.397
3l	0.343	0.417	33.25	40.48	0.0062	0.599	0.417
3m	0.437	0.451	44.88	46.39	0.0061	0.511	0.451
3n	0.51	0.52	51.15	52.16	0.0069	0.129	0.52

Table 3.1(F) Results for Subject 6

section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[Hz]	[L]	[L]	[mL]	
2g	19	19	0.3166667	0.4	0.431		0.522
2f	19	19.25	0.3208333	0.7	0.732		0.619
2e	19	19.25	0.3208333	1	1.02		0.733
2d	19	19.75	0.3291667	1.2	1.16		0.828
2c	19	19.5	0.325	1.4	1.43		0.998
3e	13	14.25	0.2375	0.4	0.421	33.8	0.629
3f	13	14.5	0.2416667	0.7	0.66	33.1	0.671
3g	13	13.75	0.2291667	1	0.99	28.2	0.861
3h	13	13.75	0.2291667	1.2	1.16	26.1	0.899
3i	13	14	0.2333333	1.4	1.35	22.2	0.887
3k	28	29.25	0.4875	0.4	0.432	22.7	0.587
3l	28	27.75	0.4625	0.7	0.798	20.13	0.767
3m	28	29	0.4833333	1	1.01	16.13	0.83
3n	28	27	0.45	1.2	1.48	15.19	0.849

section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2g	c	17.55	10.77	32.2	8.12	60	5.13
2f	c-l	27.39	4.75	31.5	14.1	59	5.92
2e	l	23.4	2.75	27.2	19.6	56	6.54
2d	m	15.6	1.97	22.6	22.9	53	7.13
2c	m	22.67	4.22	24	27.9	50	8.11
3e	l	15.09	16.07	31.1	5.9	51	5.62
3f	c	35.9	12.44	34.7	9.6	55	7.4
3g	c	41.1	16.58	32.4	13.6	57	6.4
3h	l	37.2	14.65	30.1	15.9	60	6.63
3i	m	27.25	12.15	26.1	18.9	63	6.56
3k	m	5.51	10.25	22.1	12.6	59	5.68
3l	l	10.36	12.5	22.3	22.1	62	7.08
3m	m	4.78	3.78	13.5	29.3	66	7.8
3n	v	2.22	0.681	3.52	39.9	75	7.83

section	vco2	vo2	eff o2	eff co2	SV	sn/pn	CO
	[L/min]	[L/min]			[L/beat]		[L/min]
2g	0.183	0.351	23.35	44.78	0.00585	0.614	0.351
2f	0.251	0.404	34.88	56.1	0.00685	0.173	0.404
2e	0.329	0.446	44	59.75	0.00797	0.118	0.446
2d	0.404	0.484	47.31	56.72	0.00914	0.126	0.484
2c	0.556	0.552	50.52	50.15	0.011	0.186	0.552
3e	0.239	0.383	15.66	25.04	0.0075	1.06	0.383
3f	0.341	0.504	18.99	28.08	0.0092	0.347	0.504
3g	0.374	0.433	31.41	36.4	0.0076	0.403	0.433
3h	0.407	0.451	35.36	39.22	0.0075	0.394	0.451
3i	0.397	0.447	42.33	47.61	0.0071	0.446	0.447
3k	0.232	0.386	32.71	54.56	0.00654	1.86	0.386
3l	0.369	0.48	46.11	59.9	0.0077	1.21	0.48
3m	0.444	0.531	55.15	65.9	0.008	0.791	0.531
3n	0.452	0.533	74.95	88.5	0.0071	0.307	0.533

Table 3.1(G) Results for Subject 7

Section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[Hz]	[L]	[L]	[mL]	
2f	18	18	0.3	0.4	0.451		0.552
2c	18	18	0.3	0.7	0.731		0.809
2d	18	18.5	0.3083333	1	1.02		0.9
2g	18	17	0.2833333	1.2	0.98		0.785
2e	18	15.5	0.2583333	1.4	1.19		0.865
3e	11	14.5	0.2416667	0.4	0.335	29.62	0.526
3f	11	12	0.2	0.7	0.725	25.81	0.621
3g	11	11.75	0.1958333	1	1.05	22.3	0.732
3h	11	12	0.2	1.2	1.15	21.95	0.798
3i	11	12	0.2	1.4	1.33	21.96	0.886
3k	25	26.25	0.4375	0.4	0.48	25.47	0.703
3l	25	26.25	0.4375	0.7	0.764	21.25	0.833
3m	25	25	0.4166667	1	0.857	19.66	0.846

Section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2f	c	24.85	5.78	34.82	8.11	63	4.32
2c	c	18.1	6.31	27.88	13.2	69	5.66
2d	c	7.5	6.22	17.33	18.9	77	6.45
2g	m	3.44	11.53	10.91	16.7	73	6.49
2e	m	4.16	4.09	10.87	18.4	77	6.59
3e	c	40.05	7.56	41.55	4.86	63	3.75
3f	c	51.3	11.24	36.99	8.7	65	4.56
3g	c	56.4	12.6	34.6	12.34	69	5.23
3h	c	47.9	7.84	32.4	13.8	71	5.52
3i	c	20.3	6.96	23.7	15.96	74	5.74
3k	l	11.8	6.69	27.8	12.6	67	4.97
3l	l	1.52	3.93	5.98	20.1	77	7.04
3m	m	1.09	1.65	2.09	21.4	83	6.28

Section	vco2	vo2	eff o2	eff co2	SV	sn/pn	CO
	[L/min]	[L/min]			[L/beat]		[L/min]
2f	0.17	0.3	27.06	47.8	0.0048	0.23	0.3
2c	0.318	0.391	33.64	41.4	0.0057	0.35	0.391
2d	0.407	0.445	42.37	46.3	0.0058	0.83	0.445
2g	0.351	0.449	37.1	47.5	0.0062	3.35	0.449
2e	0.395	0.455	40.6	46.6	0.0059	0.983	0.455
3e	0.133	0.256	18.9	36.6	0.0041	0.189	0.256
3f	0.193	0.311	28	45.05	0.0048	0.219	0.311
3g	0.259	0.356	34.68	47.55	0.0052	0.223	0.356
3h	0.3	0.375	36.8	45.92	0.00528	0.164	0.375
3i	0.347	0.392	40.7	45.99	0.00529	0.343	0.392
3k	0.239	0.337	37.3	52.63	0.00503	0.567	0.337
3l	0.397	0.479	41.9	50.47	0.00622	2.59	0.479
3m	0.369	0.428	50.1	57.95	0.0052	1.51	0.428

Table 3.1(H) Results for Subject 8

Section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[br/min]	[L]	[L]	[mL]	
2c	16	17.5	0.2916667	0.4	0.42		0.651
2d	16	17.75	0.2958333	0.7	0.744		0.871
2e	16	17.75	0.2958333	1	0.98		0.99
2f	16	17.5	0.2916667	1.2	1.25		1.03
2g	16	17.5	0.2916667	1.4	1.36		0.955
3e	24	25.75	0.4291667	0.4	0.488	27.4	0.752
3f	24	24.25	0.4041667	0.7	0.839	23.1	0.953
3g	24	25.5	0.425	1	0.995	19.8	1
3k	11	12.25	0.2041667	0.4	0.398	33.6	0.536
3l	11	11.75	0.1958333	0.7	0.64	29.1	0.655
3m	11	11.5	0.1916667	1	1.02	25.4	0.796
3n	11	11.75	0.1958333	1.2	1.2	22.6	0.832
3o	11	12	0.2	1.4	1.3	19.85	0.896

Section	Comfort	Vagal Tone	low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2c	c	8.82	4.22	26.4	7.35	74	5.13
2d	l	6.47	4.73	18.8	13.21	73	5.52
2e	l	3.38	2.02	10.8	17.4	83	6.41
2f	m	1.58	0.611	2	21.9	88	6.27
2g	v	2.14	2.6	3.9	23.8	89	6.52
3e	l	4.43	1.69	19.2	12.6	64	6.03
3f	l	2.73	0.622	10.2	20.3	79	6.62
3g	m	1.04	0.63	0.38	25.4	84	6.3
3k	c	8.52	1.2	26.6	4.9	60	5.31
3l	l	39.7	5.2	35.9	7.5	62	6.25
3m	m	19.9	7.91	25.8	11.7	67	6.26
3n	m	9.86	4.41	18.3	14.1	73	6.03
3o	v	13.35	3.51	20.2	15.6	74	5.43

Section	vco2	vo2	eff o2	effco2	SV	sn/pn	CO
	[L/min]	[L/min]			[L/beat]		[L/min]
2c	0.219	0.337	21.8	33.6	0.00455	0.478	0.337
2d	0.318	0.364	36.3	41.6	0.00498	0.731	0.364
2e	0.418	0.423	41.2	41.7	0.00509	0.598	0.423
2f	0.427	0.414	52.8	51.2	0.00471	0.387	0.414
2g	0.41	0.43	55.3	57.9	0.00483	1.21	0.43
3e	0.297	0.397	31.7	42.3	0.00619	0.381	0.397
3f	0.413	0.436	46.7	49.2	0.0055	0.228	0.436
3g	0.421	0.417	60.8	60.21	0.00497	0.606	0.417
3k	0.187	0.351	13.9	26.1	0.00585	0.141	0.351
3l	0.269	0.411	18.3	27.9	0.00663	0.131	0.411
3m	0.327	0.413	28.4	35.8	0.00616	0.397	0.413
3n	0.329	0.398	35.5	42.9	0.00545	0.447	0.398
3o	0.32	0.357	43.7	48.8	0.00482	0.263	0.357

Table 3.1(I) Results for Subject 9

Section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[Hz]	[L]	[L]	[mL]	
2c	17	17.5	0.2916667	0.4	0.48		0.642
2d	17	16.75	0.2791667	0.7	0.725		0.737
2e	17	17	0.2833333	1	1.04		0.815
2f	17	17.25	0.2875	1.2	1.18		0.801
2g	17	17.5	0.2916667	1.4	1.33		0.779
3d	25	24.75	0.4125	0.4	0.46	23.2	0.712
3f	25	24.75	0.4125	0.7	0.8	18.4	0.818
3k	12	14.25	0.2375	0.4	0.45	26.9	0.54
3l	12	13.5	0.225	0.7	0.713	24.1	0.628
3m	12	13.5	0.225	1	0.98	20.1	0.748
3n	12	13.5	0.225	1.2	1.18	18.14	0.78
3o	12	13.25	0.2208333	1.4	1.4	16.6	0.756

Section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2c	m	9.11	2.01	25.6	8.4	73	5.22
2d	c	9.02	0.252	21.9	12.14	78	6.2
2e	c	5.92	0.73	15.1	17.7	86	6.7
2f	l	4.5	1.24	11.6	20.4	88	6.9
2g	m	4.14	1.27	9.86	23.3	89	7.5
3d	c	10.95	0.692	27.5	11.4	69	5.4
3f	l	5.4	1.67	16.59	19.8	80	6.1
3k	c	29.3	5.24	36.3	6.41	66	4.5
3l	c	25.7	1.33	31.1	9.63	71	5.8
3m	c	21.4	1.27	26.8	13.23	75	5.6
3n	l	22.8	0.572	25.7	15.93	77	5.8
3o	m	18.03	0.92	22.2	18.55	80	6.1

Section	vco2	vo2	eff o2	eff co2	SV	sn/pn	CO
	[L/min]	[L/min]			[L/beat]		[L/min]
2c	#DIV/0!	0.319	26.34	40.89	0.00437	0.22	0.319
2d	#DIV/0!	0.38	31.93	43.66	0.00488	0.028	0.38
2e	#DIV/0!	0.41	43.16	51.82	0.00476	0.123	0.41
2f	#DIV/0!	0.421	48.28	59.73	0.00479	0.276	0.42
2g	#DIV/0!	0.458	50.77	64.79	0.00515	0.307	0.46
3d	0.54	0.331	34.41	48.85	0.00479	0.063	0.33
3f	0.55	0.374	52.95	64.48	0.00467	0.309	0.37
3k	0.53	0.276	23.23	43.13	0.00418	0.179	0.28
3l	0.22	0.356	27.02	44.38	0.00501	0.052	0.36
3m	#DIV/0!	0.341	38.81	51.84	0.00454	0.059	0.34
3n	0.2542857	0.357	44.59	57.14	0.00464	0.025	0.35
3o	0.4115789	0.372	49.85	65.76	0.00465	0.051	0.37

Table 3.1(J) Results for Subject 10

Section	Tgt RR	Act RR	Act RR	Tgt Vol	Act Vol	petco2	RQ
	[br/min]	[br/min]	[Hz]	[L]	[L]	[mL]	
2f	22	22.75	0.3791667	0.4	0.403		0.6
2g	22	22.75	0.3791667	0.7	0.707		0.82
2d	22	22.75	0.3791667	1	1.06		1.11
3e	14	14.75	0.2458333	0.4	0.41	31.2	0.63
3f	14	14.5	0.2416667	0.7	0.698	28.2	0.757
3g	14	13.5	0.225	1	1.01	24.6	0.951
3h	14	14	0.2333333	1.2	1.23	21.7	0.968
3i	14	14.5	0.2416667	1.4	1.41	20.83	0.972
3k	30	25	0.4166667	0.4	0.54	21.9	0.66
3l	30	21.5	0.3583333	0.7	1.07	17.7	0.87

Section	Comfort	Vagal Tone	Low fr. area	Gain	VE	HR	vo2
		[V^2]	[V^2]	[dB]	[L/min]	[beats/min]	[mL/Kg/min]
2f		31.26	0.412	37.8	9.2	80	4.54
2g		7.55	0.964	20.6	16.1	90	5.79
2d		0.509	1.14	-6.37	24.1	109	6.11
3e	c	49.41	6.73	41.6	6.1	80	4.3
3f	c	71.89	3.73	40.3	10.1	86	5.75
3g	c	52.14	1.94	34.3	13.6	89	6.07
3h	l	29.48	8.02	27.6	17.2	92	6.15
3i	c	55.62	3.35	31.9	20.4	92	6.42
3k	c	47.72	7.23	38.9	13.5	75	5.87
3l	l	4.59	0.592	12.6	23	92	6.84

Section	vco2	vo2	eff o2	eff co2	SV	sn/pn	CO
	[L/min]	[L/min]			[L/beat]		[L/min]
2f	0.196	0.33	27.8	46.6	0.00413	0.013	0.33
2g	0.347	0.42	38.3	46.4	0.00467	0.127	0.42
2d	0.494	0.444	54.4	48.8	0.00407	2.24	0.444
3e	0.199	0.309	19.6	30.4	0.00386	0.136	0.309
3f	0.306	0.413	24.5	33.1	0.0048	0.052	0.413
3g	0.414	0.436	31.3	32.9	0.00489	0.037	0.436
3h	0.43	0.442	39	40	0.00479	0.272	0.442
3i	0.438	0.46	44.4	46.7	0.005	0.06	0.46
3k	0.279	0.421	32.1	48.4	0.0056	0.152	0.421
3l	0.427	0.49	46.9	53.9	0.0053	0.129	0.49

APPENDIX E

GLOSSARY

Cardiac Output (CO) [Liters/minute] - Volume of blood pumped by each ventricle in one minute.

Eff CO2 [%] - Quantifies amount of exhaled air per amount of CO2 produced.

Eff O2 [%] - Quantifies amount of air taken in per amount of O2 that is consumed.

Heart Rate (HR) [Beats/minute] - Number of heart beats per minute.

Mean Arterial Pressure (MAP) [mmHg] - Average force that blood exerts against the walls of arteries.

PetCO2 [mL] - The volume of CO2 remaining in the pulmonary arteries following an exhalation.

RQ Ratio (Respiratory Quotient) - The ratio of CO2 produced / O2 consumed.

Stroke Volume (SV) [Liters/beat] - Total blood volume ejected by each ventricle with each beat.

Total Peripheral Resistance (TPR) - Overall arteriole resistance. Inversely related to overall arteriole radius.

$\dot{V}E$ (Ventilation) [Liters/minute] - Rate by which a volume of air is inhaled or exhaled.

$\dot{V}CO2$ [Liters/minute] - 1. Volume of CO2 produced by body cells per minute.
2. Volume of CO2 that diffuses from blood to the alveoli per minute.

$\dot{V}O2$ [Liters/minute] - 1. Volume of O2 per minute that is transported from the capillaries to the body cells.
2. Volume of inspired O2 that is diffused from the alveoli into the blood per minute

REFERENCES

[1] M.L. Appel, R.D. Berger, J.P. Saul, J.M. Smith, and R.J. Cohen, "Beat-to-Beat Variability in Cardiovascular Variables: Noise or Music?." *J. Am. Coll. Cardiol.*, Vol. 14, pp. 1139-1148, 1989.

[2] T.E. Brown, L.A. Beightol, J. Koh, and D.L. Eckberg, "Important Influence of Respiration on Human R-R Interval Power Spectra is Largely Ignored." *Journal of Applied Physiology*, Vol. 75(5), pp. 2310-2317,1993.

[3] T. Colton, *Statistics in Medicine*, USA: Little, Brown and Company, 1974, pp. 115-119.

[4] A.C. Guyton, *Textbook of Medical Physiology*, 8th edition, Philedelphia: W.B. Saunders Company, 1991, pp. 4-8, 106-109, 194-204.

[5] R.I. Kitney, T. Fulton, A.H. McDonald, and D.A. Linkens, "Transient Interactions Between Blood Pressure, Respiration and Heart Rate in Man". *J. Biomed. Eng.*, Vol. 7, pp. 217-224, 1985.

[6] R.E. Kleiger, J.T. Bigger, M.S. Bosner, M.K. Chung, J.R. Cook, L.M. Rolnitsky, R. Steinman, J.L. Fiess, "Stability Over Time of Variables Measuring Heart Rate Variability in Normal Subjects." *The Am. J. of Cardiology*, Vol. 68, pp. 626-630, 1991.

[7] J.M. Mathia, T.J. Mullen, M.H. Perrot, R.J. Cohen, "Heart Rate Variability: Principles and Measurement." *ACC Current Journal Review*, pp. 10-12, 1993.

[8] J.P. Saul, "Beat-to-Beat variations of Heart Rate Reflect Modulation of Cardiac Autonomic Outflow.", *NIPS*, Vol. 5,pp. 32-36, 1990.

[9] A. Selman, A. McDonald, R. Kitney, and D. Linkens, "The Interaction Between Heart Rate and Respiration: Part I-Experimental Studies in Man.", *Automedica*, Vol. 4, pp. 131-139, 1982.

[10] S. Shin, W.N. Tapp, S.S. Reisman, and B.H. Natelson, "Assessment of Autonomic Regulation by the Method of Complex Demodulation." *IEEE Trans. Biomed. Engg.*, Vol. 36, pp. 274-283, 1983.

[11] L. Wilkson, *SYSTAT, The System for Statistics*, Evanston, IL: SYSTAT, INC., 1990.

[12] A.J. Vander, J.H. Sherman, and D.S. Luciano, *Human Physiology: The Mechanisms of Body Function*, 5th edition, New York: McGraw-Hill Publishing Company, 1990, pp. 167-219, 349-471.

[13] *2300 Finapres Blood Pressure Monitor Service Manual*, 2nd edition, Wisconsin: BOC health care inc., 1992.

[14] *Q4000 Monitor Operator Manual*, 3rd edition, Quinton Instrument Co., 1992.

[15] *Q-PLEX Cardio-Pulmonary Exercise System Operator Manual*, Quinton Instrument Co., 1988.