AN INTEGRATED, DYNAMIC MODEL FOR CARDIOVASCULAR AND PULMONARY SYSTEMS

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Neval A. YILMAZ

ABSTRACT

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In this thesis an integrated, dynamic model for cardiovascular and respiratory systems has been developed. Models of cardiopulmonary system, airway mechanics and gas exchange that preexisted in literature have been reviewed, modified and combined. Combined model composes the systemic and pulmonary circulations, left/right ventricles, tissue/lung compartments, airway/lung mechanics and gas transportation. Airway resistance is partitioned into three parts (upper, middle, small airways). A collapsible airways segment and a viscoelastic element describing lung tissue dynamics and a static chest wall compliance are included. Frank-Starling Law, Bowditch effect and variable cerebral flow are also employed in the model.

The combined model predictions have been validated by laboratory data collected from two healthy, young, male subjects, by performing dynamic bicycle exercise tests, using "V_{max}–229 Sensormedics, Cardiopulmonary Exercise Testing Instrument". The transition from rest to exercise under a constant ergometric

workload is simulated. The initial anaerobic energy supply, autoregulation and the dilatation of pulmonary vessels are considered. Mean arterial blood pressure and the blood gas concentrations are assumed to be regulated by the controllers of the central nervous system namely, the heart rate and alveolar ventilation. Cardiovascular and respiratory regulation is modeled by a linear feedback control which minimizes a quadratic cost functional.

Keywords: Cardiopulmonary Modeling, Airway Mechanics, Gas Exchange, Optimal Control, Exercise Testing

ÖZ

KARDİYOVASKÜLER VE SOLUNUM SİSTEMLERİNİN DİNAMİK BÜTÜLEŞİK MODELİ

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Bu tezde kardiyovasküler ve solunum sistemleri için bütünleşik bir dinamik model oluşturulmuştur. Literatürde var olan kardiyopulmoner, hava yolları dinamiği ve gaz alışverişi modelleri incelenmiş, değiştirilmiş ve bu modellerin birleştirilmesi ile yeni bir bütünleşik model geliştirilmiştir. Tümleşik model, sistemik ve pulmoner dolaşımları, sol ve sağ karıncıkları, doku ve akciğer bölmelerini, havayolu ve akciğer mekaniklerini ve gaz alışverişini içermektedir. Havayolu direnci üst, orta ve küçük havayolları için ayrı ayrı modellenmiştir. Katlanabilir havayolları ve akciğer dokusu dinamiklerini açıklayan viskoelastik bir eleman ve statik göğüs kafesi kompliyansı modele dahildir. Frank-Starling Yasası, Bowditch etkisi ve beyin kan dolaşımı modele katılmıştır.

Bütünleşik modelin öngördükleri iki sağlıklı, genç erkek denekten, "V_{max}–229 Sensormedics, Kardiyopulmoner Egzersiz Test Aleti" ile dinamik bisiklet egzersiz testleri yapılarak toplanan laboratuar verileri ile doğrulanmıştır. Egzersiz başlangıcında kullanılan anaerobik enerji kaynakları, otoregülasyon (lokal kan akımı regülasyonu) ve akciğer damarlarının ihtiyaca göre genişleyebilirliği modelde kapsanmaktadır. Ortalama atardamar kan basıncı ve kan gazı yoğunluklarının, merkezi sinir sistemi tarafından kalp atım hızı ve solunum hızı ile kontrol edildiği varsayılmıştır. Sabit ergometrik yük altında dinlenme durumundan egzersize geçiş durumunun simülasyonu yapılmıştır. Kardiyovasküler sistem ve solunumun kontrolü ikinci dereceden bir değer fonksiyonunu en az (minimum) değerine getiren bir doğrusal geri besleme ile modellenmiştir.

Anahtar Kelimeler: Kardiyopulmoner Modelleme, Solunum Yolları Mekaniği, Gaz Alışverişi, Optimal Kontrol, Egzersiz Testi

To My Family

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CHAPTER 1

INTRODUCTION

1.1. Overview

Modeling physiological systems has long been a research subject. Hence, it is possible to find a variety of models examining the cardiovascular and pulmonary systems. In some of these modeling studies, the systems are divided into smaller compartments which are modeled separately. There are various airway mechanics models [1-4]; lung mechanics models [5-9]; gas exchange models [2, 10-12]; pulmonary circulation models [13-15] and cardiovascular system models [16-21] that handle these smaller compartments in isolation. However, models comprising more than one compartment [22-29] that provide a better prediction about the operation of the whole system have gained importance in recent years. Such models offer opportunities to understand the interrelations among systems and they are more realistic. Another benefit of developing such models is that the quantities which are impossible or difficult to measure non-invasively can be predicted and compared with common sense.

This study presents an integrated, dynamic model for the cardiovascular and respiratory systems with airway mechanics and gas transport taken into account. In this manner it is the first exercise model that combines all these features in one design.

In the integrated model presented in this thesis, models of cardiopulmonary system[27], airway mechanics[30] and gas exchange [31],[32] that pre-existed in literature have been reviewed, modified and combined. Combined model composes the systemic and pulmonary circulations, left/right ventricles, tissue/lung compartments, airway/lung mechanics and gas transportation. Airway resistance is partitioned into three parts (upper, middle, small airways). A collapsible airways segment, a viscoelastic element describing lung tissue dynamics and a static chest wall compliance are included. Frank-Starling Law, Bowditch effect and variable cerebral flow are also employed in the model.

The combined model predictions have been validated by laboratory data collected from two healthy, young, male subjects of age 24 and 32, by performing dynamic bicycle exercise tests, using "V_{max}–229 Sensormedics, Cardiopulmonary Exercise Testing Instrument". The transition from rest to exercise under a constant ergometric workload is simulated. The initial anaerobic energy supply, autoregulation and the dilatation of pulmonary vessels are considered. The model is basically a control model with negative feedback. Mean arterial blood pressure and the blood gas concentrations are assumed to be regulated by the controllers of the central nervous system namely, the heart rate and alveolar ventilation. Cardiovascular and respiratory regulations are modeled by a linear feedback control that minimizes a quadratic cost functional. One of the aims of the model is to gain insight about the mechanism of the controller. For further reading in optimal control theory in biomedical applications see [33, 34]. Background on modeling methodology in physiology and medicine can be found in the books [35],[36].

The organization of the thesis is as follows. In Chapter 1, physiological background on respiratory and cardiovascular systems is given. Regulation mechanisms for both systems are introduced. For cardiovascular regulation, baroreceptor reflex, local blood flow, cerebral blood flow, Frank-Starling Law, Bowditch Effect and transport of respiratory gases in blood are mentioned. For the respiratory regulation, respiratory center and the role of oxygen, hydrogen and carbon dioxide in respiratory center activity are examined.

Chapter 2 deals with the components of the respiratory part of the combined model for exercise. Airway/lung mechanics, gas exchange, pulmonary circulation, lung and tissue compartments are included in the respiratory model. Firstly, mass balance equations are written and arranged for the lung and tissue compartments. Secondly, pneumatic equivalent of airway mechanics model is introduced and mathematical relationships are derived. Finally, gas exchange model is examined.

In Chapter 3, cardiovascular model is presented. This chapter starts with a physiological overview of cardiovascular system. Model structure, including two ventricles, systemic and pulmonary circulations is introduced. Model equations are derived using the hydrolic equivalent circuit. Frank-Starling Law and Bowditch effect are used to derive the relations for the filling of the ventricles and heart rate-contractility dependence.

In Chapter 4, the models presented in the previous two chapters are reviewed, modified and combined. Firstly a combined model for the respiratory and cardiovascular systems is introduced. The assumptions made to connect the models are given. Secondly, physiological overview of exercise is given and the combined model is extended for the case of dynamic exercise.

Chapter 5 is dedicated to the statement of solution for the combined exercise model. Firstly, a steady state analysis is made to find out the initial values in order to solve the nonlinear set of differential model equations. Secondly, the control problem is introduced. Thirdly, the theorems to linearize the nonlinear system and derive a linear state feedback control for the linearized system are examined. Finally, these theorems are applied to the model equations to derive a solution.

In Chapter 6, the graphical user interface for the model is introduced. The input screen is divided into separate windows and each window is presented with a description followed by a table of abbreviations and a figure of the window. Also, the ways to enter the values and run the simulations are described. The graphics that

are printed in each of the airway mechanics and cardiopulmonary graphical output windows are explained.

Chapter 7 deals with the experimental side of the thesis study by which the model validation has been done. In this chapter, the experiment environment and test equipments are introduced. Also, information on the test subjects and experiment protocol are given. The experimental results are compared with the model simulations and a discussion on the comparison of results is presented. The model simulations done for a healthy subject, in a good physical condition under no environmental stresses are interpreted. Also, the effect of decreased oxygen and increased carbon dioxide partial pressures and effects of changes in pulmonary resistance dynamics are simulated and compared with the expected results.

Chapter 8 is a review of what has been done, where it can be used, shortcomings of the model and future work that can follow the current study.

In Appendix A, information on the measuring conditions of water vapor, conversion of units and ideal gas law are given. Appendix B is the glossary for notations used throughout this thesis study. Finally, Appendix C presents the numerical values from literature.

1.2. Physiological Background on Respiratory and Cardiovascular Regulation

Physiological background section is mainly based on knowledge gathered from [37] and [38]. For further reading on physiology one may refer to these references. Information from other sources is explicitly referenced throughout the text.

1.2.1. Regulation of Cardiovascular System

The nervous system controls the heart through two different sets of nerves, the parasympathetic nerves and sympathetic nerves. Stimulation of the parasympathetic nerves causes the following four effects on the heart:

1) decreased rate of rhythmicity of the S-A node,
2) decreased force of contraction of the atrial muscle,
3) decreased rate of conduction of impulses through the A-V node, which lengthens the delay period between atrial and ventricular contraction
4) decreased blood flow through the coronary blood vessels which are the vessels that supply nutrition to the heart muscle itself.

All these effects may be summarized by saying that parasympathetic stimulation decreases all activities of the heart. Usually, the heart is stimulated by the parasympathetic nerves during periods of rest. This allows the heart to rest in synchronization with the remainder of the body.

Stimulation of the sympathetic nerves has essentially the opposite effects on the heart:

1) increased heart rate,
2) increased vigor of cardiac contraction,
3) increased blood flow through the coronary blood vessels to supply increased nutrition to the heart muscle.

All the above effects can be summarized by saying that sympathetic stimulation increases the activity of the heart. This is necessary when a person is subjected to stressful conditions such as exercise, excessive heat, and other conditions that require rapid blood flow through the circulatory system. [37]

The effect of sympathetic system to blood vessels is mainly a constriction effect. This increases the resistance of the arteries and therefore decreases the flow through them. The effect on the veins is a decrease in the volume and therefore the transfer of the blood to the heart. Parasympathetic effect does not have a significant influence on the vessels.

Blood pressure is mainly elevated by the sympathetic system and decreased by the parasympathetic system. This mechanism is covered in more detail in Section 1.2.1.1.

1.2.1.1 The Baroreceptor Reflex

Baroreceptors are stretch-sensitive terminals of unmyelinated afferents which supply the walls of the larger arteries [39]. Arterial blood pressure is regulated by means of baroreceptor reflex. Since the arterial walls are elastic, any increase in circumference reflects a change in pressure, not a change in volume. Suppose arterial blood pressure falls. This reduces the stimulation of the baroreceptors located in the aortic arch and the carotid sinus, which lowers the rate at which neural impulses are sent along the glossopharyngeal and vagal afferents to the autonomic centers in the medulla. Consequently, sympathetic neural outflow is increased, leading to an increase in heart rate and cardiac contractility, as well as vasoconstriction of the peripheral vascular system. At the same time, a decreased parasympathetic outflow aids in the heart rate increase. These factors act together to raise arterial pressure [35]. See
Figure 1.1 for a schematical description of how the arterial blood pressure is regulated by baroreceptor loop events.

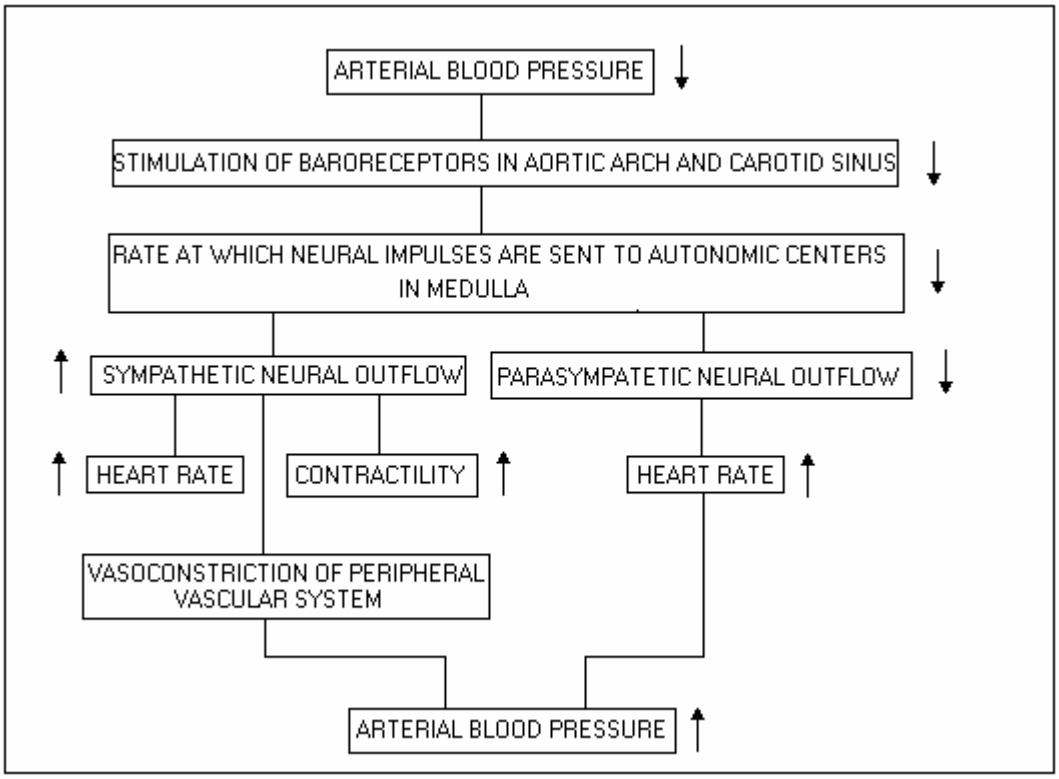

Figure 1.1 Baroreceptor Loop

1.2.1.2 Local Blood Flow Control

Not all but some blood vessels, like the ones in kidney and brain, have the ability to resist stretching during increased arterial pressure by myogenic mechanism. These vessels respond to increased wall tension or wall stretch by contraction of the vascular smooth muscle. This contraction serves to prevent over distention of the vessel and at the same time, by raising the vascular resistance, helps to prevent excessive increases in blood flow when arterial pressure increases [38].

Another important mechanism of local control is the metabolic auto regulation of the small arterioles. If there is increased metabolic activity or a lack of oxygen, the

endothelium releases locally-active vasodilators, in response to changes in levels of products of increased activity ($\downarrow O_2$, $\uparrow CO_2$, $\uparrow K^+$, etc.) which cause vasodilatation of the vessels. Metabolic vasodilatation is superimposed onto the constrictory effect caused by the sympathetic activity [27], [39].

1.2.1.3 Other Mechanisms of Blood Flow Control

Other mechanisms of blood pressure control are chemo receptors, low pressure receptors and central nervous system response.

Chemo receptors in carotid and aortic bodies are activated by low levels of O_2 and low pH (due to high CO_2). Their primary action is to stimulate ventilation, but they also increase blood pressure through sympathetic vasoconstriction. [39].

The venous system is a low pressure system and acts as a reservoir for blood. Therefore, a change in the diameter of the thin-walled vessels reflects a change in volume rather than a change in pressure. Stimulation of venous stretch receptors, especially in the atria, inhibits release of antidiuretic hormone (ADH), which in turn promotes excretion of water by the kidneys. ADH is also known as vasopressin because it increases vascular tone, and this helps to keep blood volume higher by reducing fluid levels in the tissues [39].

Another control on blood flow is the central nervous system ischemic response. It controls the arterial pressure by the brain's vasomotor center in response to diminished brain blood flow. It takes affect when blood flow to the vasomotor center in the lower brain stem becomes decreased enough to cause nutritional deficiency, that is to cause cerebral ischemia and the neurons in the vasomotor center become strongly excited and they respond directly to the ischemia themselves. The magnitude of the ischemic effect on vasomotor activity is tremendous; it can elevate the mean arterial pressure for as long as 10 minutes sometimes as high as 250 mmHg [38].

1.2.1.4 Cerebral Blood Flow

There are three major factors that affect the cerebral blood flow: oxygen, hydrogen ion and carbon dioxide concentrations. An “increase” in the carbon dioxide or hydrogen ion or a “decrease” in oxygen concentration increases cerebral blood flow. It is primarily CO_2 that determines the rate of cerebral flow. Carbon dioxide combines with water in the body fluids to form carbonic acid which subsequently transforms into hydrogen ions. The effect of hydrogen ions and in fact any other acidic substance is to cause vasodilatation of cerebral vessels and therefore to increase the blood flow. Increased blood flow then removes the excess hydrogen ions which would otherwise decrease reactivity of the brain cells. This mechanism helps maintaining a constant acidity in cerebral fluids and keeps the neuronal activity in normal range.

Except the case of intense brain activity the oxygen concentration in brain tissue is kept within narrow limits. Local blood flow regulatory mechanism for oxygen is very much the same for the brain tissue and other parts of circulatory areas of the body, namely vasodilatation.

Sympathetic nervous system plays role in regulating the cerebral blood flow only in cases when the auto regulatory mechanism fails to maintain normal limits such as the case of increased arterial pressure due any kind of excessive circulatory activity. In such a condition, sympathetic nervous system constricts the large and intermediate sized arteries so that the small blood vessels are prevented from the high pressure.

The behavior of brain flow during exercise is still debated. To some investigators it is not affected by physical exercise, where as some others claim an increase in brain blood flow during exercise [40].

1.2.1.5 Frank-Starling Mechanism and Bowditch Effect

There are several mechanisms by which the heart contractility is influenced. Two of them are the Frank-Starling [41] mechanism and the Bowditch [42] effect.

The intrinsic mechanism that allows the heart to pump automatically whatever amount of blood flows into the right atrium from the veins is called the Frank-Starling law of the heart. It dictates that within the physiologic limits, the heart pumps all of the blood that flows into it without excessive damming of blood in the veins. One important consequence of this mechanism is that changes in the arterial pressure, against which the heart pumps, have almost no effect in the stroke volume [41].

There is also the Bowditch effect which describes the heart rate dependency of contractility. The strength of contraction of heart muscles increases with an increase in heart rate. This is due to the fact that the interval between heart beats influences quantity of calcium available to the cell. This effect is also called the "interval-strength" relationship [42].

1.2.1.6 Oxygen and Carbon Dioxide Transport in Blood

Oxygen is mainly transported in combination with hemoglobin. Hemoglobin is found in the red blood cells and it enables the blood to transport 30–100 times as much oxygen to the tissue in dissolved form. Oxygen combines loosely and reversibly with the "heme" portion of hemoglobin. It binds with hemoglobin when P_{O_2} is high and released when P_{O_2} is low. This forms the basis of oxygen transport throughout the gas exchange chain [38].

The relation of O_2 with the P_{O_2} can be studied from the S shaped oxygen dissociation curve. The S shape enables adaptability to various physiological situations. In heavy exercise, for example, the oxygen need increases nearly 20 fold of normal. Since, for low P_{O_2} the curve is steep; a small decrease in P_{O_2} causes extreme amounts of oxygen to be released and therefore compensates the demand. However for high P_{O_2} the slope is small. So even a large reduction of P_{O_2} at high altitudes, remains the blood saturated with oxygen [27].

The amount of chemically bound oxygen depends on various factors. One of them is carbon dioxide concentration. This effect is called the Bohr effect and it shifts the oxygen dissociation curve to left when CO_2 concentration is decreased and vice versa [27, 38].

Like oxygen, carbon dioxide also combines with some chemicals that increase its transport in blood 15–20 times. The blood gases are transported by diffusion and movement of blood [38].

The journey of oxygen starts with its diffusion from the alveolar air to pulmonary capillary. The oxygenation of blood increases as it passes through the pulmonary capillary from arterial end to the venous end.

By this way, % 98 of blood that moves from the left atrium to the lungs passes through the alveolar capillaries and become oxygenated. The remaining 2 percent is the shunt flow, the flow that does not pass through the gas exchange areas [38].

When the arterial blood reaches the peripheral tissues, a significant pressure difference causes the oxygen to rapidly diffuse from blood to tissues. The tissue oxygen pressure is determined by a balance between the oxygen transport rate to the tissues and the rate at which oxygen is used by the tissues.

Since oxygen is used by the cells, its intracellular pressure always remains lower than that of capillaries which enables its diffusion from capillaries to the cells. As oxygen is utilized by the cells, most of it becomes carbon dioxide which increases the intracellular carbon dioxide pressure. So, CO_2 diffuses from the cells into the tissue capillaries and is then carried by blood to the lungs. In the lungs it diffuses from the pulmonary capillaries into the alveoli. In short, it can be said that carbon dioxide travels in reverse direction with oxygen throughout the whole gas transport chain.

The concentration of dissolved carbon dioxide is linearly dependent on P_{CO_2} and chemically bound carbon dioxide has a non linear dependence on P_{CO_2}.The carbon dioxide dissociation curve describes the dependence of total CO_2 on P_{CO_2}.

The influence of the oxygen-hemoglobin reaction on carbon dioxide transport is the Haldane effect. Haldane effect causes increased pick up of carbon dioxide in tissues. For example in pulmonary capillary where P_{O_2} is high, more CO_2 is released [27].

1.2.2. Regulation of Respiration

In this section, the respiratory center activities in the regulation of respiration and roles of oxygen, carbon dioxide and hydrogen in respiratory center activity are summarized.

1.2.2.1 The Respiratory Center

The respiratory system has no intrinsic driver like the heart that drives the cardiovascular system. So regulation depends on external neural drive i.e.

respiration is controlled via changing the intensity of respiratory control signals in order to match the ventilatory demands of the body.

The purpose of respiration is to maintain the optimal oxygen, hydrogen and carbon dioxide concentrations in blood and therefore in the tissues. All these three have influence on the regulation of respiration. Hydrogen and carbon dioxide concentrations have direct influence on the respiratory system whereas oxygen has an indirect effect via peripheral chemo receptors.

1.2.2.2 The Role of Carbon Dioxide, Hydrogen and Oxygen in Respiratory Center Activity

A neuronal area namely the chemo sensitive area located in the medulla is sensitive to hydrogen and carbon dioxide concentrations and it in turn excites the other portions of the respiratory center.

Chemo sensitive area is especially sensitive to excitation by hydrogen ions. However the blood-brain barrier or the blood-cerebrospinal fluid barrier is nearly impermeable to hydrogen ions. Therefore changes in blood hydrogen ions do not produce a direct effect on respiration rate.

Carbon dioxide, on the other hand has little direct effect on the chemo sensitive area. But it can react with water of the tissues and form carbonic acid which in turn dissociates into hydrogen and bicarbonate ions. Besides it passes through the blood-brain barrier or the blood-cerebrospinal fluid barrier very easily as if they do not exist.

When blood carbon dioxide increases, concentration of carbon dioxide in the fluids of the medulla and cerebrospinal fluid also increase. CO_2 in these fluids reacts with the water and forms H ions which have a potent effect on the chemo sensitive area.

So although the hydrogen has more influence on the chemo sensitive area; respiratory center activity is affected more by changes in blood carbon dioxide than by changes in blood hydrogen ions.

The respiratory activity can also be controlled via peripheral chemoreceptor system except for the chemo sensitive area. Specialized chemical receptors called chemo receptors located in carotid bodies and aortic bodies transmit signals to the respiratory center in the brain to contribute respiratory activity regulation. These chemo receptors are especially sensitive to blood oxygen but they also respond to changes in carbon dioxide and hydrogen ion. CO_2 and H ion effect on chemoreceptor activity will not be mentioned since their direct effects in chemo sensitive area are much more powerful.

Blood flow through the chemo receptors is so extreme that a negligible amount of oxygen is removed from the flowing blood. This makes the chemo receptors to be exposed to arterial blood rather than venous blood and their oxygen partial pressures to be equal to that of arteries.

When the oxygen concentration in the pulmonary blood falls below normal, the chemo receptors are strongly stimulated. The impulse rate is particularly sensitive to changes in arterial P_{O_2} in the range between 60 and 30 mmHg, the range in which arterial hemoglobin saturation with oxygen decreases rapidly. This is due to the fact that the hemoglobin oxygen buffer system delivers normal amounts of oxygen to the tissues even when pulmonary P_{O_2} ranges between 60–1000 mmHg. Because of this tolerance the brain respiratory center itself, namely the chemo sensitive area does not get stimulated with changes in oxygen partial pressure; but under conditions in which the tissues lack oxygen the peripheral chemoreceptors are involved in the regulation of respiration [38].

CHAPTER 2

THE RESPIRATORY MODEL

The first mathematical model of the respiratory system has been developed during World War II just like the control system theory in general. This first model by Gray [43] was developed to answer some practical questions like the oxygen requirements of pilots at high altitudes, the possible use of carbon dioxide to counteract anoxia and etc. It described the steady-state operation of the respiratory system via a steady-state feedback model whose controlled-system outputs were arterial carbon dioxide pressure, hydrogen ion concentration and oxygen pressure. These were fed back as input to the controlling system and the output was pulmonary ventilation.

2.1. Physiological Overview of Respiratory System

The function of respiratory system is to supply oxygen to the tissue and to remove the excess carbon dioxide. Respiration can be divided into four sub-processes:

1) pulmonary ventilation which means gas exchange between exterior and alveoli,
2) gas exchange between alveoli and blood,
3) gas exchange between blood and the cells,
4) regulation of respiration.

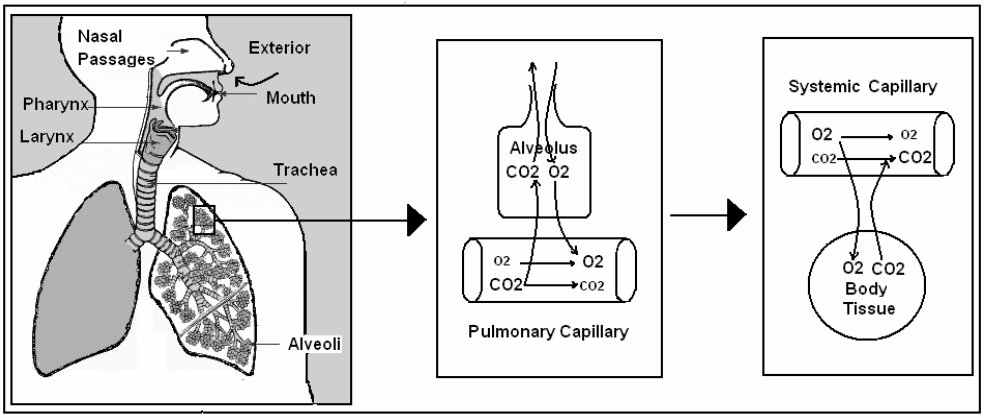

Figure 2.1 Gas Exchange Redrawn from [38], [44]

The gas exchange or in other words gas transport becomes possible by means of diffusion. And the cause of diffusion is the pressure difference between the points of transportation.

Once oxygen has diffused from alveoli into pulmonary capillary due to oxygen partial pressure gradient (see Figure 2.1), a small proportion of it (about 3 percent) dissolves in the fluids of the plasma and red cells but it is mainly carried attached to hemoglobin (about 97 percent) to systemic tissue capillaries. If oxygen transportation was only in dissolved form then the body cells would never receive enough amount of oxygen to survive. Hemoglobin is not only vital for carrying oxygen but also essential for stabilizing the oxygen pressure in tissues.

As soon as the oxygen in systemic capillary reaches the tissue, it diffuses to be used in metabolic reactions by the respiratory enzyme systems of tissue cells (see Figure 2.1). When oxygen is used by the cells, most of it becomes carbon dioxide. This increases the carbon dioxide partial pressure. This leads to the diffusion of carbon dioxide from cells to tissue capillaries. It is then carried back to the lungs by blood. In the lungs it diffuses from pulmonary capillary into the alveoli which is removed by expiration to exterior atmosphere.

2.2. The Model Structure

The respiratory model in this thesis is based on the work of Timischl, [27] .The model developed in [27] is based on the previous work done by Khoo, [45] (Also see related papers [46], [47] and [48]). Model is composed of a lung and a tissue compartment, and it is integrated with the nonlinear normal human lung model of [30] in order to incorporate airway mechanics. Also, a gas exchange part is added to the model as described in [32] and [31].

2.2.1. Respiratory Model of Timischl

Timischl [27], used the respiratory model by Khoo, [45] which has modeled the respiratory system as composed of a lung and a lumped body tissue connected by the systemic and pulmonary circulations as a basis. Model structure is shown in Figure 2.2.

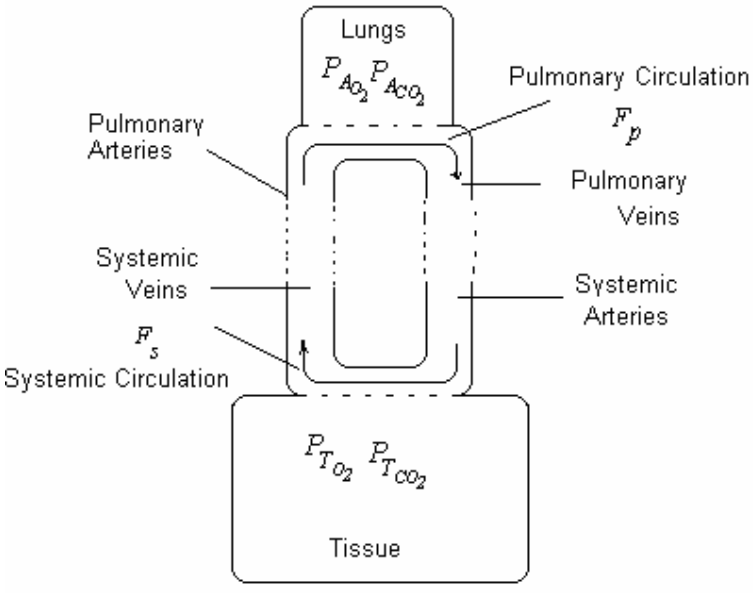

Figure 2.2 Part of the Respiratory Model Structure by Khoo [13]

2.2.1.1 The Lung Compartment

The lungs are modeled as a single, homogenous compartment that is ventilated by a continuous and unidirectional air flow. Respiratory circle events are ignored.

Basically mass balance equations for CO_2 and O_2 are written to model the respiratory behavior of the lungs. This is due to the fact that the change of CO_2 volume in the lung compartment is determined by a balance between the net rates of CO_2 expired from the lungs and the net rate of CO_2 diffusing into the lungs from the blood. Similarly, the change of O_2 volume in the lung compartment is determined by a balance between the net rate of O_2 inspired and the net rate of O_2 diffusing from the lungs to the blood. These can be expressed mathematically as [27]

$$\begin{aligned} V_{A_{O_2}} \dot{F}_{A_{O_2}}(t) &= cF_p(t)(C_{v_{O_2}}(t) - C_{a_{O_2}}(t)) + \dot{V}_{Av}(F_{I_{O_2}} - F_{A_{O_2}}(t)) \\ V_{A_{CO_2}} \dot{F}_{A_{CO_2}}(t) &= cF_p(t)(C_{v_{CO_2}}(t) - C_{a_{CO_2}}(t)) + \dot{V}_{Av}(P_{I_{CO_2}} - P_{A_{CO_2}}(t)). \end{aligned} \tag{2.1}$$

In Equation (2.1), $V_{A_{O_2}}$ denotes the effective O_2 storage volume which is assumed equal to the gaseous lung volume and $V_{A_{CO_2}}$ is the effective CO_2 storage volume. However, $V_{A_{CO_2}}$ is assumed to be larger than the gaseous lung volume since CO_2 can also be found in dissolved form in the lung tissue, pulmonary capillary blood and extra vascular lung volume.

$F_{A_{O_2}}$ and $F_{A_{CO_2}}$ denote the fractional pressures of O_2 and CO_2 in the alveolar air. $F_{I_{O_2}}$ and $F_{I_{CO_2}}$ denote the fractional pressures of O_2 and CO_2 in the inspired air and they are assumed as constants.

F_p denotes the pulmonary circulation. Pulmonary and systemic circulations are distinguished and they form the links between the respiratory and cardiovascular parts of the model.

$\dot{V}_{Av}$ is the alveolar ventilation. This notation is used instead of the conventional respiratory physiology notation $\dot{V}_A$ in order to avoid conflicts with time derivative of alveolar volume $\dot{V}_A$ that is calculated at the airway mechanics part. In respiratory physiology, $\dot{V}_{Av} = f \cdot V_A$, where f is the respiration frequency and V_A is the alveolar volume. Except that of alveolar ventilation the "dot" on top of any variable will denote the time derivative throughout this thesis report.

$C_{v_{O_2}}$ and $C_{a_{O_2}}$ are the concentrations of O_2 in the mixed venous blood and arterial blood respectively. Similar notations are also used for CO_2 . Usually, the concentrations are measured under STPD (standard temperature and pressure, dry) conditions whereas the effective storage volumes $V_{A_{CO_2}}$ and $V_{A_{O_2}}$ are measured under BTPS conditions (body temperature and pressure, saturated). The constant $c = \frac{863}{P_a - 47}$ appearing in the equation is added to account for this fact and make the conversion from STPD to BTPS conditions. (More information on this conversion can be found in Appendix A.) P_a is the ambient pressure and 47 mmHg is the vapor pressure of water at body temperature. The ambient pressure and water vapor pressure will cancel out when the fractional pressures are expressed in terms of partial pressures.

The fractional concentrations can be written in terms of partial pressures as below:

$$\begin{aligned} P_{A_{CO_2}}(t) &= F_{A_{CO_2}}(t)(P_a - 47), \\ P_{A_{O_2}}(t) &= F_{A_{O_2}}(t)(P_a - 47), \\ P_{I_{CO_2}}(t) &= F_{I_{CO_2}}(t)(P_a - 47), \\ P_{I_{O_2}}(t) &= F_{I_{O_2}}(t)(P_a - 47). \end{aligned} \tag{2.2}$$

Inserting Equation (2.2) into Equation (2.1):

$$\begin{aligned} V_{A_{O_2}} \dot{P}_{A_{O_2}}(t) &= 863 F_p(t)(C_{v_{O_2}}(t) - C_{a_{O_2}}(t)) + \dot{V}_{Av}(P_{I_{O_2}} - P_{A_{O_2}}(t)), \\ V_{A_{CO_2}} \dot{P}_{A_{CO_2}}(t) &= 863 F_p(t)(C_{v_{CO_2}}(t) - C_{a_{CO_2}}(t)) + \dot{V}_{Av}(P_{I_{CO_2}} - P_{A_{CO_2}}(t)). \end{aligned} \tag{2.3}$$

$P_{I_{O_2}}$ and $P_{I_{CO_2}}$ denote the partial pressures of O_2 and CO_2 in the inspired air. These pressures are assumed as constant. $P_{A_{O_2}}$ and $P_{A_{CO_2}}$ denote the partial pressures of O_2 and CO_2 in the alveolar region. In [27], $P_{A_{O_2}}$ and $P_{A_{CO_2}}$ are assumed to be equal to the arterial gas tensions since the diffusion of gases at the alveolar capillary membrane is considered as a rapid process. Also, the venous admixture from the bronchial circulation which causes $P_{a_{O_2}}$ to be less than the alveolar O_2 partial pressure $P_{A_{O_2}}$ is neglected. This assumption is repeated in this thesis. Equation (2.3) is rewritten as:

$$\begin{aligned} V_{A_{O_2}} \dot{P}_{a_{O_2}}(t) &= 863 F_p(t)(C_{v_{O_2}}(t) - C_{a_{O_2}}(t)) + \dot{V}_{Av}(P_{I_{O_2}} - P_{a_{O_2}}(t)), \\ V_{A_{CO_2}} \dot{P}_{a_{CO_2}}(t) &= 863 F_p(t)(C_{v_{CO_2}}(t) - C_{a_{CO_2}}(t)) + \dot{V}_{Av}(P_{I_{CO_2}} - P_{a_{CO_2}}(t)). \end{aligned} \tag{2.4}$$

2.2.1.2 The Tissue Compartment

The body tissue is assumed to be lumped into a single compartment that is homogenous. Concentrations of O_2 and CO_2 in the tissue compartments are assumed to be equal to the gas tensions in the venous blood since the diffusion of gases at the tissue-capillary boundary is considered as a rapid process [27].

Mass balance equations for CO_2 and O_2 are written to model the respiratory behavior of the lumped tissue compartment. In the tissues, the change of CO_2 (or

O_2) volume is determined by a balance between the net rate of carbon dioxide (or oxygen) transported to the tissues by the blood and the net rate at which carbon dioxide is produced (or oxygen is utilized) by the tissues.

$$\begin{aligned} V_{T_{O_2}} \dot{C}_{v_{O_2}}(t) &= -MR_{O_2} + F_s(t)(C_{a_{O_2}}(t) - C_{v_{O_2}}(t)) \\ V_{T_{CO_2}} \dot{C}_{v_{CO_2}}(t) &= MR_{CO_2} + F_s(t)(C_{aCO_2}(t) - C_{vCO_2}(t)) \end{aligned} \tag{2.5}$$

In Equation (2.5) $V_{T_{O_2}}$ denotes the effective tissue O_2 storage volume and $V_{T_{CO_2}}$ is the effective tissue CO_2 storage volume. MR_{O_2} is the metabolic oxygen consumption rate and MR_{CO_2} is the metabolic rate of CO_2 production.

F_s is the systemic flow and it is one of the links between cardiovascular and pulmonary segments of the model.

2.2.1.3 Brain Tissue and Cerebral Blood Flow

Brain and cerebral blood flow is also modeled in [27]. The chemo sensitive area of the respiratory center responds to CO_2 concentration in brain tissue. So, a single equation for CO_2 mass balance is written.

$$V_{B_{CO_2}} \dot{C}_{B_{CO_2}}(t) = MR_{B_{CO_2}} + F_B(t)(C_{a_{CO_2}}(t) - C_{vB_{CO_2}}(t)) \tag{2.6}$$

The Equation (2.6) dictates that the rate of change of CO_2 volume is determined by a balance between the net rate of carbon dioxide transported to the brain tissue by the blood and the net rate at which carbon dioxide is produced in the brain tissue.

$MR_{B_{CO_2}}$ is the metabolic rate of CO_2 production in the brain tissue. $V_{B_{CO_2}}$ is the effective brain tissue CO_2 storage volume. $C_{B_{CO_2}}(t)$ is the concentration of total CO_2 in brain and $C_{vB_{CO_2}}(t)$ is the total CO_2 concentration in the venous blood leaving the brain tissue.

$C_{vB_{CO_2}}(t)$ and $C_{B_{CO_2}}(t)$ are assumed to be equilibrated and the above equation reduces to

$$V_{B_{CO_2}} \dot{C}_{B_{CO_2}}(t) = MR_{B_{CO_2}} + F_B(t)(C_{a_{CO_2}}(t) - C_{B_{CO_2}}(t)). \quad (2.7)$$

Cerebral blood flow F_B is assumed to have a linear relation with carbon dioxide partial pressure in arterial blood

$$F_B(t) = F_{B_0}(1 + 0.03(P_{a_{CO_2}}(t) - 40)). \quad (2.8)$$

Here in Equation (2.8), F_{B_0} is the "normal" brain blood flow when for $P_{a_{CO_2}}$ = 40 mmHg. A change in $P_{a_{CO_2}}$ implies a rapid change in F_B, therefore this relationship is regarded to be valid at every instant.

2.2.1.4 The Dissociation Relations

Dissociation relations are required to relate the total gas concentration with the corresponding partial pressure. The relations are also applied during the transient state, too.

Oxygen dissociation curve is S-shaped and can be denoted by the relation

$$C_{O_2}(t) = K_1(1 - e^{-K_2 P_{O_2}(t)})^2. \quad (2.9)$$

In Equation (2.9), K_1 and K_2 are constants for O_2 dissociation curve. C_{O_2} is the partial O_2 concentration and P_{O_2} is the partial O_2 pressure.

Partial CO_2 pressure, P_{CO_2} has a narrow working range so CO_2 concentration is assumed to have a linear relationship with P_{CO_2} as,

$$C_{CO_2}(t) = K_{CO_2} P_{CO_2}(t) + k_{CO_2}. \tag{2.10}$$

In Equation (2.10), K_{co_2} is the slope of the physiological CO_2 dissociation curve. k_{co_2} is the constant for CO_2 dissociation curve. C_{CO_2} is the partial CO_2 concentration and P_{CO_2} is the partial CO_2 pressure.

The above relations hold for both the arterial and venous gas concentrations.

2.2.2. Airway and Lung Mechanics

Airway and lung mechanics part of the model is taken from [30]. In this non linear model of respiratory mechanics, the airway resistance is divided into three components as upper, middle and small airways. The model includes a collapsible airway segment, a viscoelastic element describing lung tissue dynamics and a static chest wall compliance. The pneumatic circuit of airways and its physiological representation are shown in Figure 2.3.

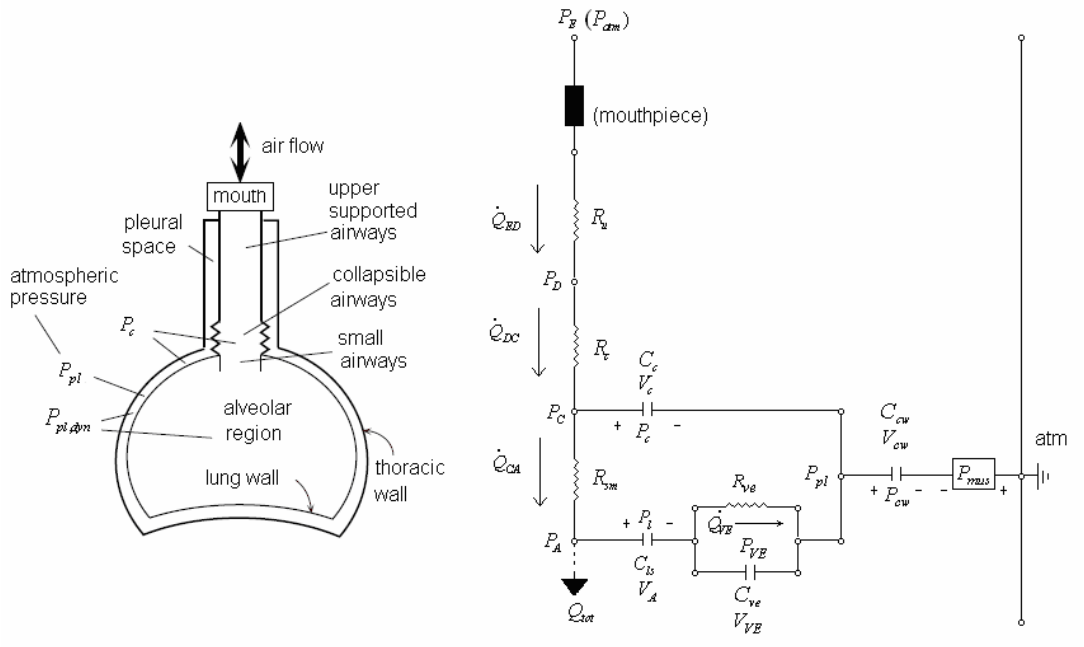

Figure 2.3 Physical Model of the Respiratory System and its Pneumatic Analog [30]

In the above model shown in Figure 2.3, the diaphragm and the thoracic wall are modeled as a static compliance and a pressure source in series. The pressure source, P_{mus} is the dynamic driving force of the model characterizing the elastic forces developed in the diaphragm due to respiratory muscles. The passive compliant element, C_{cw} is added to show that the chest wall is not rigid but it takes part in the energy expenditure of breathing effort. The volume of air contained in this compliance is the chest wall volume, V_{cw} and the pressure across it is the chest wall elastic recoil, P_{cw}.

Examining Figure 2.3 one can easily conclude that the pleural pressure is the difference of the chest wall and respiratory muscle pressures,

$$P_{pl} = P_{cw} - P_{mus}. \tag{2.11}$$

In the article P_{mus} is simply approximated by a sine wave as [30]

$$P_{mus} = A_{mus} \cdot \sin(2\pi ft) + A_{mus}, \tag{2.12}$$

where, A_{mus} is the magnitude and f is the frequency of muscle contraction.

P_{cw} is approximated by a sigmoid curve that is linear in the range of quiet breathing and saturates at the higher and lower volumes as,

$$P_{cw} = A_{cw} - B_{cw} \cdot \ln\left(\frac{TLC - RV}{V_{cw} - RV} - 0.999\right). \tag{2.13}$$

A_{cw} and B_{cw} are constants that are chosen so that C_{cw} is 0.2 lt/cmH_2O in the linear range of sigmoid namely at the quiet breathing stage. TLC is the total lung capacity and RV is the residual volume measured for the subjects.

In order to account for the viscoelastic structure of the lungs a nonlinear compliance C_{ls} in series with a linear compliance C_{ve} and resistance R_{ve} has been included in the model. The total pressure drop across these elements is the dynamic elastic recoil of lung tissue $P_{l,dyn}$. $P_{l,dyn}$, can be expressed mathematically as

$$\begin{aligned} P_{l,dyn} &= P_l + R_{ve}(\dot{V}_A - \dot{V}_{VE}), \\ P_{l,dyn} &= P_l + \frac{1}{C_{ve}} \cdot V_{VE}, \end{aligned} \tag{2.14}$$

where,

$$P_{VE} = R_{ve}(\dot{V}_A - \dot{V}_{VE}) = \frac{1}{C_{ve}} \cdot V_{VE}. \tag{2.15}$$

Here, V_A is the volume of compliance C_{ls} and V_{VE} is the volume of compliance C_{ve}. R_{ve} and C_{ve} are chosen so that the experimental records of flow and volume are matched with the calculated values.

P_l is the pressure across the static nonlinear compliance C_{ls}. It can be described as,

$$P_l = A_l \cdot e^{K_l \cdot V_A} + B_l. \tag{2.16}$$

P_l is designed so that it matches the corresponding pressure-volume characteristics of lung tissue introduced in [32]. A_l, K_l and B_l are constants chosen to achieve this matching.

Applying Newton's First Law to the pneumatic analog circuit expressions for alveolar pressure P_A and pressure in the lumen of the mid airway segment of the model or in other terms collapsible airway pressure P_C can be derived.

$$\begin{aligned} P_A &= P_{pl} + P_l + P_{ve}, \\ P_C &= P_c + P_{pl}, \end{aligned} \tag{2.17}$$

where, P_c is the collapsible airways elastic recoil described as [30]:

$$P_c = A_c + B_c \left(\frac{V_C}{V_{Cmax}} - 0.7 \right)^2, \ \frac{V_C}{V_{Cmax}} \le 0.5 \tag{2.18}$$

$$P_c = 5.6 - B_c' ln \left(\frac{V_C}{V_{Cmax}} - 0.999 \right)^2, \frac{V_C}{V_{Cmax}} \ge 0.5 \tag{2.19}$$

$$P_c = 0, \ \frac{V_C}{V_{Cmax}} \le V_{C_{crit}} \tag{2.20}$$

Airflows in the airway system can be computed in terms of the airway pressures P_A, P_C , P_D and atmospheric pressure P_{atm} by writing continuity equations applied to the nodes of the pneumatic circuit as follows:

$$\begin{aligned} \dot{Q}_{CA} &= \frac{P_C - P_A}{R_{sm}} \\ \dot{Q}_{DC} &= \frac{P_D - P_C}{R_c} \\ \dot{Q}_{ED} &= \dot{Q}_{DC} \end{aligned} \tag{2.21}$$

where, R_{sm} and R_c are the small and collapsible airways resistances respectively.

Peripheral airways are modeled so that they exhibit a nonlinear behavior with volume as described in the equation below:

$$R_{sm} = A_s \cdot e^{K_s (VA - RV)/(V^* - RV)} + B_s \tag{2.22}$$

In fact Equation (2.22) dictates that the peripheral resistance decreases exponentially as the lung volume V_A increases. As lungs expand the small airways are also opened and the air can freely flow hence, the resistance decreases and vice versa [30].

Collapsible airways resistance R_c and upper airways resistance R_u are taken from [30]. The expressions are similar to those listed in other studies like [49]. K_1, K_2, K_3 are constants, V_C is the collapsible airway volume, $V_{C_{max}}$ is the maximum collapsible airway volume in liters.

$$R_c = K_3 \left(\frac{V_{C_{\max}}}{V_C} \right) \tag{2.23}$$

$$R_u = K_1 + K_2 \left| \dot{V}_{cw} \right| \tag{2.24}$$

Rate of volume changes can be expressed in terms of the component airflows in the airway system by writing node equations at nodes P_C and P_A as follows:

$$\begin{aligned} \dot{V}_C &= \dot{Q}_{DC} - \dot{Q}_{CA} \\ \dot{V}_A &= \dot{Q}_{CA} - \Phi_{tot} \end{aligned} \tag{2.25}$$

Φ_{tot} in Equation (2.25) denotes the total gas flux rate across the boundary of alveoli and capillary and it is explained in Section 2.2.3.

2.2.3. Gas Exchange Model

There are several assumptions about the gas exchange between air in the lungs and blood [31]:

1) inspired air is assumed to be instantly warmed to body temperature and saturated with water vapor,
2) gaseous content is assumed to obey the ideal gas law (see Appendix A),
3) blood is assumed to be a uniform homogeneous medium,
4) reactions between the gaseous species and blood are assumed to equilibrate instantaneously.

Several assumptions have been made in the gas exchange model for integration purposes when developing the combined model. These will be mentioned in Chapter 4. Here, a complete description of the original gas exchange model is given.

In the gas exchange model the lumped pulmonary capillary is spatially discretized into equal compartments [32], [31]. The gas exchange is modeled by writing the species conservation law applied to inspiration and expiration as follows:

Inspiration:

$$\begin{aligned}
\dot{P}_{D_i} &= \frac{1}{V_D}\left(\dot{Q}_{ED}\,P_{atm,i} - \dot{Q}_{DC}\,P_{D_i}\right) \\
\dot{P}_{C_i} &= \frac{1}{V_C}\left(\dot{Q}_{DC}\,P_{D_i} - \dot{Q}_{CA}\,P_{C_i} - P_{C_i}\,\dot{V}_C\right) \\
\dot{P}_{A_i} &= \frac{1}{V_A}\left\{\dot{Q}_{CA}\,P_{C_i} - P_{A_i}\,\dot{V}_C - \sum_{j=1}^{N_{seg}} \frac{D_{L_i}\left(P_{A_i} - P_{b_i}^{j}\right)\Delta V_{PC}^{j}}{V_{PC}}\right\}
\end{aligned} \tag{2.26}$$

Expiration:

$$\begin{aligned}
\dot{P}_{D_i} &= \frac{1}{V_D}\left(\dot{Q}_{ED}\,P_{D_i} - \dot{Q}_{DC}\,P_{C_i}\right) \\
\dot{P}_{C_i} &= \frac{1}{V_C}\left(\dot{Q}_{DC}\,P_{C_i} - \dot{Q}_{CA}\,P_{A_i} - P_{C_i}\,\dot{V}_C\right) \\
\dot{P}_{A_i} &= \frac{1}{V_A}\left\{\dot{Q}_{CA}\,P_{A_i} - P_{A_i}\,\dot{V}_A - \sum_{j=1}^{N_{seg}} \frac{D_{L_i}\left(P_{A_i} - P_{b_i}^{j}\right)\Delta V_{PC}^{j}}{V_{PC}}\right\}
\end{aligned} \tag{2.27}$$

P_{D_i} , P_{C_i} , P_{A_i} are the partial pressures of gas species "i" (CO_2 , O_2 and N_2) in the upper, middle and small airways respectively. $P_{atm,i}$ is the partial pressure of gas species "i" in the atmosphere. $P_{b_i}^{j}$ denotes the partial pressure of gas species in blood in jth capillary segment and ΔV_{PC}^{j} denotes the blood volume in the jth segment.

The diffusing capacity for the i^{th} gaseous species (D_{L_i}) characterizes its diffusion across the alveolar-capillary membrane. These are designed to account for changing capillary blood volume by scaling the nominal values [22], [10], [2]. This can be expressed in $ml_{STPD}.min^{-1}.mmHg^{-1}$ as,

$$D_{L_{O_2}} = \sqrt{\frac{V_{pc}}{V_{pc\,\max}}}(23.86 + 0.5119 P_{O_2} - 0.007983 {P_{O_2}}^2 + 2.306 \times 10^{-5} {P_{O_2}}^3)$$

$$D_{LC_{O_2}} = \sqrt{\frac{V_{pc}}{V_{pc\,\max}}} \times 400.0 \tag{2.28}$$

$$D_{L_{N_2}} = \sqrt{\frac{V_{pc}}{V_{pc\,\max}}} \times 15.0.$$

The total gas flux rate of both CO_2, O_2, N_2 across the alveolar capillary membrane can be expressed as follows:

$$\Phi_{tot} = \sum_{i=1}^{3} \sum_{j=1}^{N_{seg}} \frac{D_{L_i} \left[P_{A_i} - P_{b_i}^j \right] \Delta V_{PC}^j}{\Delta V_{PC}} \tag{2.29}$$

Species molar balance is written to describe the dynamics of the species concentration in each of the discretized pulmonary segments as

$$\frac{\partial C_{b_i}^j}{\partial t} = -\frac{\partial v_{z_b}^j C_{b_i}^j}{\partial z} + \frac{D_{L_i} \left[P_{A_i} - P_{b_i}^j \right]}{V_{PC}}, \tag{2.30}$$

where, $v_{z_b}^j$ is the blood flow velocity in the jth capillary and z is the length coordinate of the pulmonary capillary.

CHAPTER 3

THE CARDIOVASCULAR MODEL

3.1. Physiological Overview of CVS

The cardiovascular system circulates blood within the body, delivering oxygen and other nutrients to all of the tissues and removing unwanted end products of metabolism. In general, it is responsible of maintaining the optimal environment for the proper functioning of the cells.

The cardiovascular system is composed of the heart and blood vessels in particular arteries, arterioles, capillaries, venules and veins.

Heart is a four chamber hydrolic pump whose function is to maintain blood flow through all the vessels and tissue compartments involved in the circulatory system. It consists of two separate pumps to achieve this aim: right heart and left heart. Right heart is responsible for pumping blood from the heart through the lungs. Left heart pumps the blood from the heart to the tissue compartments. The atria act as primer pumps that increase effectiveness of the ventricular pumps. The main pumping action is done by the ventricles. In this thesis work, it is assumed that the model has two pumps: right and left ventricles.

Circulation has two major subdivisions: systemic and pulmonary circulations. Pulmonary circulation involves the path from the heart through the lungs and back to the heart. Systemic circulation is the blood flow from the heart to the rest of the

body compartments and back to the heart. So, in fact the blood flows in a closed loop, continuous circuit.

Arteries transport the blood under high pressure to the tissues. They end in arterioles which are the last small branches of the arterial system. Blood is released into capillaries through the arterioles. Capillaries are the place to exchange fluid, nutrients, electrolytes, hormones, and other substances between blood and the interstitial fluid. The venules collect blood from capillaries and they gradually grow into veins where the transport of the waste end products produced by the metabolic activities in the cells back to the heart occurs. The veins also act as a controllable blood reservoir of the body.

3.2. The Model Structure

Cardiovascular model developed by [27] is used in this thesis. The model is based on previous four compartment models introduced by [21], [50] which was later modified and adapted by [16] and in related papers [18], [17], [51] and [52].

As explained in Chapter 1, the human circulation and its associated systems form a distributed, non-linear, time-varying system. The proposed model is a lumped approximation to the actual system.

The model involves the systemic and pulmonary circulations connected in series. The right and left ventricles are modeled as mechanical pumps whose outputs are independent of blood pressures.

Arteries, veins, arterioles, venules and capillaries are lumped into a single elastic artery, a single vein and a single resistance vessel. Atria are lumped with their related veins, too.

See the Figure 3.1 for an illustration of the physiological structure of cardiovascular system and its hydrolic circuit equivalent.

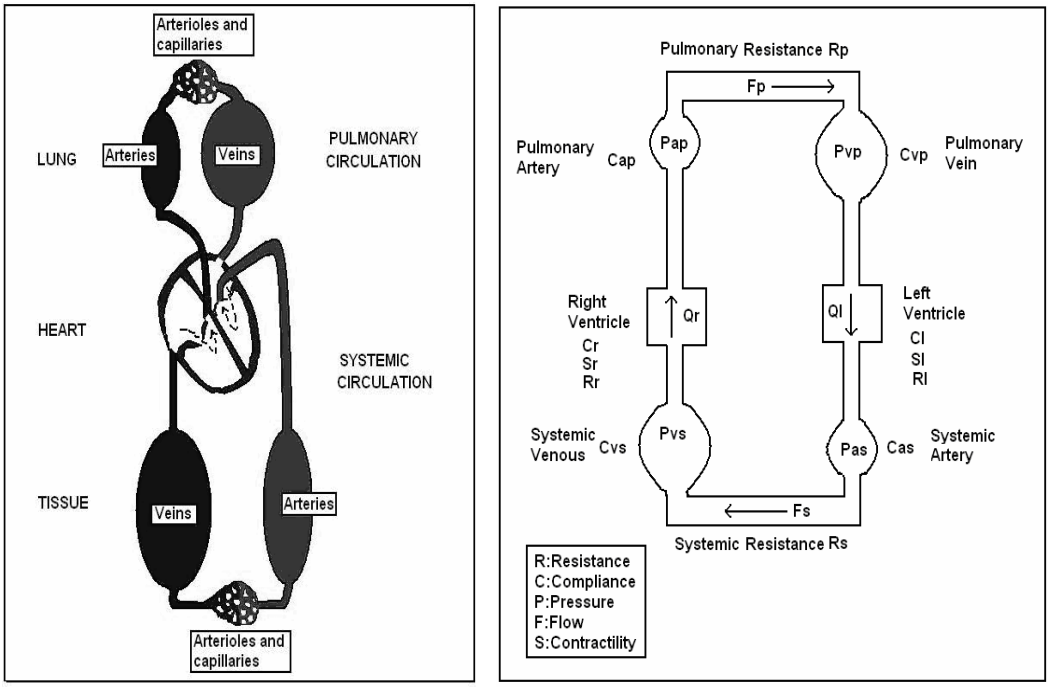

Figure 3.1 Physiological Structure of Cardiovascular System and its Equivalent Hydrolic Circuit ([38],[27])

The fixed blood volume V_0 is assumed to be stored in the systemic and pulmonary circulations ignoring pumps and resistance channels.

Cardiac circle events are ignored. A unidirectional, non pulsatile blood flow is assumed through the pumps. This means that at steady state all pressures related to the components of cardiovascular system model and cardiac outputs are assumed to be constant.

While deriving the model equations making an analogy between hydrolic and electrical circuits is a useful approach to uncover the relations between model components.

A hydrolic circuit can be interpreted in terms of its electrical equivalent circuit. The physical quantities of the hydrolic circuit, namely flows, pressures, resistances and compliances correspond to current, voltage, electrical resistance and compliance of the electrical equivalent. Components of a vascular compartment, its electrical analog and mathematical description is given in the Figure 3.2.

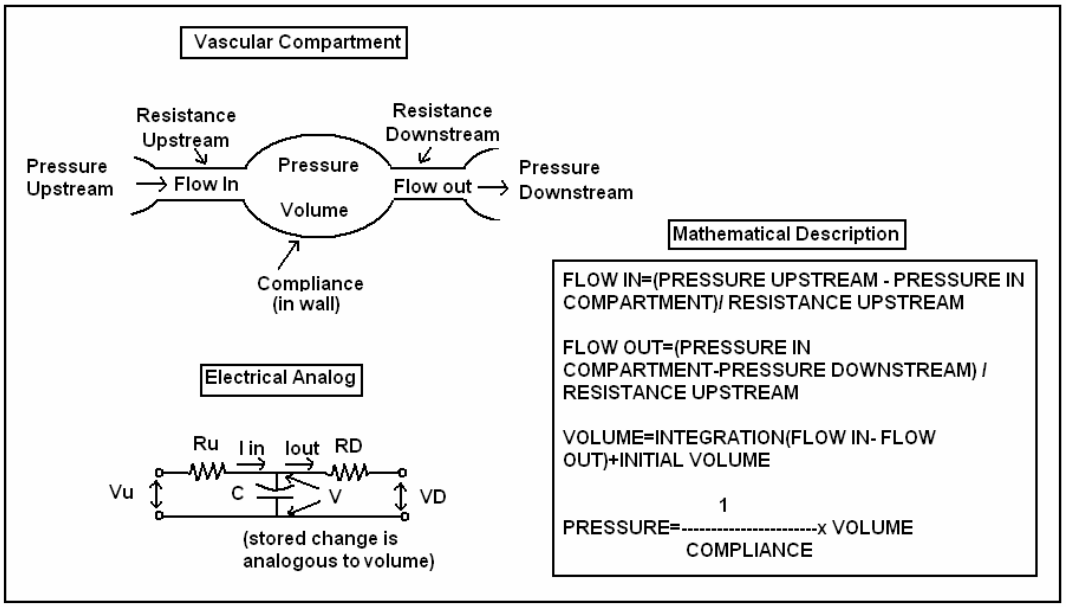

Figure 3.2 A Vascular Compartment, its Electrical Analog and Mathematical Description [53]

Blood pressure means the force exerted by the blood against any unit area of the vessel wall. Resistance is the impediment to the blood flow in a vessel.

Blood flow is the quantity of blood that passes through a given point in the circulation in a given period. The blood flow through a vessel is determined by two factors: (1) the pressure gradient that pushes the blood through the vessel. (2) the resistance that blocks the blood flow.

Compliance (capacitance) is the total quantity of the blood that can be stored in a given portion of the circulation for each millimeter mercury of rise in pressure.

Using the vascular compartment description in Figure 3.2 electrical equivalent circuit can be drawn as follows:

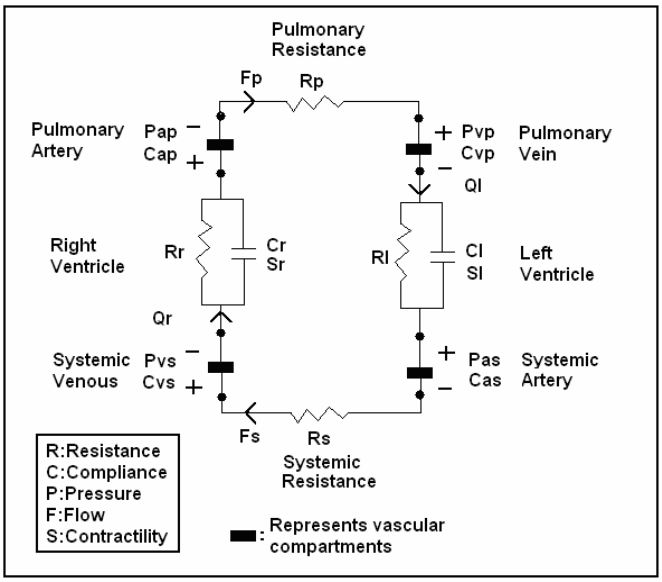

Figure 3.3 Electrical Equivalent Circuit for Cardiovascular Sytem

3.3. The Model Equations

Mathematical relationships can be derived by writing the continuity equations for each node in the above electrical circuit.

It can be seen from the Figure 3.3 that charge stored is analogous to volume in hydrolic circuit.

Table 3-1 Charge-Volume Relationship 1

$V_{as} \Leftrightarrow Q_{as}$
Volume in hydrolic circuit $\Leftrightarrow$ Charge in electrical equivalent

Therefore, it can be concluded that time derivative of volume is analogous to flow in an electrical circuit. Writing Kirchoff's Law at the node denoting the arterial systemic compartment,

$$\dot{V}_{as}(t) = Q_l(t) - F_s(t), \tag{3.1}$$

where Q_l is the left cardiac output which is the amount of blood that is pumped by the left heart in a unit period.

It is also known that the charge is related to the product of capacitance and voltage. Analogously, the volume will be equal to the product of compliance and pressure. Expressing this mathematically:

Table 3-2 Charge-Volume Relationship 2

$Q_{as} = C_{as} V_{as} \Leftrightarrow V_{as} = C_{as} P_{as}$
Charge =Capacitance.Voltage $\Leftrightarrow$ Volume=Compliance.Pressure

Using the relations in tables Table 3-1 and Table 3-2 and Equation (3.1)

$$C_{as}\,\dot{P}_{as}(t) = Q_l(t) - F_s(t) \tag{3.2}$$

The above relation can be rewritten for all of the four compartments namely, arterial systemic, pulmonary arterial, pulmonary venous, systemic venous as follows,

$$\begin{aligned} C_{ap}\,\dot{P}_{ap}(t) &= Q_r(t) - F_p(t) \\ C_{vs}\,\dot{P}_{vs}(t) &= F_s(t) - Q_r(t) \\ C_{vp}\,\dot{P}_{vp}(t) &= F_p(t) - Q_l(t). \end{aligned} \tag{3.3}$$

Here $P_{as}, P_{ap}, P_{vp}, P_{vs}$ stands for pressures of arterial systemic, pulmonary arterial, pulmonary venous, systemic venous.

Using the fact that a fixed volume is distributed among the four compartments one of the above relations can be written algebraically rather than differentially:

$$V_o = V_{as} + V_{vs} + V_{vp} + V_{ap} \tag{3.4}$$

$$P_{ap}(t) = \frac{1}{C_{ap}}\left(V_o - C_{as}P_{as}(t) - C_{vs}P_{vs}(t) - C_{vp}P_{vp}(t)\right) \tag{3.5}$$

In the above derivation, sympathetic influence upon the unstressed vessel volume is neglected. Also, myogenic effects in vessel volume which occur particularly in arterial vessels are ignored. Also, constant compliances are assumed.

Now let us derive expressions for pulmonary and systemic flows. Again flows can be written considering the analogy between current in electricity and flow in hydrolic circuit as:

$$i = \frac{\Delta V}{R} \Leftrightarrow flow = \frac{Pressure\_difference}{tissue\_resistance} \tag{3.6}$$

Looking at Equation (3.6) and Figure 3.3 one can write:

$$F_s(t) = \frac{P_{as}(t) - P_{vs}(t)}{R_s}$$
$$F_p(t) = \frac{P_{ap}(t) - P_{vp}(t)}{R_p} \tag{3.7}$$

Here R_p and R_s stands for the tissue and pulmonary resistances respectively. So far, the resistances are considered as parameters independent of pressures and the vessels are modeled as rigid tubes. But a modification will be done to include metabolic auto regulation in the case of exercise.

One can conclude this relation from Hagen-Poiseuille's law which dictates that the flows of homogenous fluids like blood depend on the driving pressure difference and on the opposing viscous resistance, too.

3.4. The Dependence of Ventricle Output on the Blood Pressures

Cardiac outputs are assumed constant and are defined as mean blood flow over the length of a pulse at steady state. This can be expressed mathematically in terms of stroke volumes and heart rate. Stroke volume is the amount of blood that is ejected at each heart beat. So, for both right and left ventricles cardiac outputs can be written as follows,

$$Q_l = HV_{str,l}, \tag{3.8}$$

$$Q_r = HV_{str,r}. \tag{3.9}$$

This equation can also be considered as valid for non-steady state. In such a case, $Q_l(t)$ and $Q_r(t)$ are taken to be averaged cardiac outputs.

In Section 3.3 the blood pressures are written in terms of cardiac outputs via continuity equations (see Equation (3.2) and Equation (3.3)). Writing the cardiac outputs in terms of blood pressures is a rather complicated task. From Equation (3.8) and Equation (3.9) it is seen that the task is now reduced to writing the stroke volume in terms of blood pressures for both filling and emptying processes. Here, the equation for the right ventricle will be derived. Expression for the left ventricle can be derived similarly.

The right ventricle has a residual volume, V_r at the start of the filling process. It gets filled during diastole. At the end of t_d minutes, ventricle volume reaches the end-diastolic volume V_d. Filling is forced by the systemic venous pressure, P_{vs} and opposed by viscous resistance of the heart (right ventricle), R_r. Compliance of the relaxed right ventricle is shown with C_r. Such a process can be modeled by first order differential equations as follows:

$$R_r \dot{V}(t) + \frac{1}{C_r} V(t) = P_{vs}\,,\; V(0) = V_r\,. \tag{3.10}$$

Solution of Equation (3.10) is:

$$V(t) = (V_r - C_r P_{vs}) e^{-\frac{t}{RrCr}} + C_r P_{vs}\,. \tag{3.11}$$

At time t_d this equation takes the form,

$$V_d = (V_r - C_r P_{vs}) e^{-\frac{td}{RrCr}} + C_r P_{vs}\,. \tag{3.12}$$

In the emptying process, the ventricle ejects the stroke volume, $V_{str,r}$ against the pulmonary arterial pressure, P_{ap}. In the ideal case, only the residual volume remains in the ventricle after systole. This can be expressed as:

$$V_{str} = V_d - V_r, \quad \frac{S_r}{P_{ap}} \leq 1 \tag{3.13}$$

For modeling purposes the dynamic of the ejection process can be ignored and using Frank Starling Law of the Heart one can write a relation between arterial pressure, end diastolic volume, contractility and stroke volume.

Guyton's "Textbook of Medical Physiology" [38] describes Frank-Starling law of the heart as the principal mechanism by which the heart adapts to changing inflow of blood. When the cardiac muscle becomes stretched an extra amount, as it does when extra amounts of blood enter the heart chambers, the stretched muscle contracts with a greatly increased force, thereby automatically pumping the extra blood into the arteries.

The condition of Equation (3.13) says nothing but a physiological fact that a volume not contained in the ventricle can not be ejected or in other words stroke volume is less than the end diastolic volume. This equation can be rewritten in the form below to include the condition within the equation,

$$V_{str,r} = f(S_r, P_{ap}) \frac{V_d}{P_{ap}} \tag{3.14}$$

where,

$$f(s, p) = 0.5(s + p) - 0.5((p - s)^2 + 0.01)^{1/2}. \tag{3.15}$$

This function in Equation (3.15) is a minimum function that has an offset of 0.01 for smoothing at the s=p point.

Using the above derived equations one can write the stroke volume as:

$$V_{str,r} = f(S_r, P_{ap}) \frac{V_d}{P_{ap}}. \tag{3.16}$$

Let us arrange Equation (3.16). Firstly let us write the residual volume in terms of end diastolic volume,

$$V_{str,r} = V_d - V_r = f(S_r, P_{ap})\frac{V_d}{P_{ap}}$$
$$V_r = V_d(1 - \frac{f(S_r, P_{ap})}{P_{ap}}). \tag{3.17}$$

Secondly let us rearrange the equation for end diastolic volume,

$$V_d = (V_r - C_r P_{vs})e^{-\frac{td}{RrCr}} + C_r P_{vs}$$
$$V_d = (V_d(1 - \frac{f(S_r, P_{ap})}{P_{ap}}) - C_r P_{vs})e^{-\frac{td}{RrCr}} + C_r P_{vs} \tag{3.18}$$
$$V_d = V_d(1 - \frac{f(S_r, P_{ap})}{P_{ap}})e^{-\frac{td}{RrCr}} - C_r P_{vs}e^{-\frac{td}{RrCr}} + C_r P_{vs}$$

$$V_d = V_d(1 - \frac{f(S_r, P_{ap})}{P_{ap}})e^{-\frac{td}{RrCr}} + (C_r P_{vs} - C_r P_{vs}e^{-\frac{td}{RrCr}})$$
$$V_d(1 - (1 - \frac{f(S_r, P_{ap})}{P_{ap}})e^{-\frac{td}{RrCr}})) = (C_r P_{vs} - C_r P_{vs}e^{-\frac{td}{RrCr}})$$
$$V_d = \frac{(C_r P_{vs} - C_r P_{vs}e^{-\frac{td}{RrCr}})}{(1 - (1 - \frac{f(S_r, P_{ap})}{P_{ap}})e^{-\frac{td}{RrCr}}))}.$$

If the above relation is used for end diastolic volume in stroke volume expression:

$$V_{str,r} = f(S_r, P_{ap})\frac{\frac{(C_r P_{vs} - C_r P_{vs}e^{-\frac{td}{RrCr}})}{(1 - (1 - \frac{f(S_r, P_{ap})}{P_{ap}})e^{-\frac{td}{RrCr}}))}}{P_{ap}} = f(S_r, P_{ap})\frac{(C_r P_{vs} - C_r P_{vs}e^{-\frac{td}{RrCr}})}{(P_{ap} - (P_{ap} - f(S_r, P_{ap}))e^{-\frac{td}{RrCr}}))} \tag{3.19}$$

$$V_{str,r} = f(S_r, P_{ap})\frac{C_r P_{vs}(1 - e^{-\frac{td}{RrCr}})}{P_{ap}(1 - e^{-\frac{td}{RrCr}}) + (f(S_r, P_{ap})e^{-\frac{td}{RrCr}})}.$$

Duration of diastole is assumed to be,

$$td = \frac{60}{H} - \kappa\left(\frac{60}{H}\right)^{1/2}, \tag{3.20}$$

where κ=0.4 is an empirical factor. (see [18]).

Finally, cardiac output can be written using Equations (3.8), (3.9)and (3.19) as,

$$Q_r(t) = H\,\frac{c_r P_{vs}(t) f(S_r(t), P_{ap}(t))(1-e^{-\frac{t_d}{R_r c_r}})}{P_{ap}(t)(1-e^{-\frac{t_d}{R_r c_r}}) + f(S_r(t), P_{ap}(t))e^{-\frac{t_d}{R_r c_r}}} \tag{3.21}$$

$$Q_l(t) = H\,\frac{c_l P_{vp}(t) f(S_l(t), P_{as}(t))(1-e^{-\frac{t_d}{R_l c_l}})}{P_{as}(t)(1-e^{-\frac{t_d}{R_l c_l}}) + f(S_l(t), P_{as}(t))e^{-\frac{t_d}{R_l c_l}}}. \tag{3.22}$$

3.5. Relationships between Heart Rate and Contractilities

One should take into account the force-interval (strength-interval) relation when modeling the contractilities. Force interval relation is the sensitivity of the contractile force developed at the heart muscle to the interval between contractions. This relation is considered to be an intrinsic property of the heart muscle. It was first introduced by Bowditch and hence also known as the Bowditch effect [42].

Bowditch effect was included in the cardiopulmonary model [27] by assuming that the contractility is increased if heart rate is increased. The relation between heart rate and contractilities are directly used from [18],

$$\ddot{S}(t) + \gamma \dot{S}(t) + \alpha S(t) = \beta H. \tag{3.23}$$

In Equation (3.23) it is seen that contractilities follow the heart rate with a second order delay for a good experimental match [18].

To obtain differential equations of first order Equation (3.24) is introduced,

$$\sigma = \dot{S}. \tag{3.24}$$

Inserting Equation (3.24) to Equation (3.23),

$$\begin{aligned} \dot{S}(t) &= \sigma(t) \\ \dot{\sigma}(t) &= -\gamma\sigma(t) - \alpha S(t) + \beta H \end{aligned} \tag{3.25}$$

two first order differential equations can be written instead of one second order differential equation.

CHAPTER 4

COMBINED MODEL FOR EXERCISE

The equations derived for cardiovascular and pulmonary systems in Chapter 2 and Chapter 3 are integrated into a combined model that simulates the cardiopulmonary behavior with airway mechanics and gas transport phenomena. This combined model is extended for the case of aerobic, sub maximal, constant workload dynamic exercise. To the authors' knowledge, it is the first exercise model that combines a cardio pulmonary model with airway mechanics and gas transport phenomena.

4.1. Combined Model

In this section, the combined model that integrates cardiopulmonary, airway mechanics and gas transportation models is introduced. The assumptions made for integration purposes are given. Later, in Section 4.2, this model will be extended for the case of exercise. See Figure 4.1 for an illustration of the combined model and Section 4.1.1 for a list of model equations.

4.1.1. Model Equations for the Combined Model

The differential equations derived for cardiovascular and respiratory systems in the previous chapters up to now are listed below:

$$
\begin{aligned}
&C_{as}\,\dot{P}_{as}(t) = Q_l(t) - F_s(t)\\
&C_{vs}\,\dot{P}_{vs}(t) = F_s(t) - Q_r(t)\\
&C_{vp}\,\dot{P}_{vp}(t) = F_p(t) - Q_l(t)\\
&V_{A_{O_2}}\,\dot{P}_{a_{O_2}}(t) = 863F_p(t)(C_{v_{O_2}}(t) - C_{a_{O_2}}(t)) + \dot{V}_{Av}(P_{I_{O_2}} - P_{a_{O_2}}(t))\\
&V_{A_{CO_2}}\,\dot{P}_{a_{CO_2}}(t) = 863F_p(t)(C_{v_{CO_2}}(t) - C_{a_{CO_2}}(t)) + \dot{V}_{Av}(P_{I_{CO_2}} - P_{a_{CO_2}}(t))\\
&V_{B_{CO_2}}\,\dot{C}_{B_{CO_2}}(t) = MR_{B_{CO_2}} + F_B(t)(C_{a_{CO_2}}(t) - C_{v_{BCO_2}}(t))\\
&V_{T_{O_2}}\,\dot{C}_{v_{O_2}}(t) = -MR_{O_2} + F_s(t)(C_{a_{O_2}}(t) - C_{v_{O_2}}(t))\\
&V_{T_{CO_2}}\,\dot{C}_{v_{CO_2}}(t) = MR_{CO_2} + F_s(t)(C_{a_{CO_2}}(t) - C_{v_{CO_2}}(t))\\
&\dot{S}_l(t) = \sigma_l(t)\\
&\dot{S}_r(t) = \sigma_r(t)\\
&\dot{\sigma}_l(t) = -\gamma_l\sigma_l(t) - \alpha_l S_l(t) + \beta_l H\\
&\dot{\sigma}_r(t) = -\gamma_r\sigma_r(t) - \alpha_r S_r(t) + \beta_r H
\end{aligned}
\qquad (4.1)
$$

Inspiration:

$$
\begin{aligned}
&\dot{P}_{D_{CO_2}} = \frac{1}{V_D}\left(\dot{Q}_{ED}\,P_{atm,CO_2} - \dot{Q}_{DC}\,P_{D_{CO_2}}\right)\\
&\dot{P}_{C_{CO_2}} = \frac{1}{V_C}\left(\dot{Q}_{DC}\,P_{D_{CO_2}} - \dot{Q}_{CA}\,P_{C_{CO_2}} - P_{C_{CO_2}}\,\dot{V}_C\right)\\
&\dot{P}_{A_{CO_2}} = \frac{1}{V_A}\left\{\dot{Q}_{CA}\,P_{C_{CO_2}} - P_{A_{CO_2}}\,\dot{V}_C - D_{L_{CO_2}}\left(P_{A_{CO_2}} - P_{b_{CO_2}}\right)\right\}\\
&\dot{P}_{D_{O_2}} = \frac{1}{V_D}\left(\dot{Q}_{ED}\,P_{atm,O_2} - \dot{Q}_{DC}\,P_{D_{O_2}}\right)\\
&\dot{P}_{C_{O_2}} = \frac{1}{V_C}\left(\dot{Q}_{DC}\,P_{D_{O_2}} - \dot{Q}_{CA}\,P_{C_{O_2}} - P_{C_{O_2}}\,\dot{V}_C\right)\\
&\dot{P}_{A_{O_2}} = \frac{1}{V_A}\left\{\dot{Q}_{CA}\,P_{C_{O_2}} - P_{A_{O_2}}\,\dot{V}_C - D_{L_{O_2}}\left(P_{A_{O_2}} - P_{b_{O_2}}\right)\right\}
\end{aligned}
$$

Equation (4.1) Continued…

Expiration:

$$\dot{P}_{D_{CO_2}} = \frac{1}{V_D}\left(\dot{Q}_{ED} P_{D_{CO_2}} - \dot{Q}_{DC} P_{C_{CO_2}} \right)$$

$$\dot{P}_{C_{CO_2}} = \frac{1}{V_C}\left(\dot{Q}_{DC} P_{C_{CO_2}} - \dot{Q}_{CA} P_{A_{CO_2}} - P_{C_{CO_2}} \dot{V}_C \right)$$

$$\dot{P}_{A_{CO_2}} = \frac{1}{V_A}\left\{ \dot{Q}_{CA} P_{A_{CO_2}} - P_{A_{CO_2}} \dot{V}_A - D_{L_{CO_2}} \left(P_{A_{CO_2}} - P_{b_{CO_2}} \right) \right\}$$

$$\dot{P}_{D_{O_2}} = \frac{1}{V_D}\left(\dot{Q}_{ED} P_{D_{O_2}} - \dot{Q}_{DC} P_{C_{O_2}} \right)$$

$$\dot{P}_{C_{O_2}} = \frac{1}{V_C}\left(\dot{Q}_{DC} P_{C_{O_2}} - \dot{Q}_{CA} P_{A_{O_2}} - P_{C_{O_2}} \dot{V}_C \right)$$

$$\dot{P}_{A_{O_2}} = \frac{1}{V_A}\left\{ \dot{Q}_{CA} P_{A_{O_2}} - P_{A_{O_2}} \dot{V}_A - D_{L_{O_2}} \left(P_{A_{O_2}} - P_{b_{O_2}} \right) \right\}$$

Equation (4.1) can be thought to be divided into two parts; the equations describing the cardiopulmonary behavior and a second set that explains the airway mechanics and gas transport equations for inspiration and expiration.

Some approximations have been made when adapting the gas exchange model to the combined model presented here. First of all, the diffusion at the alveolar capillary membrane is assumed rapid and ignored in the model following the assumptions in [27], as described in Section 2.2.1.1. So that the Φ_{tot} term is omitted in gas exchange model. However, a simplification is made in Φ_{tot} to be used in steady state analysis to prove that the assumption of $P_{A_i} = P_{a_i}$ (i, denotes the gas species) is inherent in the gas exchange model, too. For this purpose, the capillary segments are modeled as having uniform volume which leads a simplification of Φ_{tot} as follows:

$$\Phi_{tot} = \sum_{i=1}^{3} D_{L_i} \left[P_{A_i} - P_{b_i} \right] \tag{4.2}$$

Besides, one may notice that because of the assumption of $P_{A_i} = P_{a_i}$; P_{A_i} , the alveolar gas partial pressures can be omitted from the above equations and P_{a_i} , the arterial gas partial pressures which are more accurate can be used instead of P_{A_i} in the combined model equations.

Secondly, the pulmonary capillary volume V_{pc} is considered to be equal to maximum pulmonary capillary volume $V_{pc_{max}}$ and Equation (2.30) is not used in our combined model. This leads a simplification in relations introduced in Equation (2.28), too.

$$\begin{aligned} D_{L_{O_2}} &= (23.86 + 0.5119 P_{O_2} - 0.007983 {P_{O_2}}^2 + 2.306 \times 10^{-5} {P_{O_2}}^3) \\ D_{L_{CO_2}} &= 400.0 \\ D_{L_{N_2}} &= 15.0 \end{aligned} \tag{4.3}$$

Thirdly, N_2 is not included in our model since its concentration and partial pressure were not included and being calculated in the rest of the cardiopulmonary model derived from [27]. So the last relation in Equation (4.3) is not used.

Finally, last condition of collapsible airways elastic recoil equation is ignored (see Equation (4.4)) since a value for $V_{C_{crit}}$ could not found from literature. And the multiplier of B_c in Equation (2.18) is negated. The final set of equations for P_c is as follows:

$$P_c = A_c + B_c \left(\frac{V_C}{V_{Cmax}} - 0.7 \right)^2 , \frac{V_C}{V_{Cmax}} \leq 0.5 \tag{4.5}$$

$$P_c = 5.6 - B_c^{'} ln \left(\frac{V_C}{V_{Cmax}} - 0.999 \right)^2 , \frac{V_C}{V_{Cmax}} \geq 0.5 \tag{4.6}$$

By these modifications the cardiopulmonary equations remain unchanged whereas the gas exchange part reduces into:

Inspiration:

$$\dot{P}_{D_i} = \frac{1}{V_D}\left(\dot{Q}_{ED}\, P_{atm,i} - \dot{Q}_{DC}\, P_{D_i}\right)$$
$$\dot{P}_{C_i} = \frac{1}{V_C}\left(\dot{Q}_{DC}\, P_{D_i} - \dot{Q}_{CA}\, P_{C_i} - P_{C_i}\, \dot{V}_C\right)$$

Expiration:

(4.7)

$$\dot{P}_{D_i} = \frac{1}{V_D}\left(\dot{Q}_{ED}\, P_{D_i} - \dot{Q}_{DC}\, P_{C_i}\right)$$
$$\dot{P}_{C_i} = \frac{1}{V_C}\left(\dot{Q}_{DC}\, P_{C_i} - \dot{Q}_{CA}\, P_{a_i} - P_{C_i} V_C\right)$$

The algebraic relations for cardiovascular and pulmonary systems are also summarized below:

Arterial pulmonary pressure:

$$P_{ap}(t) = \frac{1}{C_{ap}}\left(V_o - C_{as} P_{as}(t) - C_{vs} P_{vs}(t) - C_{vp} P_{vp}(t)\right) \tag{4.8}$$

Pulmonary and systemic flows:

$$F_s(t) = \frac{P_{as}(t) - P_{vs}(t)}{R_s}$$
$$F_p(t) = \frac{P_{ap}(t) - P_{vp}(t)}{R_p} \tag{4.9}$$

Brain blood flow:

$$F_B(t) = F_{B_0}(1 + 0.03(P_{a_{CO_2}}(t) - 40)) \tag{4.10}$$

Cardiac outputs:

$$Q_r(t) = H\frac{c_r P_{vs}(t) f(S_r(t), P_{ap}(t))(1-e^{-\frac{t_d}{R_r c_r}})}{P_{ap}(t)(1-e^{-\frac{t_d}{R_r c_r}}) + f(S_r(t), P_{ap}(t))e^{-\frac{t_d}{R_r c_r}}}$$
$$Q_l(t) = H\frac{c_l P_{vp}(t) f(S_l(t), P_{as}(t))(1-e^{-\frac{t_d}{R_l c_l}})}{P_{as}(t)(1-e^{-\frac{t_d}{R_l c_l}}) + f(S_l(t), P_{as}(t))e^{-\frac{t_d}{R_l c_l}}} \quad (4.11)$$

Dissociation equations relating concentrations with pressures:

$$\begin{aligned} C_{a_{O_2}}(t) &= K_1(1-e^{-K_2 P_{a_{O_2}}(t)})^2 \\ C_{v_{O_2}}(t) &= K_1(1-e^{-K_2 P_{v_{O_2}}(t)})^2 \\ C_{a_{CO_2}}(t) &= K_{CO_2} P_{a_{CO_2}}(t) + k_{CO_2} \\ C_{v_{CO_2}}(t) &= K_{CO_2} P_{v_{CO_2}}(t) + k_{CO_2} \\ C_{B_{CO_2}}(t) &= K_{CO_2} P_{B_{CO_2}}(t) + k_{CO_2} \end{aligned} \quad (4.12)$$

Pleural pressure:

$$P_{pl} = P_{cw} - P_{mus} \quad (4.13)$$

Muscle pressure:

$$P_{mus} = A_{mus} \cdot \sin(2\pi\pi ft) + A_{mus} \quad (4.14)$$

Chest wall elastic recoil:

$$P_{cw} = A_{cw} - B_{cw} \cdot ln\left(\frac{TLC - RV}{V_{cw} - RV} - 0.999\right) \quad (4.15)$$

Collapsible airways elastic recoil:

$$P_c = A_c + B_c\left(\frac{V_C}{V_{Cmax}} - 0.7\right)^2 \qquad , \frac{V_C}{V_{Cmax}} \le 0.5 \tag{4.16}$$

$$P_c = 5.6 - B_c' ln\left(\frac{V_C}{V_{Cmax}} - 0.999\right)^2 \qquad , \frac{V_C}{V_{Cmax}} \ge 0.5 \tag{4.17}$$

Static elastic recoil of lung tissue:

$$P_l = A_l \cdot e^{K_l \cdot V_A} + B_l \tag{4.18}$$

Alveolar pressure:

$$P_A = P_{pl} + P_l + P_{ve} \tag{4.19}$$

Collapsible airways pressure:

$$P_C = P_c + P_{pl} \tag{4.20}$$

Flow from collapsible region to alveoli:

$$\dot{Q}_{CA} = \frac{P_C - P_A}{R_s} \tag{4.21}$$

Flow from dead space to collapsible region:

$$\dot{Q}_{DC} = \frac{P_D - P_C}{R_c} \tag{4.22}$$

Flow from external to dead space:

$$\dot{Q}_{ED} = \dot{Q}_{DC} \tag{4.23}$$

Small airways resistance:

$$R_{sm} = A_s \cdot e^{K_s (VA - RV)/(V^* - RV)} + B_s \tag{4.24}$$

Collapsible (middle airways resistance):

$$R_c = K_3 \left(\frac{V_{C\max}}{V_C} \right) \tag{4.25}$$

Upper airways resistance:

$$R_u = K_1 + K_2 \left| \dot{V}_{cw} \right| \tag{4.26}$$

Rate of change of collapsible airways volume:

$$\dot{V}_C = \dot{Q}_{DC} - \dot{Q}_{CA} \tag{4.27}$$

Rate of change of alveolar volume:

$$\dot{V}_A = \dot{Q}_{CA} \tag{4.28}$$

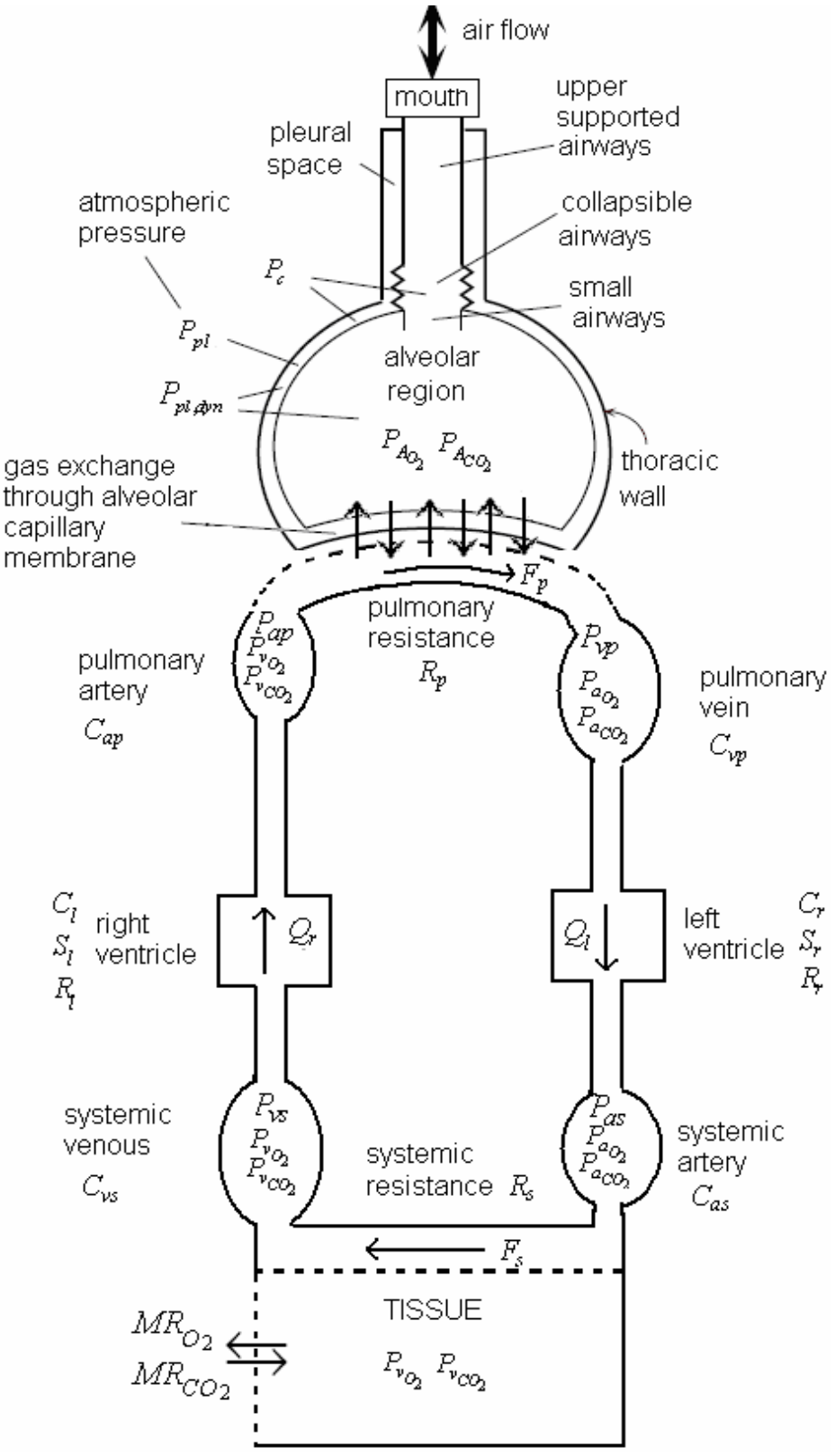

Figure 4.1 Combined Model

4.2. The Combined Model for Exercise

In this section, a physiological overview of exercise is given and the combined model is extended for the case of dynamic exercise. See Figure 4.4 for an illustration of the combined exercise model and Section 4.2.2 for a list of exercise model equations.

The model treats the case of exercise below the anaerobic threshold. In such a case the energy consumed by the muscles is equal to the aerobic energy supply. Initial anaerobic energy sources are also included in the model (See Section 4.2.1.2).

4.2.1. Physiological Overview of Exercise

In this section information on physiology of exercise is given. Firstly information on aerobic and anaerobic exercise is presented. Later the effect of exercise on blood vessels, metabolic rates, alveolar ventilation and heart rate are explained.

4.2.1.1 Aerobic and Anaerobic Exercise

There are three dominant metabolic systems for the case of exercise: (1) the phosphagen system, (2) the glycogen-lactic acid system, and (3) the aerobic system [38]. See Figure 4.2.

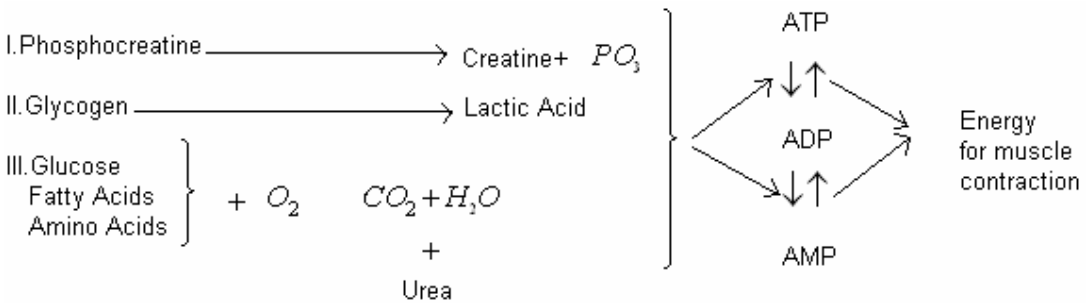

Figure 4.2 Basic Metabolic Systems that Supply Energy for Muscle Contraction [38]

The first mechanism listed in Figure 4.2 uses the cell ATP and phosphocreatine in order to supply maximal muscle power for very short durations about 8-10 seconds. In short, this is the initial anaerobic energy supply system of the muscles.

The glycogen stored in the muscles is used by the second metabolic system: the glycogen-lactic acid system. Breakdown of glycogen into glucose called glycolysis is another anaerobic process during which each glucose molecule is split into two pyruvic acid molecules and four ATP molecules are released. Normally, pruvic acid reacts with oxygen in the mitochondria of muscle cells to continue producing ATP. However, if available oxygen is not enough for the oxidative stage to occur pruvic acid is transformed into lactic acid. Although much of the pruvic acid is transformed into lactic acid, sufficient energy for moderate exercise is produced without the need of oxygen using this mechanism.

The final energy mechanism is the aerobic energy in which glucose, fatty acids and amino acids from nutrition are burned with oxygen to release great amounts of energy. This is an unlimited energy source that continues as long as nutrients last.

When these three systems are compared, the phosphagen system is used for activities in which bursts of power is needed for short durations whereas aerobic system is for prolonged activity. Glycogen-lactic acid system lies between these two extremes and is used during moderate exercise.

4.2.1.2 The Metabolic Rates during Exercise

A metabolic rate for the brain is not involved in the model. This is a valid approach since previous studies [54] showed that no significant changes in the metabolic rates are observed for the brain over a wide range of conditions including exercise. So brain metabolism $MR_{B_{CO_2}}$, is assumed to be constant during exercise.

However for tissue compartment, the O_2 consumption and CO_2 production both increase in the muscles that work during exercise. This was shown with the relations below in Section 2.2.1.2:

$$\begin{aligned} V_{T_{O_2}} \dot{C}_{v_{O_2}}(t) &= -MR_{O_2} + F_s(t)(C_{a_{O_2}}(t) - C_{v_{O_2}}(t)) \\ V_{T_{CO_2}} \dot{C}_{v_{CO_2}}(t) &= MR_{CO_2} + F_s(t)(C_{a_{CO_2}}(t) - C_{v_{CO_2}}(t)) \end{aligned} \tag{4.29}$$

At the very first moments of exercise, the oxygen supplied by the blood flow to the working muscles is not sufficient to comply with the energy demand. Because of this, the initial energy need is supplied anaerobically. (See section 4.2.1.1 for details of anaerobic exercise.) This means that the energy demand for exercise, namely $MR^e_{O_2}$, has both aerobic and anaerobic terms:

$$MR^e_{O_2} = MR_{O_2}(t) + M_{sp}(t), \tag{4.30}$$

where, MR_{O2} is the aerobic term and M_{sp} is the anaerobic term. Below the anaerobic threshold, the aerobic term increases exponentially whereas the anaerobic term decreases exponentially. The initial energy supply can be incorporated into the equations by assuming that the metabolic rate for oxygen rises exponentially from a constant, initial rest value $MR^r_{O_2}$ to its new value at exercise $MR^e_{O_2}$:

$$MR_{O_2}(t) = MR^r_{O_2} + (MR^e_{O_2} - MR^r_{O_2})(1 - e^{-t/\tau a}) \quad (4.31)$$

τ_a is the time constant and it is chosen as τ_a=0.5 [27]. One can conclude that after $4\tau_a$ the exponential term will decay and the metabolic rate for oxygen will reach its exercise value.

The increase in metabolic rate is assumed to be proportional to workload [27], [18]).

$$MR^e_{O_2} = MR^r_{O_2} + \rho W, \quad (4.32)$$

where ρ depends on the physical condition of the person and W is the workload applied.

Metabolic rate for carbon dioxide is taken to be proportional to oxygen metabolic rate and they are related with the respiratory quotient, RQ

$$MR_{CO_2}(t) = RQ \cdot MR_{O_2}(t). \quad (4.33)$$

4.2.1.3 Vessel Resistance during Exercise

Sympathetic neural outflow increases during exercise. This has several consequences like increase in heart rate, increase in contractility and vasoconstriction of peripheral vascular system which in the end causes an increase in arterial blood pressure. This effect can be seen from Figure 4.3.

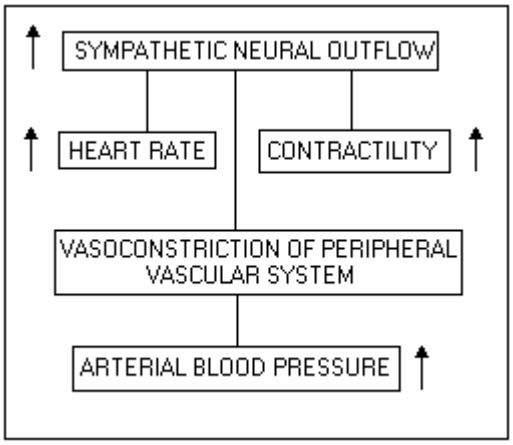

Figure 4.3 Effects of Increased Sympathetic Neural Outflow

Metabolic autoregulation (vasodilatation) counteracts sympathetic neural activity in order to compensate the increasing needs of tissue during exercise. So it can be said that metabolic autoregulation should also be accounted when modeling exercise.

In the cardiopulmonary model, systemic and pulmonary resistances (R_s, R_p) are modeled individually. Pulmonary resistance decreases during exercise [55], [56]. This effect is simply modeled as exponential decrease from a rest value to an exercise value both of which were determined by parameter identification technique in [16]. This can be expressed mathematically as

$$R_p(t) = R_p^r + (R_p^e - R_p^r)(1 - e^{-t/\tau_p}) \tag{4.34}$$

where R_p^r stands for the rest value, R_p^e stands for the exercise value and τ_p is the time constant of pulmonary resistance.

Systemic resistance decreases during exercise to supply the tissue with more blood flow. The decrease in systemic flow is mainly related with the decrease in oxygen concentration. This relation is modeled as

$$R_s(t) = A_{pesk} C_{v_{O_2}}(t) \tag{4.35}$$

which is a relation introduced by [57]. Different values for rest and exercise are chosen for the value of A_{pesk} for better match with experiment data [27] and it is formulated as,

$$A_{pesk}(t) = A^r_{pesk} + (A^e_{pesk} - A^r_{pesk})(1 - e^{-t/\tau_s}), \tag{4.36}$$

where A^r_{pesk} stands for the rest value, A^e_{pesk} stands for the exercise value and τ_s is the time constant of A_{pesk}.

4.2.1.4 Heart Rate during Exercise

The effects of exercise on cardiovascular system are mainly increase in muscle blood flow, muscle work output, cardiac output and oxygen consumption. During exercise, muscle work output increases the need for oxygen tremendously. This dictates an increase the oxygen consumption; in turn the blood vessels are dilated. Blood flow increases due to dilatation and also due to the increased arterial pressure. Consequently the venous return is increased, too. This causes the cardiac output to follow this increase. The increase in cardiac output is due to two factors: heart rate and stroke volume. Among these two the main effect is due to the increased heart rate. Because when stroke volume reaches its maximum, the cardiac output reaches only half of its maximum value. So any further increase should be mainly due to increased heart rate.

Same assumptions as [16] are made for modeling the dynamic behavior of the heart rate. The controllers determining the heart rate are assumed to be lumped into one controller. The variation of the heart rate is regarded as an output of this lumped controller,

$$\dot{H} = u_1(t) \tag{4.37}$$

Mean blood pressure and blood gas concentrations are chosen as the input of the controller.

4.2.1.5 Alveolar Ventilation during Exercise

Although oxygen is utilized and carbon dioxide is produced in great amounts during exercise the concentrations of these gases in blood do not decrease/increase far

below/above normal. This demonstrates the ability of the respiratory system to regulate (increase) ventilatory rate in order to maintain adequate oxygenation.

The increase in ventilation is thought to be caused by two neurogenic factors. One of them is the brains' intrinsic mechanism that transmits signals to the brain stem as it sends impulses to the contracting muscles. The second is the body movements. During exercise, arms and legs move and they stimulate joint and muscle proprioceptors that then transmit excitatory signals the respiratory center.

Concerning the above regulative effects of respiratory center, variation in ventilation rate is also considered as an output of the controller.

$$\ddot{V}_{Av}(t) = u_2(t) \tag{4.38}$$

($\ddot{V}_{Av}$ denotes the second derivative of alveolar ventilation.)

4.2.2. The Model Equations for Exercise

Gathering all the information given in previous sections, the set of model equations are modified for the case of exercise condition (Equation (4.39)). See Figure 4.4 for an illustration of the combined exercise model.

Like Equation (4.1), Equation (4.39) can also be thought to be divided into two parts; the equations describing the cardiopulmonary behavior and a second set that explains the airway mechanics and gas transport equations for inspiration and expiration.

$$
\begin{aligned}
&C_{as}\,\dot{P}_{as}(t) = Q_l(t) - F_s(t)\\
&C_{vs}\,\dot{P}_{vs}(t) = F_s(t) - Q_r(t)\\
&C_{vp}\,\dot{P}_{vp}(t) = F_p(t) - Q_l(t)\\
&V_{A_{O_2}}\,\dot{P}_{a_{O_2}}(t) = 863F_p(t)(C_{v_{O_2}}(t) - C_{a_{O_2}}(t)) + \dot{V}_{Av}(P_{I_{O_2}} - P_{a_{O_2}}(t))\\
&V_{A_{CO_2}}\,\dot{P}_{a_{CO_2}}(t) = 863F_p(t)(C_{v_{CO_2}}(t) - C_{a_{CO_2}}(t)) + \dot{V}_{Av}(P_{I_{CO_2}} - P_{a_{CO_2}}(t))\\
&V_{B_{CO_2}}\,\dot{C}_{B_{CO_2}}(t) = MR_{B_{CO_2}} + F_B(t)(C_{a_{CO_2}}(t) - C_{vB_{CO_2}}(t))\\
&V_{T_{O_2}}\,\dot{C}_{v_{O_2}}(t) = -MR_{O_2} + F_s(t)(C_{a_{O_2}}(t) - C_{v_{O_2}}(t))\\
&V_{T_{CO_2}}\,\dot{C}_{v_{CO_2}}(t) = MR_{CO_2} + F_s(t)(C_{aCO_2}(t) - C_{vCO_2}(t))\\
&\dot{S}_l(t) = \sigma_l(t)\\
&\dot{S}_r(t) = \sigma_r(t)\\
&\dot{\sigma}_l(t) = -\gamma_l\sigma_l(t) - \alpha_l S_l(t) + \beta_l H\\
&\dot{\sigma}_r(t) = -\gamma_r\sigma_r(t) - \alpha_r S_r(t) + \beta_r H\\
&\dot{H} = u_1(t)\\
&\ddot{V}_{Av} = u_2(t)
\end{aligned}
\tag{4.39}
$$

(Equation (4.39) is continued…)

Inspiration:

$$\dot{P}_{D_{CO_2}} = \frac{1}{V_D}\left(\dot{Q}_{ED}\,P_{atm,CO_2} - \dot{Q}_{DC}\,P_{D_{CO_2}}\right)$$
$$\dot{P}_{C_{CO_2}} = \frac{1}{V_C}\left(\dot{Q}_{DC}\,P_{D_{CO_2}} - \dot{Q}_{CA}\,P_{C_{CO_2}} - P_{C_{CO_2}}\,\dot{V}_C\right)$$
$$\dot{P}_{D_{O_2}} = \frac{1}{V_D}\left(\dot{Q}_{ED}\,P_{atm,O_2} - \dot{Q}_{DC}\,P_{D_{O_2}}\right)$$
$$\dot{P}_{C_{O_2}} = \frac{1}{V_C}\left(\dot{Q}_{DC}\,P_{D_{O_2}} - \dot{Q}_{CA}\,P_{C_{O_2}} - P_{C_{O_2}}\,\dot{V}_C\right)$$

Expiration:

$$\dot{P}_{D_{CO_2}} = \frac{1}{V_D}\left(\dot{Q}_{ED}\,P_{D_{CO_2}} - \dot{Q}_{DC}\,P_{C_{CO_2}}\right)$$
$$\dot{P}_{C_{CO_2}} = \frac{1}{V_C}\left(\dot{Q}_{DC}\,P_{C_{CO_2}} - \dot{Q}_{CA}\,P_{a_{CO_2}} - P_{C_{CO_2}}\,\dot{V}_C\right)$$
$$\dot{P}_{D_{O_2}} = \frac{1}{V_D}\left(\dot{Q}_{ED}\,P_{D_{O_2}} - \dot{Q}_{DC}\,P_{C_{O_2}}\right)$$
$$\dot{P}_{C_{O_2}} = \frac{1}{V_C}\left(\dot{Q}_{DC}\,P_{C_{O_2}} - \dot{Q}_{CA}\,P_{a_{O_2}} - P_{C_{O_2}}\,\dot{V}_C\right)$$

The following relations regarding exercise accompany Equation (4.39).

O_2 Consumption Rate:

$$MR_{O_2}(t) = MR^r_{O_2} + (MR^e_{O_2} - MR^r_{O_2})(1 - e^{-t/\tau a}) \tag{4.40}$$

Steady State metabolic CO_2 production rate during exercise:

$$MR^e_{O_2} = MR^r_{O_2} + \rho W \tag{4.41}$$

CO_2 Production rate:

$$MR_{CO_2}(t) = RQ \cdot MR_{O_2}(t) \tag{4.42}$$

Resistance in the peripheral region of the pulmonary circuit:

$$R_p(t) = R_p^r + (R_p^e - R_p^r)(1 - e^{-t/\tau_p}) \tag{4.43}$$

Peripheral resistance in systemic circuit:

$$R_s(t) = A_{pesk} C_{v_{O_2}}(t) \tag{4.44}$$

Constant relating systemic resistance to venous O_2 Concentration:

$$A_{pesk}(t) = A_{pesk}^r + (A_{pesk}^e - A_{pesk}^r)(1 - e^{-t/\tau_s}) \tag{4.45}$$

Output of Controllers:

$$\dot{H} = u_1(t) \tag{4.46}$$

$$\ddot{V}_{Av} = u_2(t) \tag{4.47}$$

All other algebraic relations follow directly from Section 4.1.1.

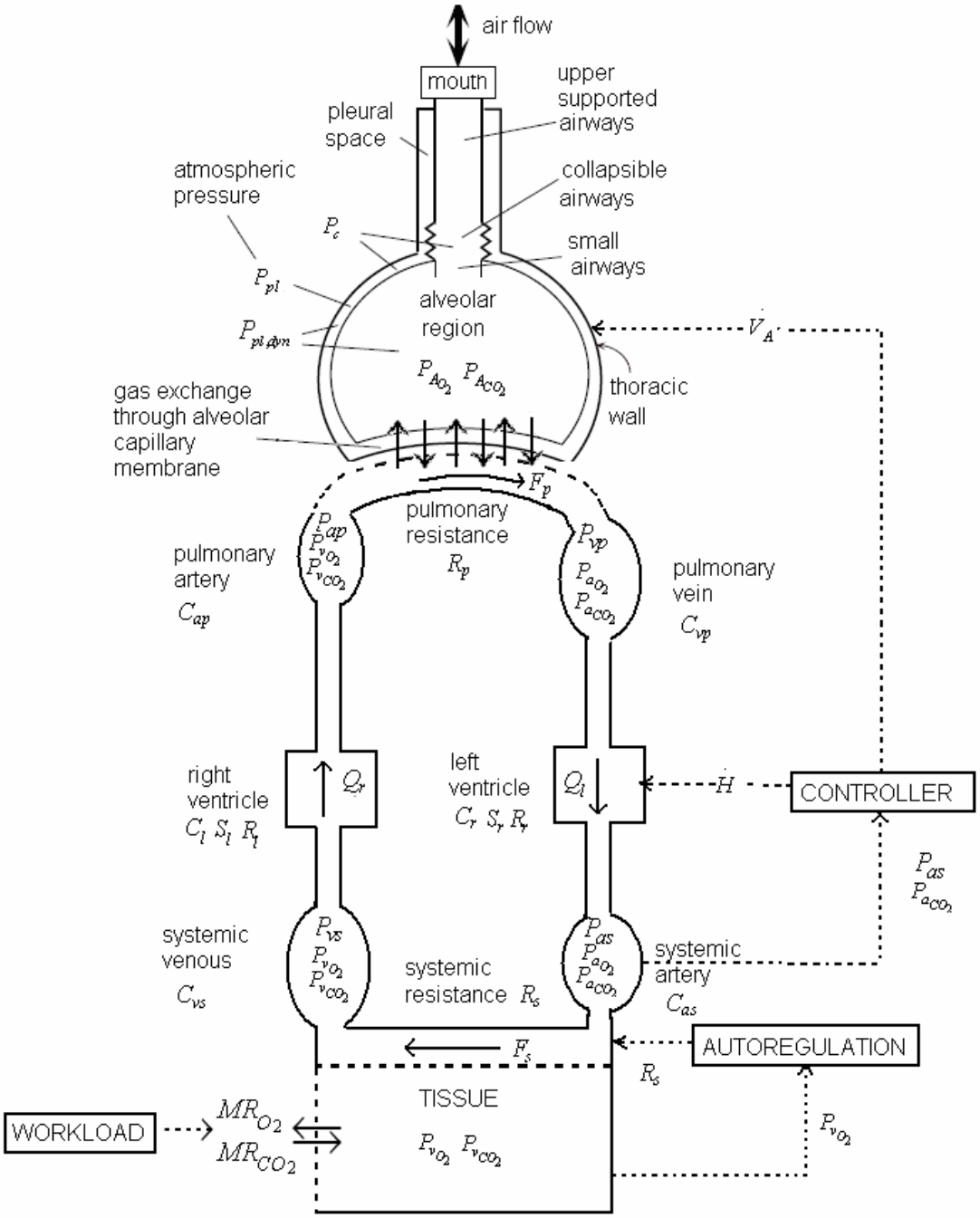

Figure 4.4 Combined Model for Exercise

CHAPTER 5

STATEMENT OF SOLUTION FOR THE EXERCISE MODEL

In this chapter, the steps to solve the mathematical equations describing the combined exercise model are explained. A linear state feedback is implemented for the equations describing the cardiopulmonary behavior and differential equations describing the airway mechanics and gas transport are integrated with this feedback applied cardiopulmonary equations.

5.1. Determination of a Steady State

To solve the set of differential equations described in Equation (4.39) a steady state should be determined first. During steady state, by definition, variations in time vanish. This transforms the set of cardiopulmonary differential equations (first part in Equation (4.39)) into an algebraic set of equations as shown in Equation (5.1).

$$
\begin{aligned}
0 &= Q_l(t) - F_s(t) \\
0 &= F_s(t) - Q_r(t) \\
0 &= F_p(t) - Q_l(t) \\
0 &= 863F_p(t)(C_{v_{O_2}}(t) - C_{a_{O_2}}(t)) + \dot{V}_{Av}(P_{I_{O_2}} - P_{A_{O_2}}(t)) \\
0 &= 863F_p(t)(C_{v_{CO_2}}(t) - C_{a_{CO_2}}(t)) + \dot{V}_{Av}(P_{I_{CO_2}} - P_{A_{CO_2}}(t)) \\
0 &= MR_{B_{CO_2}} + F_B(t)(C_{a_{CO_2}}(t) - C_{vB_{CO_2}}(t)) \\
0 &= -MR_{O_2} + F_s(t)(C_{a_{O_2}}(t) - C_{v_{O_2}}(t))
\end{aligned}
\tag{5.1}
$$

(Equation 5.1 continued…)

$$
\begin{aligned}
0 &= MR_{CO_2} + F_s(t)(C_{aCO_2}(t) - C_{vCO_2}(t)) \\
0 &= \sigma_l(t) \\
0 &= \sigma_r(t) \\
0 &= -\gamma_l\sigma_l(t) - \alpha_l S_l(t) + \beta_l H \\
0 &= -\gamma_r\sigma_r(t) - \alpha_r S_r(t) + \beta_r H \\
0 &= u_1(t) \\
0 &= u_2(t)
\end{aligned}
$$

However, equations for inspiration and expiration in Equation (4.39) give no information about airway mechanics and gas transport variables since both sides of the differential equations go to zero during the steady state. So, for these variables, the steady state values are determined from literature (See Appendix C and Figure 6.8 for the values used). There will be no feedback control on airway mechanics and gas transport variables so steady state values need not be separately determined for rest and exercise.

Let us consider the alveolar gas partial pressure equations given in Equation (4.1) at steady state. The equations are rewritten as:

inspiration:

$$
\begin{aligned}
\dot{P}_{A_{O_2}} &= \frac{1}{V_A}\left\{\dot{Q}_{CA}\,P_{C_{O_2}} - P_{A_{O_2}}\,\dot{V}_C - D_{L_{O_2}}\left(P_{A_{O_2}} - P_{b_{O_2}}\right)\right\} \\
\dot{P}_{A_{CO_2}} &= \frac{1}{V_A}\left\{\dot{Q}_{CA}\,P_{C_{CO_2}} - P_{A_{CO_2}}\,\dot{V}_C - D_{L_{CO_2}}\left(P_{A_{CO_2}} - P_{b_{CO_2}}\right)\right\}
\end{aligned}
\tag{5.2}
$$

expiration:

$$
\begin{aligned}
\dot{P}_{A_{O_2}} &= \frac{1}{V_A}\left\{\dot{Q}_{CA}\,P_{A_{O_2}} - P_{A_{O_2}}\,\dot{V}_A - D_{L_{O_2}}\left(P_{A_{O_2}} - P_{b_{O_2}}\right)\right\} \\
\dot{P}_{A_{CO_2}} &= \frac{1}{V_A}\left\{\dot{Q}_{CA}\,P_{A_{CO_2}} - P_{A_{CO_2}}\,\dot{V}_A - D_{L_{CO_2}}\left(P_{A_{CO_2}} - P_{b_{CO_2}}\right)\right\}
\end{aligned}
\tag{5.3}
$$

These were the equations that were omitted by the assumption of the diffusion process at the alveolar capillary membrane is rapid. At steady state these equations reduce to:

inspiration & expiration:

$$\begin{aligned} 0 &= \left(P_{A_{O_2}} - P_{b_{O_2}} \right) \\ 0 &= \left(P_{A_{CO_2}} - P_{b_{CO_2}} \right) \end{aligned} \tag{5.4}$$

Here, P_{b_i} is the arterial blood gas concentration. So it can be concluded that at steady state the gas exchange equations omitted for integration purposes are also in accordance with the assumption of rapid diffusion in this thesis at steady state.

From Equation (5.1) one can determine the steady state values for variables $P_{as}, P_{vs}, P_{vp}, P_{a_{O_2}}, P_{a_{O_2}}, C_{B_{CO_2}}, C_{v_{CO_2}}, C_{v_{O_2}}, S_l, S_r, H, \dot{V}_{av}$. Last two equations in (5.1) are related to control and they give no information. So, more equations and assumptions are needed to solve this set.

It has been observed in many experiments that the increase in heart rate during exercise is proportional to the increase in oxygen demand. (see [55]). So there is a linear relationship between steady state value of the heart rate and oxygen consumption.[27]

$$H = aMR_{O_2} + b \tag{5.5}$$

The constants “a” and “b” in Equation (5.5) are determined by a mathematical method called parameter identification as “35” and “66” respectively ($H = 35MR_{O_2} + 66$). They have been used in [27] as presented by [18]. This assumption is repeated in this thesis.

There is also a fact that arterial carbon dioxide pressure is kept close to 40 mmHg by respiratory control [27]. The second equation follows from this fact as,

$$P_{a_{CO_2}} = 40mmHg. \tag{5.6}$$

Before moving further in calculating steady states, relations for R_p and A_{pesk} should be determined.

R_p is assumed to have a linear relationship with workload as described in Equation (5.7). The constants in this equation are chosen to match with the values of pulmonary resistance at rest and exercise which were determined in [18] by parameter identification [27].

$$Rp = 1.965 - 0.020901W. \tag{5.7}$$

A_{pesk} also has a linear relationship with workload as described in Equation. The constants in this equation are chosen in [27] to match mean arterial pressure values with the measurements in [18].

$$A_{pesk} = 177.3 + 1.17W \tag{5.8}$$

In order to determine a solution for the algebraic equation set introduced in Equation (5.1), firstly the workload to be applied to the patient is chosen. Values of A_{pesk} and R_p directly follow from Equations (5.7) and (5.8). Equations (4.41) and (4.42) can be used to determine values of MR_{O_2} and MR_{CO_2} . $MR^r_{O_2}$ is taken as 0.350 from [27]. Heart rate and arterial carbon dioxide pressure can be derived from Equations (5.5) and (5.6) respectively. The steady state system presented in Equation (5.1) can now be solved using the parameter set given in Figure 6.4 and Figure 6.5. Descriptions of the abbreviations in the figures are given Table 6-3 and Table 6-4. Calculated steady state values are presented in Figure 6.13 and abbreviation in the figure are given in Table 6-10.

5.2. The Control Problem

In this section the control problem is written for the cardiopulmonary model. Firstly the notation used is introduced. Then the assumptions made are explained and the control problem for the case of exercise is presented.

5.2.1. Notation

The cardiopulmonary part of the equation set (4.39) describing the combined exercise model can be rewritten in a more compact fashion as follows.
Let $x'(t)$ be the state vector at time t where

$$x'(t) = (P_{as}, P_{vs}, P_{vp}, P_{a_{CO_2}}, P_{a_{O_2}}, C_{B_{CO_2}}, C_{v_{CO_2}}, C_{v_{O_2}}, S_l, S_r, \sigma_l, \sigma_r, H, \dot{V}_{Av})^T. \quad (5.9)$$

In the right hand side of Equation (5.9) time dependency is suppressed to save place. Making another simplification, the state vector can be written as

$$\dot{x}' = (\dot{x}_1', \dot{x}_2', ... \dot{x}_{14}')^T. \quad (5.10)$$

Similarly a control vector is introduced as

$$u(t) = (u_1, u_2)^T = (\dot{H}, \ddot{V}_{Av}). \quad (5.11)$$

Right hand side of Equation is expressed as $f(x;W)$ with the last two equations that represent control replaced with zeros where W is the applied workload.

Using the above representations in the equation sets yields:

$$\dot{x}'(t) = f(x'(t);W) + Bu(t), \tag{5.12}$$

where,

$$B = \begin{pmatrix} 0.....010 \\ 0.....001 \end{pmatrix}^T. \tag{5.13}$$

5.2.2. Predefined Operating Point for the Baroreflex Assumption

In the cardiopulmonary model of Timischl [27], it is assumed that the baroreflex is reset during exercise. This assumption follows from the hypothesis of Rowel [58] p465. At the beginning of the exercise, cerebral cortex sends a command to reset the arterial baroreflex to a higher operating pressure. This is sensed by the central nervous system and in order to correct the arterial pressure error the sympathetic activity is increased. This increase raises the cardiac output and therefore reduces the "perceived" arterial pressure error. This way, cardiovascular regulation operates as a combined feed forward and feedback control; the resetting of the operating point standing for the feed forward control and the baroreceptor reflex standing for feedback control.

This assumption of pre-defined point for baroreflex is repeated in this thesis. The computed steady state values (see Section 5.1) are used as operating points.

5.2.3. Optimal Behavior Assumption

Evolution in biological systems is based on optimization. The systems are optimized to fit the changing needs of the environment in such a way that the organism would survive. One of the basic rules of survival is to minimize energy expenditure. Optimization hypothesis can be extended to other quantities like minimization of stress on the organs, or keeping it within tolerable bounds and etc.

In order to employ optimization to the case of exercise one should think of the controlled variables. During exercise, respiratory and cardiovascular regulation work to keep arterial pressure and extracellular CO_2 pressure within certain bounds while maintaining heart rate and alveolar ventilation not to change too fast.

5.2.4. Control Problem for the Case of Exercise

All the requirements listed above in Chapter 5 can be formulated using the new notation introduced in Section 5.2 into a control problem as:

Control Problem for the Case of Exercise:

Find control functions $u_1(t)$ and $u_2(t)$ such that the quadratic cost functional

$$\int_0^{\infty} \left(q_{as}(P_{as}(t) - P_{as}^e(t))^2 + q_c(P_{a_{CO_2}}(t) - P_{a_{CO_2}}^e(t))^2 + q_1 u_1(t)^2 + q_2 u_2(t)^2 \right) dt \qquad (5.14)$$

is minimized subject to the state equations

$$\dot{x}(t) = f(x(t); W^e) + Bu(t), \qquad x(0) = x^r \qquad (5.15)$$

where, q_{as}, q_c, q_1 and q_2 are constants determining the relative importance of each integrand in the quadratic cost functional. $P_{as}^e(t)$ and $P_{a_{CO_2}}^e(t)$ represent the values of

arterial systemic and arterial CO_2 partial pressures at the exercise steady state. Also, W^e is the workload applied for the case of exercise. Squares of the components in the integrand are taken in order to account for both positive and negative deviations.

5.3. Control Theory

In this section, the theorems needed for the implementation of a linear feedback for the nonlinear control problem introduced in Section 5.2 are given. These theorems are taken from [27]. For detailed information on control theory and derivations one can refer to [27] Chapter 7, [59] and [60].

5.3.1. Linear State Feedback Control

In feedback control systems, the inputs are compared to the outputs and the error term is used to make the correction between the actual and desired operation. By applying feedback one can stabilize an otherwise unstable system or improve its stability.

Consider a linear system containing a control function *u(t)*:

$$\dot{x}(t) = Ax(t) + Bu(t). \tag{5.16}$$

Here t denotes the time variable. *x(t)* is a real, time varying, n-dimensional column vector called the state or the response of the system. $A \in M_n(R)$ ($M_n(R)$ is used to represent the vector space of nxn matrices with real entries). $B \in M_{n,k}(R)$.($M_{n,k}(R)$ is used to represent the vector space of nxk matrices with real entries). *u(t)* is real, k dimensional and assumed to be piecewise continuous. If it is assumed that the state *x(t)* can be measured at all times and available for feedback, then it is possible to implement a linear control law of the form:

$$u(t) = -F(t)x(t), \tag{5.17}$$

where *F(t)* is called the feedback gain matrix. If a constant matrix *F* is used as the feedback gain matrix then the stability of the system is determined by the eigenvalues of *A-BF*. It is possible to stabilize a completely controllable system by state feedback, or to improve its stability by assigning the closed loop poles to locations in the left-half complex plane. If the system is stabilizable but not completely controllable, not all but at least the unstable poles of the system can be moved to arbitrary locations by choosing *F* suitably [27]. The location of the poles in the left half complex plane can be determined by optimal linear regulator theory described below.

Consider a linear time varying system

$$\dot{x}(t) = A(t)x(t) + B(t)u(t), \tag{5.18}$$

with initial condition

$$x(t_0) = x_0, \tag{5.19}$$

and controlled variable $z \in R^s$

$$z(t) = D(t)x(t). \tag{5.20}$$

Here, the matrix *A(t)* is continuous and the matrices *B(t)* and *D(t)* are piecewise continuous functions and that all matrices are bounded. The deterministic linear optimal regulator problem asks for an input *u(t)*, $t_0 \le t \le t_1$ such that the criterion

$$\left(\int_{t_0}^{t_1} \left(z^T(t) R_3(t) z(t) + u^T(t) R_2(t) u(t) \right) dt \right) + x^T(t_1) P_1 x(t_1) \tag{5.21}$$

is minimal. P_1 is a nonnegative-definite symmetric matrix and $R_2(t)$ and $R_3(t)$ are positive definite symmetric matrices. $z^T(t)R_3(t)z(t)$ in this criterion, is added to reduce the controlled variable as quickly as possible to zero during interval $[t_0,t_1]$. $u^T(t)R_2(t)u(t)$ term is added to prevent large input amplitudes and the term

$x^T(t_1)P_1x(t_1)$ is added to keep the terminal state as close as possible to the zero state. Such an input can be determined using the Theorem 5.1 below:

Theorem 5.1: *Consider the deterministic linear optimal regulator problem. Then the optimal input u(t) can be generated through a linear control law of the form*

$$u(t) = -F(t)x(t) \tag{5.22}$$

where,

$$F(t) = R_2^{-1}(t)B^T(t)P(t). \tag{5.23}$$

The matrix P(t) is symmetric and nonnegative-definite and satisfies the matrix Riccati equation

$$-\dot{P}(t) = D^T(t)R_3(t)D(t) - P(t)B(t)R_2^{-1}(t)B^T(t)P(t) + P(t)A(t) + A^T(t)P(t), \tag{5.24}$$

with terminal condition

$$P(t_1) = P_1. \tag{5.25}$$

The minimal value of the cost criterion is equal to $x_0^T P(t_0)x_0$.

The above theorem dictates that the control law (5.22) generates the optimal input for any initial state. It means that the deterministic optimal regulator problem always has a unique solution. Theorem 5.1 is rewritten for the time invariant systems in Theorem 5.2

Theorem 5.2: *Consider the time invariant system*

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t), \\ z(t) &= Dx(t), \end{aligned} \tag{5.26}$$

and the criterion

$$\left(\int_{t_0}^{t_1} \left(z^T(t) R_3 z(t) + u^T(t) R_2 u(t) \right) dt \right) + x^T(t_1) P_1 x(t_1) \tag{5.27}$$

The matrices A, B, D, $R_3 > 0$, $R_2 > 0$, and $P_1 \geq 0$ are constant and R_3, R_2, and P_1 are symmetric. The associated Riccati equation is

$$-\dot{P}(t) = D^T R_3 D - P(t) B R_2^{-1} B^T P(t) + P(t) A + A^T P(t), \tag{5.28}$$

with terminal condition

$$P(t_1) = P_1. \tag{5.29}$$

Assume that the system (5.26) *is stabilizable and detectable. Then the following is true.*

1) The solution of the Riccati equation (5.28) *approaches the unique value* $\bar{P}$ *as* $t_1 \to \infty$ *which is independent of* P_1.

2) $\bar{P}$ *is the unique non-negative-definite symmetric solution of the algebraic Riccati equation*

$$0 = D^T R_3 D - P B R_2^{-1} B^T P + P A + A^T P \tag{5.30}$$

3) The steady state control law

$$u(t) = -Fx(t), \tag{5.31}$$

with

$$F = R_2^{-1} B^T \overline{P} \qquad (5.32)$$

minimizes

$$\int_0^\infty (z^T(t) R_3(t) z(t) + u^T(t) R_2(t) u(t)) dt + x^T(t_1) P_1 x(t_1) \qquad (5.33)$$

for all $P_1 \geq 0$. *For the optimal input the criterion takes the value* $x^T(0)\overline{P}x(0)$.

4) The steady state control law (5.31) asymptotically stabilizes the control system (5.26).

5.3.2. Nonlinear Systems

In real life the systems are never linear. However it is difficult to handle nonlinear systems. So they are usually linearized. In the following theorems the stability properties of a nonlinear and its linearized form are compared for time invariant systems.

Theorem 5.3: *Consider the nonlinear time-invariant system*

$$\dot{x} = f(x(t)) \qquad (5.34)$$

Suppose that the system has an equilibrium x^e *and that f is at least twice continuously differentiable with respect to x in* x^e. *Consider furthermore the linearized system around* x^e,

$$\dot{x} = Ax, \qquad (5.35)$$

where A denotes the Jacobian of f at x^e. *Then if A is asymptotically stable,the equilibrium* x^e *is locally asymptotically stable for the nonlinear system.*

If an initially unstable nonlinear system is linearized to find a controller which makes the linearized system stable, Theorem 5.5 explains that the nonlinear system with this controller will at least be asymptotically stable for small deviations from the equilibrium state.

Theorem 5.4: *Consider the linearized system*

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t), \\ z(t) &= Dx(t), \end{aligned} \tag{5.36}$$

where A and B denote the Jacobians of f(x,u) with respect to x and u at $(x^e,u^e)=(0,0)$. *Let the linearized system be stabilizable and observable. Then there is a neighborhood N of* $x^e=0$ *such that the following holds.*

1) There exists a unique feedback law u=-K(x) which solves the nonlinear control problem for $x \in N$.

2) If $x(0) \in N$ *then the solution of the closed loop system* $\dot{x} = f(x,-K(x))$ *always remains in N and has the property*

$$\lim_{x\to\infty} x(t) = 0. \tag{5.37}$$

In other words, the equilibrium $x^e = 0$ *is locally asymptotically stable for the nonlinear closed-loop system.*

3) Write K(x) as

$$K(x) = \hat{K}x + k(x), \tag{5.38}$$

where $\hat{K}$ *is the Jacobian of K(x) at* $x^e=0$ *and* $k(x) = o(\|x\|),\ x \to 0$. *(o(.) denotes the Landau symbol* $(f(x)=o(g(x)): \Leftrightarrow \|f(x)\|/\|g(x)\| \to 0 \text{ as } x \to \infty.)$ *Then A-B* $\hat{K}$ *is a stable matrix and* $\hat{K}$ *is the optimal feedback matrix for the linear control problem*

$$\dot{x}(t) = Ax(t) + Bu(t), \tag{5.39}$$

with cost functional

$$\int_0^\infty (Dx(t))^T R_3 Dx(t) + u^T(t) R_2 u(t)) dt. \tag{5.40}$$

4) If $x(0) \in N$ *then the solution of the closed loop system* $\dot{x} = f(x, -\hat{K}x)$ *always remains in N and has the property*

$$\lim_{x \to \infty} x(t) = 0. \tag{5.41}$$

In other words, for $x(0) \in N$ *also the feedback law* $u = -\hat{K}x$ *stabilizes the nonlinear system.*

So it can be concluded that the optimal control for the linearized control problem is suboptimal control for the nonlinear control problem.

5.4. Linear Feedback for the Nonlinear System

A linear feedback is implemented for the nonlinear system (5.15) to obtain a solution in a suboptimal way as described in Section 5.3.2.

Firstly the nonlinear system has to be linearized. The nonlinear system is

$$\dot{x}(t) = f(x(t); W^e) + Bu(t), \; x(0) = x_r. \tag{5.42}$$

The controlled variables can be written in the form:

$$y(t) = Dx(t) = (P_{as}(t), P_{a_{CO_2}}(t))^T, \tag{5.43}$$

where, $D \in M_{2,14}(\mathbb{R})$ is given by

$$D = \begin{pmatrix} 1000.....0 \\ 0001.....0 \end{pmatrix}. \tag{5.44}$$

In order to linearize the system, two new variables which are the shifted versions of *x(t)* and *y(t)* in the origin of the state space, namely ξ and η are introduced.

$$\begin{aligned} \xi(t) &= x(t) - x^e, \\ \eta(t) &= y(t) - y^e. \end{aligned} \tag{5.45}$$

If Equation (5.42) is rewritten with x expressed in terms of ξ and a Taylor series expansion around x^e is made

$$\dot{x} = \dot{\xi} = f(x^e + \xi; W^e) + Bu = A\xi + Bu + o(\xi). \tag{5.46}$$

Here o(.) denotes the Landau symbol (f(x)=o(g(x)): $\Leftrightarrow \|f(x)\|/\|g(x)\| \to 0$ as $x \to \infty$)

The matrix $A \in M_{14,14}(R)$ is the Jacobian of *f(x,W)* evaluated at exercise condition

$$A = \frac{\partial f(x^e; W^e)}{\partial x}. \tag{5.47}$$

Similarly,

$$\eta(t) = (P_{as} - P_{as}^e, P_{a_{CO_2}} - P_{a_{CO_2}}^e)^T = D\xi(t). \tag{5.48}$$

By neglecting terms of order o(ξ), linear approximations of ξ_l and η_l for ξ and η can be written as

$$\begin{aligned} &\dot{\xi}_l(t) = A\xi_l + Bu(t), \quad \xi_l(0) = x^r - x^e, \\ &\eta_l(t) = D\xi_l. \end{aligned} \tag{5.49}$$

Secondly, the linear quadratic cost functional for the linearized system in Equation (5.49) can be written as

$$\int_0^\infty (\eta_l^T(t) R_3(t) \eta_l(t) + u^T(t) R_2(t) u(t)) dt, \tag{5.50}$$

where, $R_3 = \begin{pmatrix} q_{as} & 0 \\ 0 & q_c \end{pmatrix}$ and $R_2 = \begin{pmatrix} q_1 & 0 \\ 0 & q_2 \end{pmatrix}$.

Due to the Theorem 5.2 the desired control is given by,

$$u_l(t) = -F\xi_l(t), \qquad F = -R_2^{-1} B^T E, \tag{5.51}$$

where, E is the unique positive definite symmetric solution algebraic Riccati-equation ,

$$EA + A^T E - EBR_2^{-1} B^T E + D^T R_3 D = 0. \tag{5.52}$$

When the linear feedback law is inserted into the nonlinear system described in Equation (5.42) then a suboptimal feedback that transfers the system from resting conditions to exercise conditions will be implemented as described in Theorem 5.5.

5.5. Solution of Combined Exercise Model Equations

The above derived solution for the cardiopulmonary model (the linear feedback law inserted nonlinear system equations) is combined with equations of airway mechanics and gas transport for inspiration and expiration. The new differential equation set is solved together to yield a solution for the combined model of exercise using the relations derived in Chapter 4 for the combined exercise model.

CHAPTER 6

GRAPHICAL USER INTERFACE

The combined exercise model described in Chapter 4 and Chapter 5 is implemented in MATLAB 7.0.1. An interface has been prepared for a user friendly and easy to use code. In this section, graphical user interface of the MATLAB code is introduced. The user is expected to enter the input parameters from the input screen and the graphics are displayed on two separate windows, classified as cardiopulmonary and airway mechanics parameters.

The MATLAB code is enclosed in the CD given with this thesis report. There are several versions of the code. One version is for the combined exercise model. There are also standalone working versions of the airway mechanics and cardiopulmonary models enclosed in the CD.

6.1. Input Screen

The input screen shown in Figure 6.1 is divided into windows. The titles of the windows in the input screen are informative of the parameters that are listed in them. Definitions of the abbreviations are listed below with a screenshot of the corresponding window on the input screen. They can also be checked from Appendix B.

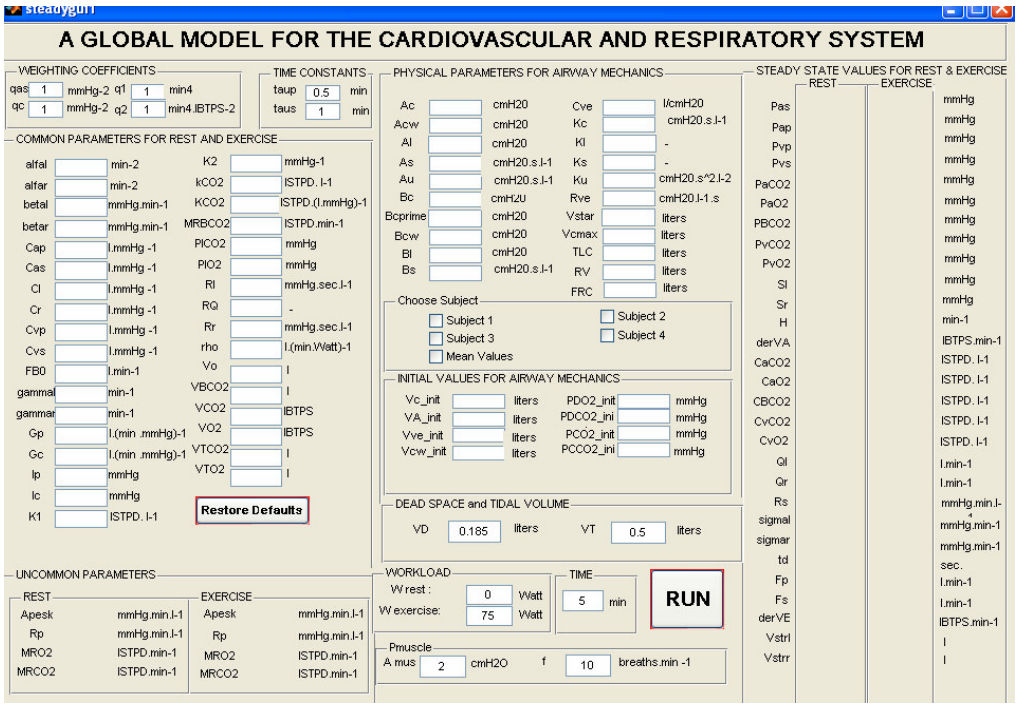

Figure 6.1 GUI-Input Screen

6.1.1. Weighting Coefficients Window

Coefficients of cost functional of the optimization problem can be entered from this window. (See Equation (5.14)) These weights have no physical meaning. They are all assumed to be equal and assigned to 1 throughout this study. By this way, the deviations of the quantities from their final value in the cost functional are equally weighted. For a more detailed information on weighting coefficients see [27].

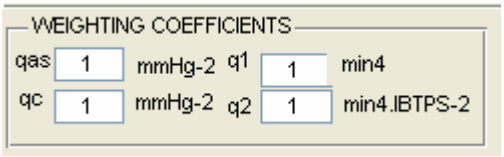

Figure 6.2 Weighting Coefficients Window

The meanings of the abbreviations in "Weighting Coefficients" window are given in Table 6-1.

Table 6-1 Weighting Coefficients Window

qas	: weighting factor of P_{as} in the cost functional $(mmHg^{-2})$
qc	: weighting factor of $P_{a_{CO_2}}$ in the cost functional $(mmHg^{-2})$
q1	: weighting factor of u_1 in the cost functional (min^4)
q2	: weighting factor of u_2 in the cost functional $(min^4.l_{BTPS}^{-2})$

6.1.2. Time Constants Window

The time constants for pulmonary resistance and A_{pesk} parameter that relates systemic resistance to venous oxygen concentration can be entered manually using "Time Constants" window shown in Figure 6.3. Default values of τ_p and τ_s are also shown in Figure 6.3. Definitions are given in Table 6-2.

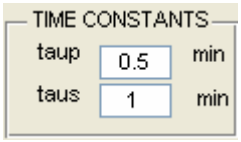

Figure 6.3 Time Constants Window

Table 6-2 Time Constants Window

taup	: time constant of R_p *(min)*
taus	: time constant of A_{pesk} *(min)*

Choosing τ_p smaller, R_p decreases faster and hence there would be a greater increase in pulmonary flow. This implies greater changes of mean blood pressures. In case of tremendous increase in pulmonary flow, $P_{a_{CO_2}}$ increases rather than decreases, since more CO_2 than can be expired is brought by pulmonary blood [27].

6.1.3. Common Parameters for Rest and Exercise Window

The parameters whose values remain unchanged for both rest and exercise conditions are listed in “Common Parameters for Rest and Exercise” window

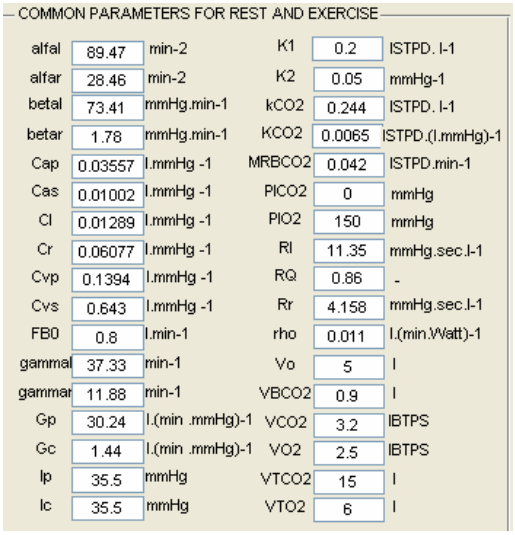

Figure 6.4 Common Parameters for Rest and Exercise Window

The definitions of the abbreviations in "Common Parameters for Rest and Exercise" window are listed in Table 6-3. The selected default values and alternatives can also be checked from Appendix C.

Table 6-3 Common Parameters for Rest and Exercise Window

alfal	: Coefficient of S_l in the Differential Equation for σ_l (min^{-2})
alfar	: Coefficient of S_r in the Differential Equation for σ_r (min^{-2})
betal	: Coefficient of H in the Differential Equation for σ_l $(Mmhg.Min^{-1})$
betar	: Coefficient of H in the Differential Equation for σ_r $(mmHg.min^{-1})$
Cap	: Compliance of the Arterial Part of the Pulmonary Circuit $(l.mmHg^{-1})$
Cas	: Compliance of the Arterial Part of the Systemic Circuit $(l.mmHg^{-1})$
Cl	: Compliance of the Relaxed Left Ventricle $(l.Mmhg^{-1})$
Cr	: Compliance of the Relaxed Right Ventricle $(l.mmHg^{-1})$
Cvp	: Compliance of the Venous Part of the Pulmonary Circuit $(l.mmHg^{-1})$
Cvs	: Compliance of the Venous Part of the Systemic Circuit $(l.mmHg^{-1})$

Table 6-3 (Continued)

FB0 : Cerebral Blood Flow for $P_{a_{CO_2}} = 40$ *(l.min^{-1})*

gammal : Coefficient Of σ_l in the Differential Equation for σ_l *(min^{-1})*

gammar : Coefficient Of σ_r in the Differential Equation for σ_r *(min^{-1})*

Gp : Peripheral Controller Gain Factor *(l. (min .mmHg)$^{-1}$)*

Gc : Central Controller Gain Factor *(l. (min .mmHg)$^{-1}$)*

Ip : Constant for Peripheral Drive of Ventilation *(mmHg)*

Ic : Constant for Central Drive of Ventilation *(mmHg)*

K1 : Constant for the O_2 Dissociation Curve *(l_{STPD}. l^{-1})*

K2 : Constant for the O_2 Dissociation Curve *(mmHg^{-1})*

kCO2 : Constant for the Physiological CO_2 Dissociation Curve *(l_{STPD}. l^{-1})*

KCO2 : Slope of the Physiological CO_2 Dissociation Curve, l_{STPD}. *(l.mmHg)$^{-1}$*

MRBCO2 : Metabolic Rate of CO_2 Production in Brain Tissue *(l_{STPD}.min^{-1})*

PICO2 : Partial Pressure of CO_2 in Inspired Air *(mmHg)*

PIO2 : Partial Pressure of O_2 in Inspired Air *(mmHg)*

Rl : Viscous Resistance of the Left Ventricle *(mmHg.sec.l^{-1})*

RQ : Respiratory Quotient of the Chemical Reactions in the Tissues *(-)*

Rr : Viscous Resistance of the Right Ventricle *(mmHg.sec.l^{-1})*

rho : Constant Relating Imposed Workload and Metabolic Rate *l.(min.Watt)$^{-1}$*

Vo : Total Blood Volume *(l)*

VBCO2 : Effective Brain Tissue Storage Volume for CO_2 *(l)*

VCO2 : Effective CO_2 Storage Volume of the Lung Compartment *(l_{BTPS})*

VO2 : Effective O_2 Storage Volume of the Lung Compartment *(l_{BTPS})*

VTCO2 : Effective Tissue Storage Volume for CO_2 *(l)*

VTO2 : Effective Tissue Storage Volume for O_2 *(l)*

6.1.4. Uncommon Parameters for Rest and Exercise Window

The parameters whose rest and exercise steady state values are calculated using the selected workload in the program are displayed in "Uncommon Parameters for Rest and Exercise" window.

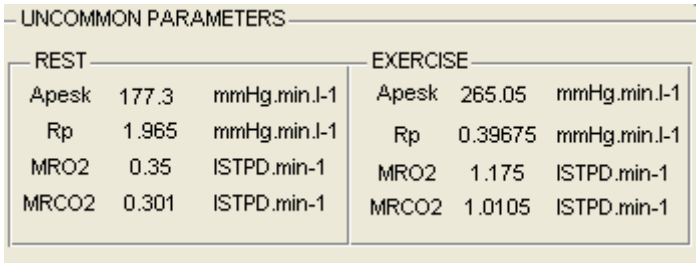

Figure 6.5 Uncommon Parameters for Rest and Exercise Window

Definitions of abbreviations are listed in Table 6-4.The selected default values and alternatives can also be checked from Appendix C.

Table 6-4 Uncommon Parameters for Rest and Exercise Window

Apesk : $R_s = A_{pesk} * C_{v_{O_2}}$ $(mmHg.min.l^{-1})$
Rp : Resistance in the Peripheral Region of the Pulmonary Circuit $(mmHg.min.l^{-1})$
MRO2 : Steady State Metabolic O2 Consumption Rate $(l_{STPD}.min^{-1})$
MRCO2 : Steady State Metabolic CO2 Production Rate $(l_{STPD}.min^{-1})$

6.1.5. Physical Parameters for Airway Mechanics

"Physical parameters for airway mechanics" window is shown in Figure 6.6.

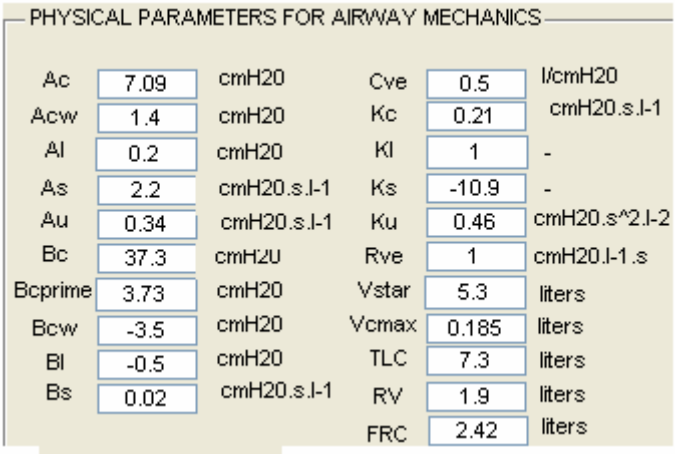

Figure 6.6 Physical Parameters for Airway Mechanics Window

Definitions of abbreviations are listed in Table 6-5. The selected default values and alternatives can also be checked from Appendix C.

Table 6-5 Physical Parameters for Airway Mechanics Window

Ac	: Offset for collapsible airways recoil pressure, (cmH_2O)
Acw	: CONSTANT
Al	: Lung recoil pressure scaling parameter, (cmH_2O)
As	: Small airways resistance scaling parameter, ($cmH_2O.sec.l^{-1}$)
Au	: Offset for upper airways resistance, ($cmH_2O.sec.l^{-1}$)
Bc	: Collapsible airways recoil pressure scaling parameter, (cmH_2O)
Bcprime	: Collapsible airways recoil pressure scaling parameter, (cmH_2O)

Table 6-5 (Continued)

Bcw	: CONSTANT
Bl	: Offset for lung recoil pressure, (cmH_2O)
Bs	: Offset for small airways resistance, ($cmH_2O.sec.l^{-1}$)
Cve	: Viscoelastic compliance of lung, ($l.cmH_2O$)
Kc	: Collapsible airways resistance scaling parameter, ($cmH_2O.sec.l^{-1}$)
Kl	: Lung recoil pressure scaling parameter, (l^{-1})
Ks	: Small airways resistance scaling parameter, *(-)*
Ku	: Upper airways resistance scaling parameter, ($cmH_2O.sec^2.l^{-2}$)
Rve	: Resistance of lung viscoelastance, ($cmH_2O.sec.l^{-1}$)
Vstar	: Small airways resistance parameter, (*l)*
Vcmax	: Collapsible airways resistance parameter, (*l)*
FRC	: Min Lung Volume, (*l)*
RV	: Residual Volume, (*l)*
TLC	: Total Lung Capacity, (*l)*

"Physical Parameters for Airway Mechanics" window can be filled manually or by using the checkboxes shown in "Choose Subject" window shown in Figure 6.7. Selecting the "Subject 1", "Subject 2", "Subject 3", "Subject 4" boxes will load the values that belong to the four subjects whose values were used to validate the airway mechanics model of [30]. "Mean values" checkbox loads the mean of the values for four subjects. The values for TLC, RV and FRC are determined for each subject by experimental methods (See Section 7.2). These individual data are entered manually and others that can not be determined experimentally are loaded from the database.

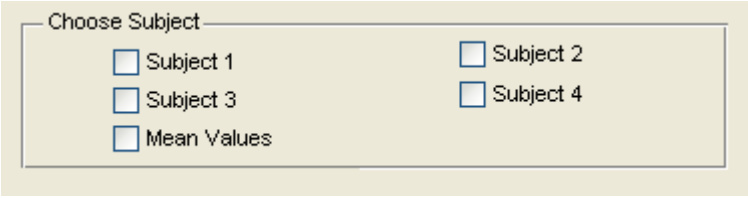

Figure 6.7 Choose Subject Window

6.1.6. Initial Values for Airway Mechanics Window

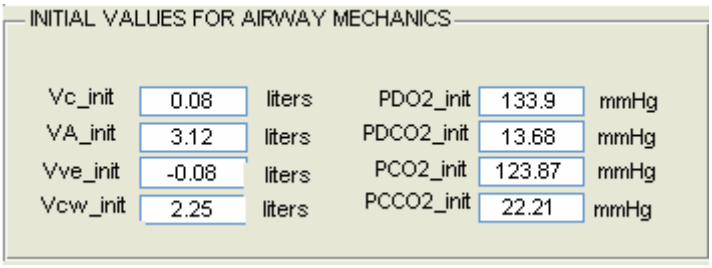

Figure 6.8 Initial Values for Airway Mechanics Window

For solving the differential equation of airway mechanics and gas transport the initial values for the state variables listed in "Initial Values for Airway Mechanics" window shown in Figure 6.8 have to be used. The meanings of abbreviations are listed in Table 6-6.

Table 6-6 Initial Values for Airway Mechanics Window

Vc_init	: Initial Volume of Collapsible Airways, *(l)*
VA_init	: Initial Alveolar Volume, *(l)*
Vve_init	: Initial Lung Viscoelastic Volume, *(l)*
Vcw_init	: Initial Chest Wall Volume, *(l)*

Table 6-6 (Continued)

PDO2_init	: Initial O_2 Pressure across Dead Space, *(mmHg)*
PDCO2_init	: Initial CO_2 Pressure across Dead Space, *(mmHg)*
PCO2_init	: Initial O_2 Pressure across Collapsible Airways, *(mmHg)*
PCCO2_init	: Initial CO_2 Pressure across Collapsible Airways, *(mmHg)*

6.1.7. Dead Space and Tidal Volume Window

Dead space and tidal volume values can be entered from this window as the name implies. Meanings of abbreviations are listed in Table 6-7.

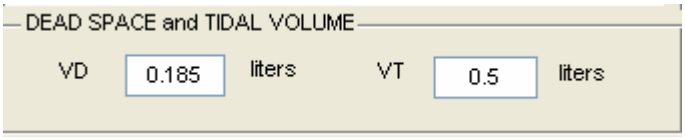

Figure 6.9 Dead Space and Tidal Volume Window

Table 6-7 Dead Space and Tidal Volume Window

VD	: Dead Space, *(l)*
VT	: Tidal Volume, *(l)*

6.1.8. Workload Window

The workload is 0 watts for rest and 75 watts for exercise by default. The values can vary from subject to subject and the "Workload Window" shown in Figure 6.10 can be used to enter this data manually. Meanings of abbreviations are listed in Table 6-8.

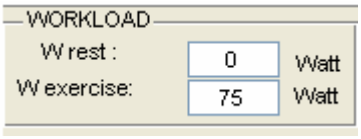

Figure 6.10 Workload Window

Table 6-8 Workload Window

Wrest	: Imposed Workload at Rest Condition *(Watt)*
Wexercise	: Imposed Workload at Exercise Condition *(Watt)*

6.1.9. Time Window

Simulation time can be entered from "TIME" window in minutes. The experiment duration shoud be noted during the experiments to be used in the simulations.

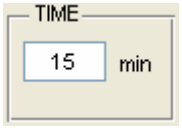

Figure 6.11 Time window

6.1.10. P_{muscle} Window

The magnitude of muscle pressure and its frequency are entered using "P_{muscle}" window shown in Figure 6.12 (See Equation (2.12) for a description of muscle pressure). Meanings of abbreviations are listed in Table 6-9.

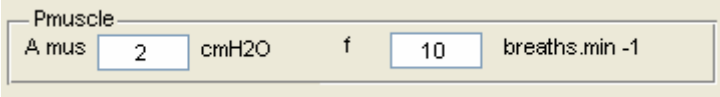

Figure 6.12 P_{muscle} Window

Table 6-9 P_{muscle} Window

Amus	: Magnitude of Muscle Pressure, (*watt*)
f	: Frequency of Muscle Pressure,($breaths.min^{-1}$)

6.1.11. Steady State Values for Rest and Exercise Window

The steady state values for rest and exercise are calculated in the program and they are displayed in the "Steady State Values for Rest and Exercise" window shown in Figure 6.13. Meanings of abbreviations are listed in Table 6-10.

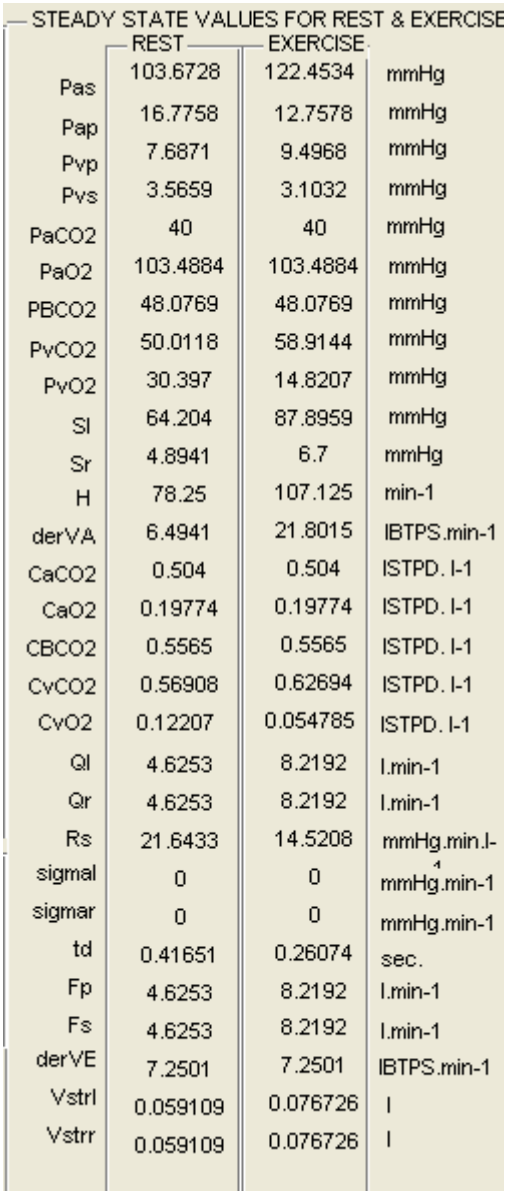

Figure 6.13 Steady State Values for Rest and Exercise Window

Table 6-10 Steady State Values for Rest and Exercise Window

Pas : Mean Blood Pressure in the Arterial Region of the Systemic Circuit *(mmHg)*
Pap : Mean Blood Pressure in the Arterial Region of the Pulmonary Circuit *(mmHg)*
Pvp : Mean Blood Pressure in the Venous Region of the Pulmonary Circuit *(mmHg)*
Pvs : Mean Blood Pressure in the Venous Region of the Systemic Circuit *(mmHg)*
PaCO2 : Partial Pressure of CO_2 in Arterial Blood *(mmHg)*

Table 6-10 (Continued)

PaO2 : Partial Pressure of O_2 in Arterial Blood *(mmHg)*

PBCO2 : Partial Pressure of CO_2 in Brain Tissue *(mmHg)*

PvCO2:Partial Pressure of CO_2 in Mixed Venous Blood Entering the Lungs*(mmHg)*

PvO2 : Partial Pressure of O_2 in Mixed Venous Blood Entering the Lungs*(mmHg)*

Sl : Contractility of the Left Ventricle *(mmHg)*

Sr : Contractility of the Right Ventricle *(mmHg)*

H : Heart Rate (min^{-1})

derVA : Alveolar Ventilation $(l_{BTPS}.min^{-1})$

CaCO2 : Concentration of Bound and Dissolved CO2 in Arterial Blood $(l_{STPD}.l^{-1})$

CaO2 : Concentration of Bound and Dissolved O2 in Arterial Blood $(l_{STPD}.l^{-1})$

CBCO2 : Concentration of Bound and Dissolved CO2 in Brain Tissue $(l_{STPD}.l^{-1})$

CvCO2 : Concentration of Bound and Dissolved CO2 in the Mixed Venous Blood Entering the Lungs $(l_{STPD}.l^{-1})$

CvO2 : Concentration of Bound and Dissolved O2 in the Mixed Venous Blood Entering the Lungs $(l_{STPD}.l^{-1})$

Ql : Left Cardiac Output $(l.min^{-1})$

Qr : Right Cardiac Output $(l.min^{-1})$

Rs : Peripheral Resistance in the Systemic Circuit $(mmHg.min.l^{-1})$

sigmal : Derivative of S_l $(mmHg.min^{-1})$

sigmar : Derivative of *Sr* $(mmHg.min^{-1})$

td : Duration of the Diastole *(sec)*

Fp : Blood Flow Perfusing the Lung Compartment $(l.min^{-1})$

Fs : Blood Flow Perfusing the Tissue Compartment $(l.min^{-1})$

derVE : Total Ventilation $(l_{BTPS}.min^{-1})$

Vstrl : Stroke Volume of the Left Ventricle *(l)*

Vstrr : Stroke Volume of the Right Ventricle *(l)*

6.1.12. Buttons

There are two buttons other than the windows. One of them is the “Restore Defaults” button. Pressing this button shown in Figure 6.14 , one can enter the default values collected from literature for “Common Parameters for Rest and Exercise”, “Initial Values for Airway Mechanics” and “Parameters from Literature”.(See Appendix C for values from literature.)

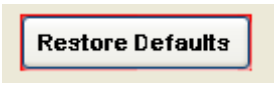

Figure 6.14 Restore Defaults Push Button

The second button is the “RUN” button, which starts the main program with the input from GUI, as its name implies.

Figure 6.15 RUN Push Button

6.1.13. Graphics Windows

After the simulations the outputs are printed on the two graphics windows. In the Cardiopulmonary Graphics window shown in Figure 6.16, pressures P_{as}, P_{vs}, P_{vp} ; heart rate H ; ventilation rate V_{av} ; partial blood gas pressures $P_{a_{CO_2}}, P_{a_{O_2}}$; contractilities blood gas concentrations $C_{a_{CO_2}}, C_{a_{O_2}}, C_{B_{CO_2}}$ are printed. One may see Table 6-10 for the meanings of the variables in Figure 6.16

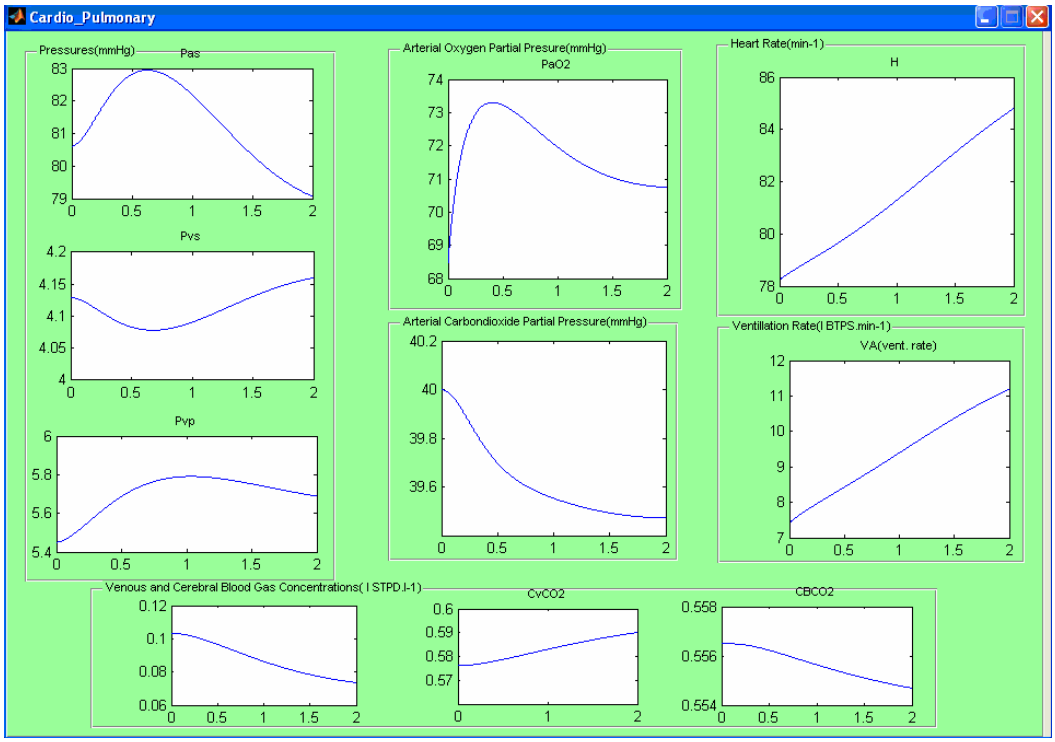

Figure 6.16 Cardiopulmonary Graphics Window

In the second graphics window, namely the Airway Mechanics Graphics window shown in Figure 6.17, airway partial gas pressures $P_{D_{CO_2}}, P_{D_{O_2}}, P_{C_{CO_2}}, P_{C_{O_2}}$ and

volumes V_c, V_A, V_{VE} are printed. The meanings of abbreviations in Figure 6.17 are presented in Table 6.11.

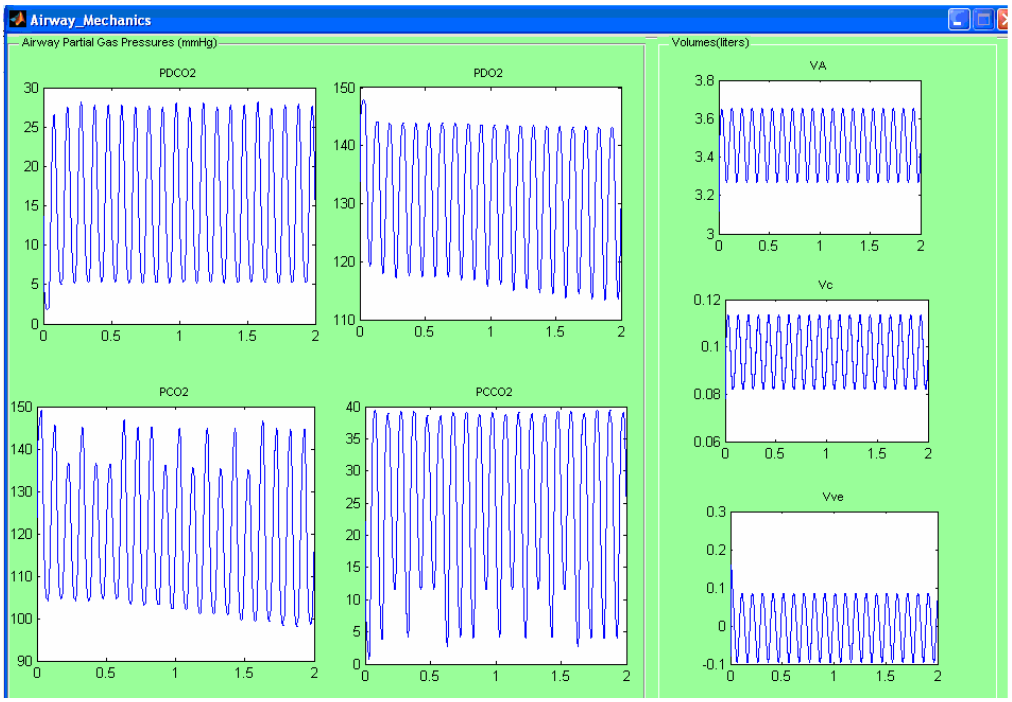

Figure 6.17 Airway Mechanics Graphics Window

Table 6-11 Airway Mechanics Graphics Window

Volumes
Vc : Volume of Collapsible Airways, *l* VA : Alveolar Volume, *l* Vve : Lung Viscoelastic Volume, *l*
Airway partial Gas Pressures
PDO2 : O_2 Pressure across Dead Space, *mmHg* PDCO2: CO_2 Pressure across Dead Space, *mmHg* PCO2 : O_2 Pressure across Collapsible Airways, *mmHg* PCCO2: CO_2 Pressure across Collapsible Airways, *mmHg*

6.1.14. Conclusion

The graphical user interface has been prepared for easy usage and a compact representation of the state variables that are calculated in the program. The graphics windows can be extended to include more variables. However it would lead to a longer execution time since additional followers should be maintained for the variables other than the state variables. The interface is easy to use and it is tried to keep it simple with two buttons, one to restore default values and another for running the program.

CHAPTER 7

VALIDATION OF THE MODEL

The model developed in this thesis for the simulation of cardiopulmonary system during constant workload, submaximal bicycle ergometer test is validated by performing CPET (cardiopulmonary exercise testing).

Exercise testing is a noninvasive procedure that provides diagnostic and prognostic information and evaluates an individual's capacity for dynamic exercise. Although submaximal exercise testing is not as precise as maximal exercise testing, it has advantages. For example, submaximal testing can provide a measure of an individual's fitness status without the cost, risk, effort (on the part of the individual), and time involved in maximal testing. Also, it is a good tool for monitoring fitness changes over time. If an individual is given repeated submaximal exercise tests and his heart rate response to a given workload is found to decrease over time, it is reasonably safe to conclude that his level of aerobic fitness has improved.

Before exercise testing a pulmonary function test have been performed to measure TLC (total lung capacity), RV (residual volume) and FRC (functional residual capacity) in order to be used as input to the airway mechanics model. A description of the experimental set-up, test equipment and test protocol are given below. The experimental results are compared with simulation results. In addition to experimental validation, the model simulations for exercise under normal conditions has been interpreted, different test scenarios have been applied to the model and results are evaluated as if they match with the expected behavior.

7.1. Experimental Set-Up

The exercise testing has been performed at Pulmonary Function Laboratories of Başkent University Hospital, Division of Pulmonary Diseases and Tuberculosis (See Figure 7.1). There was adequate space in the laboratory for walking and accessing to the patient in an emergency situation. It was well lighted, clean, and well ventilated. The temperature and humidity was controlled with the help of an air conditioner since heart rate and perceived stress rise with an increase in ambient temperature. The room had windows on two sides that minimized the feel of boredom and anxiety. The towels, tape, single use mouthpiece, nose clips and other items were ready for patient preparation and testing. The interruptions were minimized with restricted access to the room. This also provided the privacy and allowed the patient and laboratory staff to concentrate on the testing procedure.

7.1.1. Test Equipment

An electrocardiographic (ECG) recording system was available for continuous monitoring of heart rhythm and evaluation of ECG changes during baseline, warm up, exercise, and recovery stages of the exercise test. Commercially available disposable electrodes were used in the test.

Manual auscultation has been used to monitor blood pressure. Measurements at rest and exercise have been taken by manual cuff measurements. Automatic blood pressure measurement units were not preferred since they do not produce reliable readings when patient is in motion.

There were two kinds of ergometers for exercise testing namely treadmill and cycle ergometers. Cycle ergometer has been preferred since it enables accurate work rate measurements. See Figure 7.1. for the cycle ergometer used in the tests. Work

intensity has been adjusted by variations in resistance and cycling rate. Work rate has been calculated in watts.

Figure 7.1 Cycle Ergometer Test

A face mask covering the patients' nose and mouth have been used so that the inspired and expired gases are routed through a plastic mouthpiece.

A pulse oximetry has been used to estimate arterial blood saturation using pulsatile changes in light absorption. This device uses two wavelengths of light produced by light emitting diodes and a detector that measures transmitted or reflected light placed at the tip of the finger. Differential absorption of light at these two wavelengths provides enough information to determine the ratio of oxyhemoglobin to total hemoglobin assuming that all the pulsatile change is due to arterial blood.

Sometimes during exercise testing blood gases are sampled by systemic arterial catheter and pulmonary artery catheter. See Figure 7.2 for brachial artery

catheterization. This is an uncomfortable, painful and risky procedure for the patients and not preferred unless there is a special need for it. Besides blood samples need to be investigated in very short durations after they are collected. Due to its risks and the limitations of the exercise testing laboratory blood gas sampling have not been performed in our experiments.

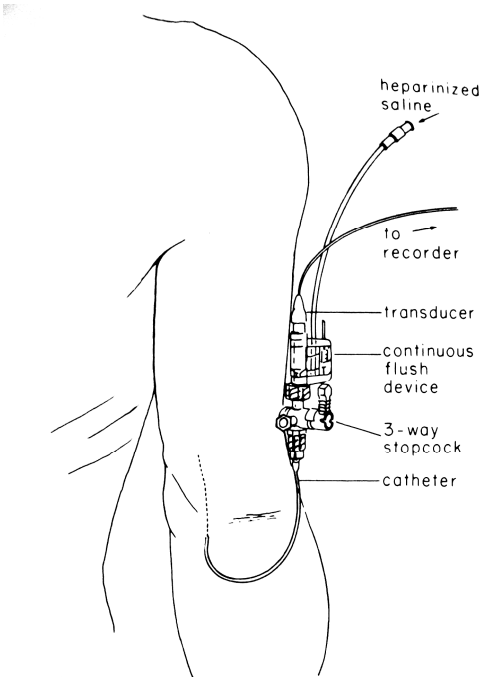

Figure 7.2 Brachial Artery Catheter Placement [61]

7.2. Experiment Protocol

Before the exercise testing, pulmonary function testing (PFT) has been done to determine TLC (total lung capacity), RV (residual volume) and FRC (functional residual capacity). PFT measures how well the lungs take in and exhale air. TLC is the amount of air in the lungs after inhaling as deeply as possible. FRC is the amount of air in the lungs at the end of a normally exhaled breath. RV is the amount of air in the lungs after a forceful exhalation. See Figure 7.3 for an illustration of the subdivisions of lung volume.

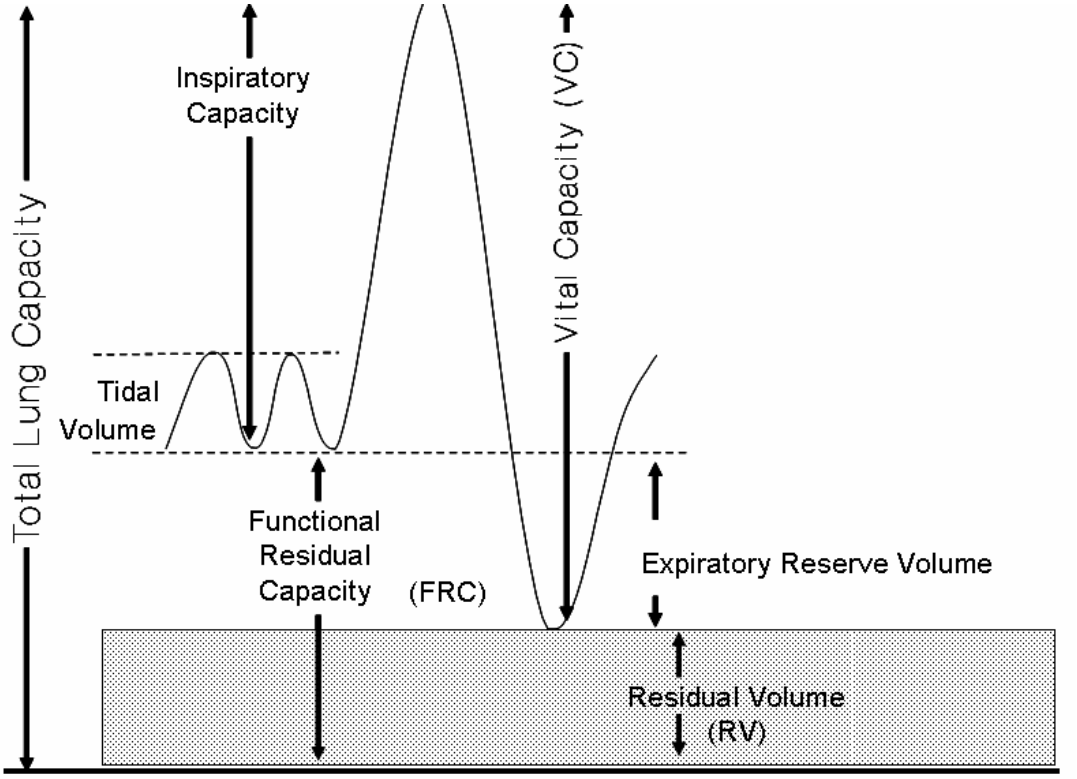

Figure 7.3 Subdivisions of Lung Volume[38]

In pulmonary function test, the patients' nose has been closed with a nose clip to route the inspired and expired gases through a plastic mouthpiece. (See Figure 7.4.) Then he was asked to breathe into the mouthpiece connected to a spirometer. The spirometer records the amount and the rate of air that is breathed in and out over a specified time. He was asked to inhale as deeply as possible and then to exhale as fast and as hard as possible. Later he was asked to breathe in and out as deeply and rapidly as possible for 15 seconds. From the measurements TLC, RV and FRC were determined.

Figure 7.4 Pulmonary Function Testing (PFT)

After PFT, the cardiopulmonary exercise testing has been performed. This is an excellent tool for validation of a cardiopulmonary model since it allows the simultaneous study of the responses of both systems to a known exercise stress through the gas exchange at the airway. The gas exchange measurements are accompanied by the ECG (electrocardiogram), heart rate, and blood pressure measurements.

In CPET, the ECG electrodes were placed as in Figure 7.5 for heart rate measurements.

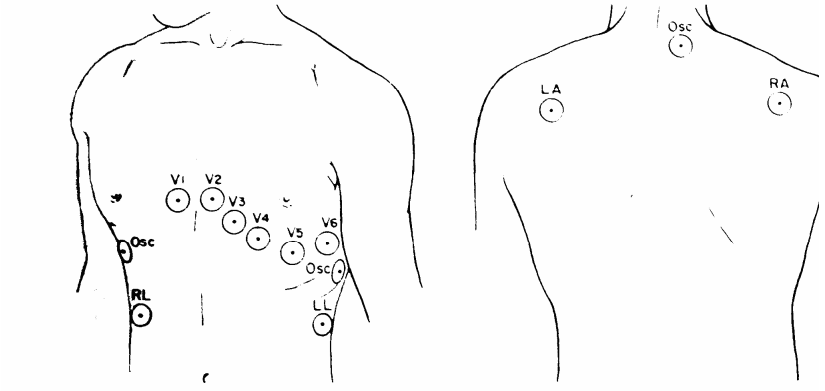

Figure 7.5 Electrode Placement in ECG[61]

A constant workload, submaximal (up to anaerobic threshold) exercise test have been performed. The experiment protocol had four phases namely, the baseline, warm-up, exercise and recovery. In baseline stage, the patient cycled freely with no workload imposed on him. In the second stage low rates of workload has been applied as name "warm up" implies. The third stage is the main stage whose data has been compared with our model. In the final recovery stage, patient slowly returned to resting condition by gradually decreasing workloads. In each stage the patient cycled against a constant workload that increased/decreased in predefined amounts in certain amounts of time needed for the patient to get used to the new work level. The tests were done until the patient reached his anaerobic threshold since the developed model is restricted to aerobic exercise. At the rest and end exercise levels, the arterial systemic pressure (systolic pressure) has been determined by manual cuff measurements.

There are several methods for the determination of anaerobic threshold. In this study, it has been done by using the "v- slope method" introduced in [62]. $\dot{V}_{CO_2}$ (amount of CO_2 produced in one minute) is drawn as a function of $\dot{V}_{O_2}$ (amount of oxygen used in one minute) by the exercise test equipment during the test. This is called V-slope plot. This curve initially follows a linear progression with a slope of

1.0 or less during aerobic metabolism. The curve then breaks, with $\dot{V}_{CO_2}$ increasing faster than $\dot{V}_{O_2}$ so that the slope increases above 1.0. The underlying fact to this increase in slope is the production of additional CO_2 from HCO_3^- buffering of lactic acid over that produced by aerobic metabolism that results from exercise above AT. If two lines fitting to collected data are drawn with these slopes in mind, they intersect at the breakpoint which is called the anaerobic threshold. The point determined by this method is then used in heart rate versus $\dot{V}_{O_2}$ graph to determine the anaerobic threshold heart rate. This technique is illustrated in Figure 7.6, on the graphs drawn by the exercise test instrument during the tests of Subject 1.

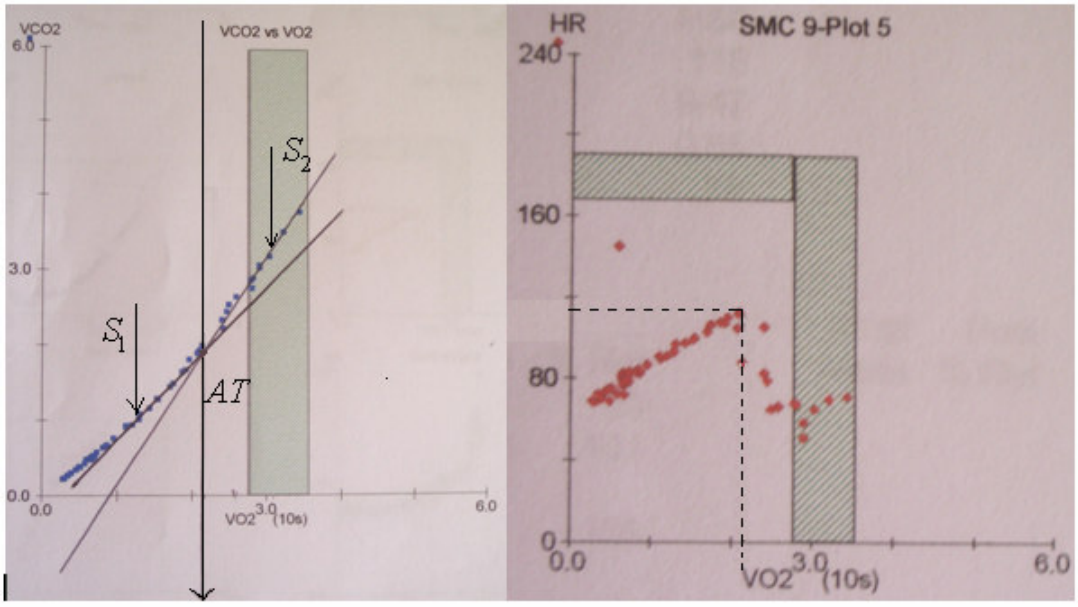

Figure 7.6 Determination of Anaerobic Threshold. Left Figure: $\dot{V}_{CO_2}$ vs. $\dot{V}_{O_2}$ Graph. Right Figure: Heart Rate vs. $\dot{V}_{O_2}$ Graph

7.3. Experimental Results vs. Simulation Results

The tests have been held on two subjects. Subject 1 is of age 32, height 1.80 m, weight 72 kg, male and in a good physical condition. Subject 2 is of age 24, height 1.74 m, weight 67 kg and male. The data collected from Subject 2 is not reliable due to incorrect heart rate readings during the exercise stage. Besides the subject had too high initial systolic pressure above normal values in addition to being in an unfit physical condition. This prevented him to be handled as a normal case. Due to this inconvenience only the results of Subject 1 have been investigated and compared with the model predictions. All of the experimental data belonging to both subjects obtained by dynamic, submaximal cycle ergometer tests are presented in Appendix D.

The values determined for TLC, RV and FRC by PFT are also input to the model. (See Table 7-1 for the PFT results collected from the subjects). The average RQ (respiratory quotient) values that were determined by the exercise test equipment have been entered as the RQ value to the program (See Table 7-2).

Table 7-1 PFT Results

	Subject 1	Subject 2
TLC	7,22 liters	7.06 liters
RV	1,73 liters	1,96 liters
FRC	3,59 liters	4,26 liters

Table 7-2 Measured Mean RQ Values for Stages of Exercise Test

mean RQ(baseline)	0,741905
mean RQ(warmup)	0,745965
mean RQ(exercise)	0,914982
mean RQ(recovery)	1,391167
average RQ(warm up & exercise)	0,830474

The heart rate output collected by exercise testing from Subject 1 is presented in Figure 7.7. This data is measured by gradually increasing the workload at approximately one minute intervals to levels 19, 37, 56, 74, 93, 111 and 130 watts up to anaerobic threshold in seven minutes.

A similar simulation has been done repeat the experiment conditions. The workload has been increased from 0-19, 19-37, 37-56, 56 -74, 93-111, 111-130 watts and the outputs has been concatenated. This simulation graph is presented in Figure 7.8

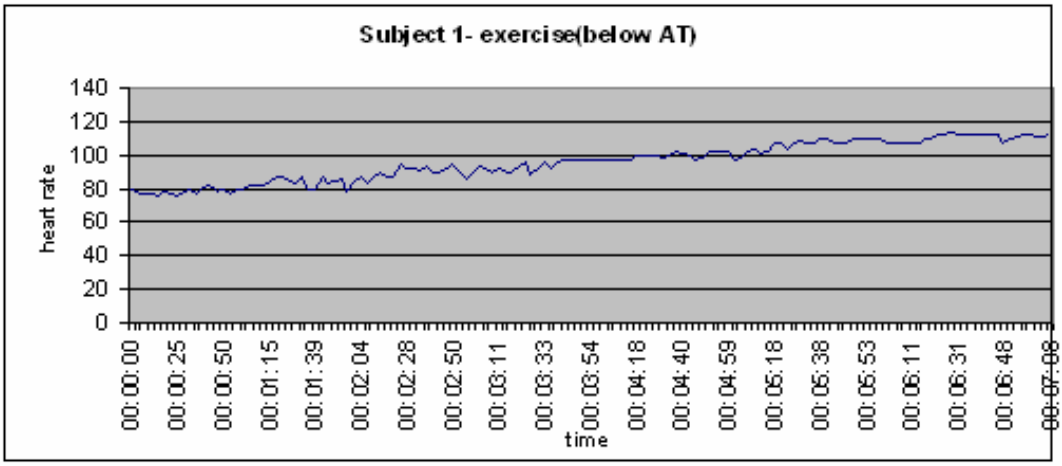

Figure 7.7 Experimental Data Collected from Subject 1 Before Anaerobic Threshold

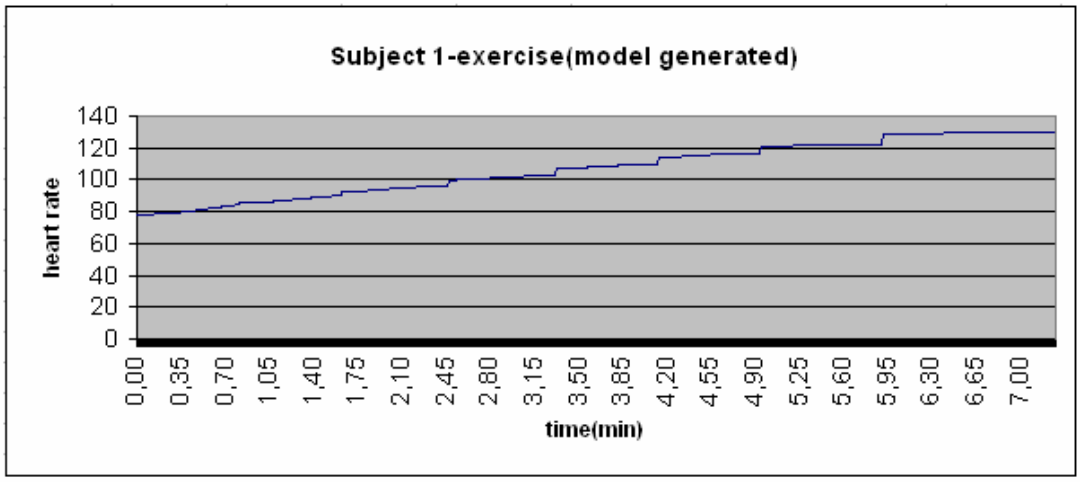

Figure 7.8 Model Generated Data for Subject 1

The simulation result is well correlated with experimental data. The stepwise increments in Figure 7.8 are due to the difference of simulations from the experimental routine. In experimental routine the heart rate changes in continuity as the workload is increased gradually. However when the case is simulated with the program, a distinct simulation is done for each interval. That leads to using the precalculated values for the steady state of heart rate for each of the workload intervals. Steady state value for heart rate is calculated by using the formula below used in steady state analysis in the model (See 5.1 for details).

$$\begin{aligned} H &= aMR_{O_2} + b, \\ MR_{O_2} &= 0.350 + \rho W. \end{aligned} \tag{7.1}$$

So the rest and exercise values for heart rate are determined by the above linear relation dependent on the entered workload. However the final value that the heart rate reaches is determined by the feedback control and is usually less than this precalculated value. So when the outputs of distinct intervals are directly concatenated this fact is underestimated and simulation starts from a point which can not actually be reached in a continuous experiment. This is graphically illustrated in Figure 7.9.

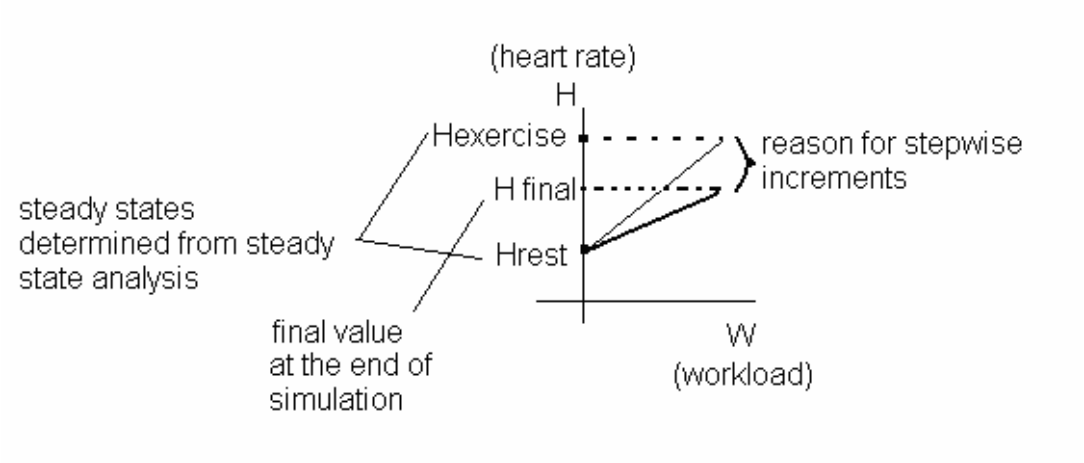

Figure 7.9 Graphical Interpretation of Stepwise Increments in Model Generated Exercise Test Data.

To make a correction that accounts for this fact, an actual value of initial steady state is determined for each interval looking at the final value from the previous interval and instead of using the formula in Equation (7.1) the final state of the previous run has been entered as the initial heart rate. The final value is also estimated by removing the offset between calculated initial value and final value from previous run, from the calculated final value. It leads to the graph in Figure 7.10 and shows a far better match with the experiments.

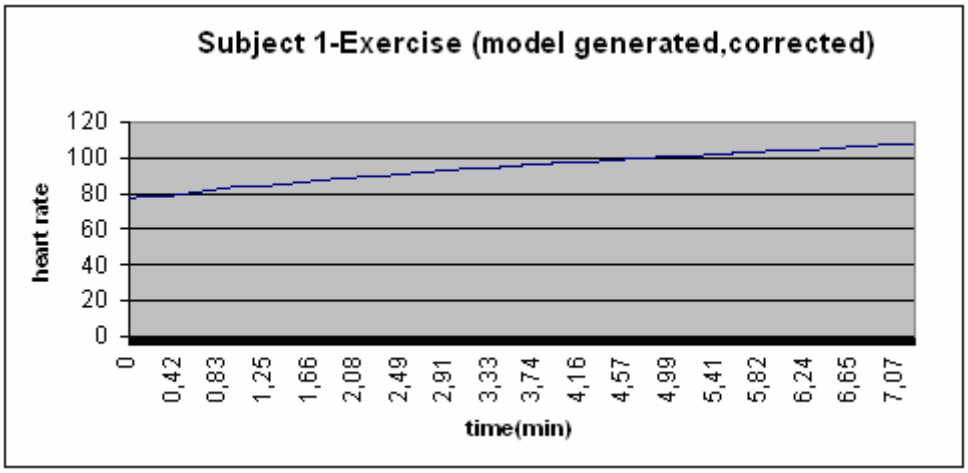

Figure 7.10 Model Generated Data Corrected for the Discontinuity in Simulations

The anaerobic threshold values used in the simulations are determined by v-slope technique (See Table 7-3). The v-slope technique is explained in Section 7.2.

Table 7-3 Anaerobic Threshold Values

Anaerobik Threshold Degerleri	
AT VO2	2.100 L/min
AT HR	120(bpm)
AT VE	53 L/min
AT RQ	0.9

The systolic and diastolic pressures measured at rest and exercise conditions have been compared with the model generated data. This also showed a good match between data collected and predicted by the model as shown in Table 7-4.

Table 7-4 Measured Arterial Systemic Pressures Compared with Model Output (P_{as})

	Systolic Pressure	Diastolic Pressure	Model Pas
rest	110	80	105
exercise	150	80	155.2

7.4. Computer Simulations

In this section, firstly, the case of exercise has been simulated for a healthy subject, in good physical condition, with no environmental stresses and the results for exercise under these normal conditions have been interpreted. Secondly, the outputs of the model for decreased oxygen and increased carbon dioxide partial pressure have been investigated and compared with expected results. Finally, dynamic effects of pulmonary resistance at the onset of exercise have been studied.

7.4.1. Interpretation of Simulations for Exercise under Normal Conditions

The Figure 7.11 to Figure 7.16 show the variations in ventilation rate, heart rate, arterial oxygen and carbon dioxide pressures and arterial systemic and venous systemic pressures predicted by the simulations of exercise under normal conditions.

The nervous system normally makes adjustments on the rate of alveolar ventilation in order to meet the demands of the body so that the arterial blood oxygen and carbon dioxide pressures are regulated and held at normal values during moderate to strenuous exercise [38].

When the figures below are carefully investigated one may notice that the arterial carbon dioxide pressure decreases at the onset of exercise whereas arterial oxygen pressure has a slight increase. This may seem to be conflicting with the fact that during exercise oxygen consumption and carbon dioxide formation increases. However the cause is the anticipatory stimulation of respiration at the onset of exercise by the brain. This stimulation causes extra alveolar ventilation even before it is needed. So, ventilation increase is ahead of the build up of carbon dioxide due to exercise. The result is an initial decrease in carbon dioxide and increase in oxygen pressures in arterial blood. As time progresses the carbon dioxide build up forges ahead of ventilatory rate that causes the expected increase in arterial carbon dioxide pressure. However this does not last long and with more increase in ventilation carbon dioxide and oxygen are regulated to their normal values in blood whereas the ventilation is also stabilized at a higher value for exercise [38].

Heart rate is another very important link in the delivery of adequate oxygen to the exercising muscles. When skeletal muscles contract during exercise, they compress blood vessels throughout the body. The resulting effect is the translocation of large quantities of blood from the peripheral vessels into the heart and lungs and therefore to increase the cardiac output. The increase is compensated mainly by the increase in heart rate. Also, the increase in cardiac output is an essential factor in increasing the arterial pressure during exercise [38]. In the simulations, it can be observed that heart rate increases due to exercise and arterial systemic pressure is also regulated to a higher value and the model works as predicted for heart rate and arterial systemic pressure, too.

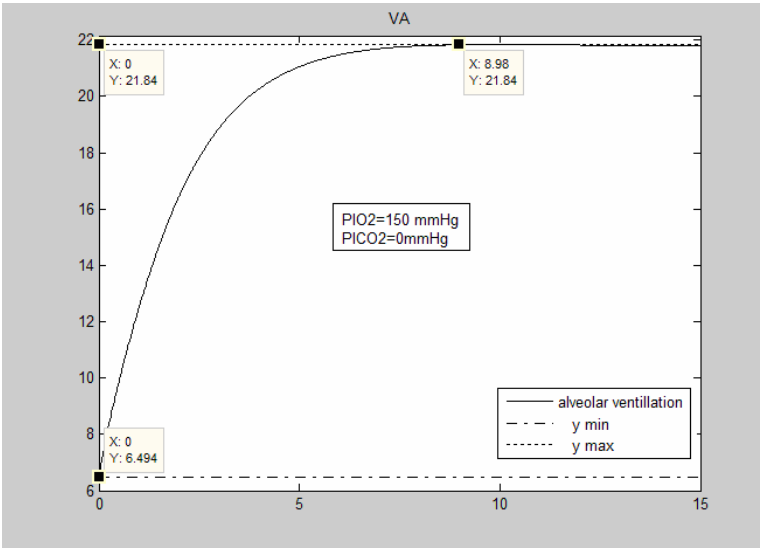

Figure 7.11 Alveolar Ventilation for Normal Oxygen Partial Pressure

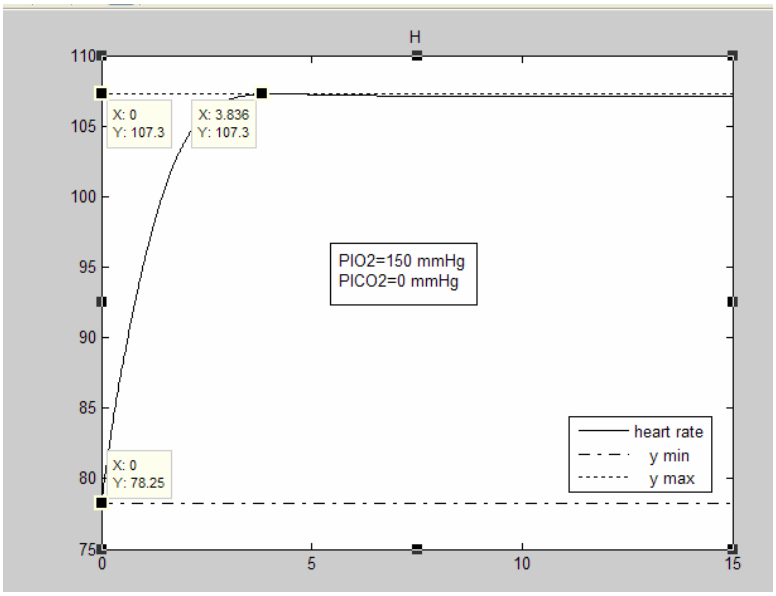

Figure 7.12 Heart Rate for Normal Oxygen Partial Pressure

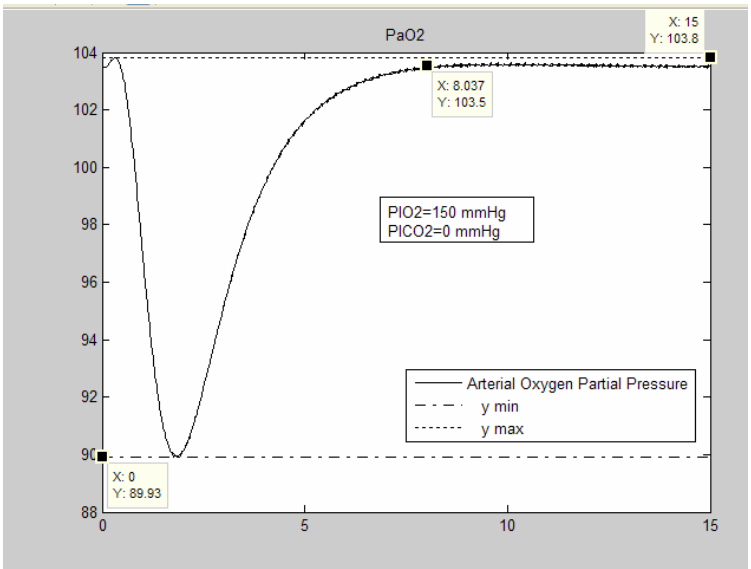

Figure 7.13 Arterial Oxygen Partial Pressure for Normal Oxygen Partial Pressure

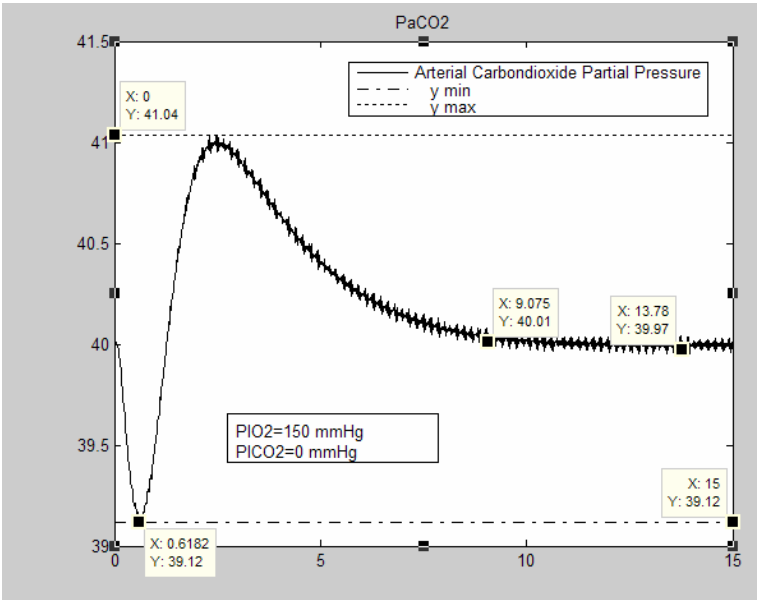

Figure 7.14 Arterial Carbon Dioxide Partial Pressure for Normal Oxygen Partial Pressure

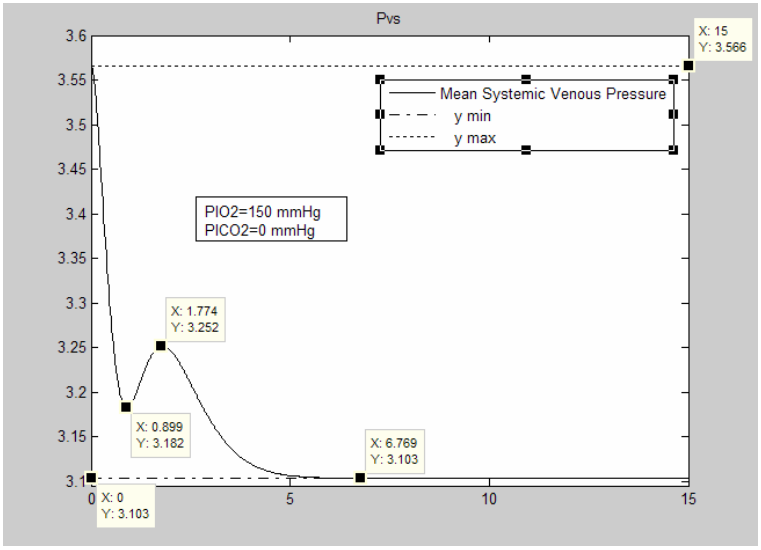

Figure 7.15 Mean Systemic Venous Pressure for Normal Oxygen Partial Pressure

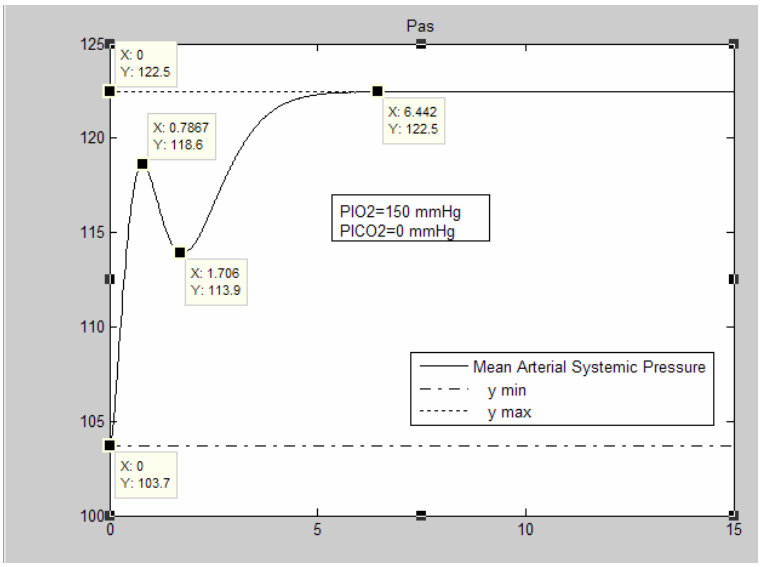

Figure 7.16 Mean Arterial Systemic Pressure for Normal Oxygen Partial Pressure

7.4.2. Decreased Oxygen and Increased Carbon Dioxide in Inspired Air

Normally when a person breathes air that has too little oxygen, this decreases the blood P_{O_2} and excites the carotid and aortic chemoreceptors, which leads to an increase in ventilation. The effect is usually much less than one would expect because the increased respiration removes carbon dioxide from the lungs and thereby decreases both blood P_{CO_2} and hydrogen ion concentration. This decrease suppresses the respiratory center so that the effect of chemoreceptors in increasing respiration in response to low P_{O_2} is almost counteracted. (See Section 1.2.2.2 for information on respiratory center and chemoreceptors). However if carbon dioxide level is increased at the same time with the decrease in oxygen, the ventilatory drive of low P_{O_2} is not suppressed by changes in carbon dioxide level. Therefore, the combined effect of decreased oxygen and increased carbon dioxide is a strong ventilatory drive.

Between Figure 7.17 and Figure 7.34, the partial oxygen pressure in inspired air is gradually decreased and partial carbon dioxide pressure inspired air is gradually increased. The combined effect of decreased oxygen and increased carbon dioxide is a strong ventilatory drive. So, what is expected to see in the simulations is an increase in heart rate and alveolar ventilation to compensate for lack of oxygen with faster responses to larger oxygen deficiency and larger increase in carbon dioxide. The model works to regulate $P_{a_{CO_2}}$, and P_{as} so that the change in these variables is minimal. Also it is known that the chemo receptors sensing oxygen and carbon dioxide levels, primarily change the ventilation rate to handle the change [38]. Therefore the responses observed in alveolar ventilation are much faster and larger than any other effect. Also, it can be observed that $P_{a_{O_2}}$ is decreased with the decrease in oxygen in inspired air but regulated to normal levels in time.

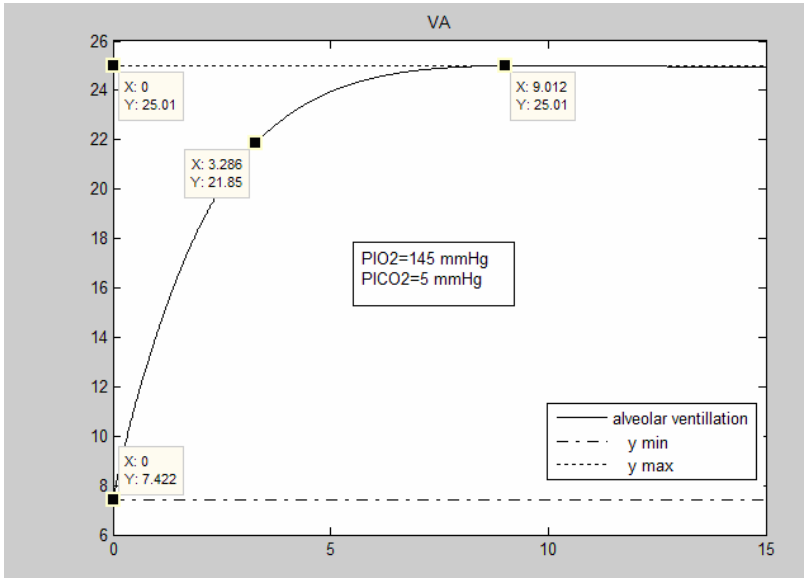

Figure 7.17 Alveolar Ventilation for Inspired Oxygen Partial Pressure=145 mmHg

($P_{I_{O_2}} = 145 mmHg$)

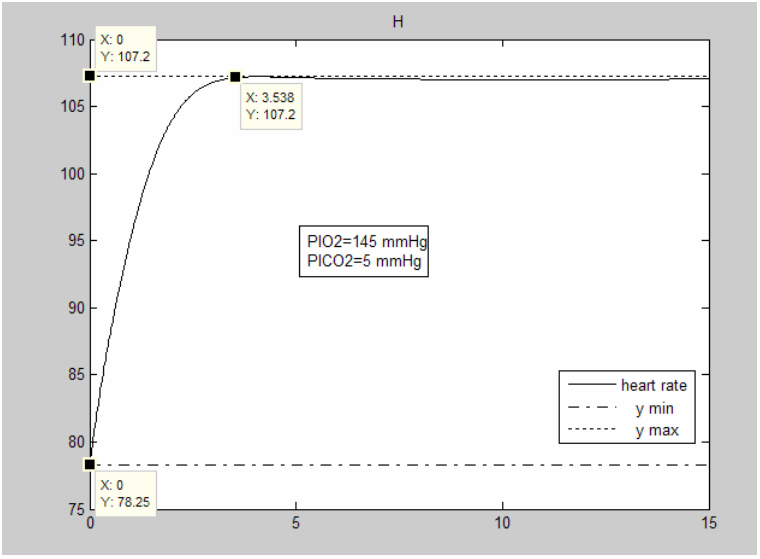

Figure 7.18 Heart Rate for Inspired Oxygen Partial Pressure=145 mmHg ($P_{I_{O_2}} = 145 mmHg$)

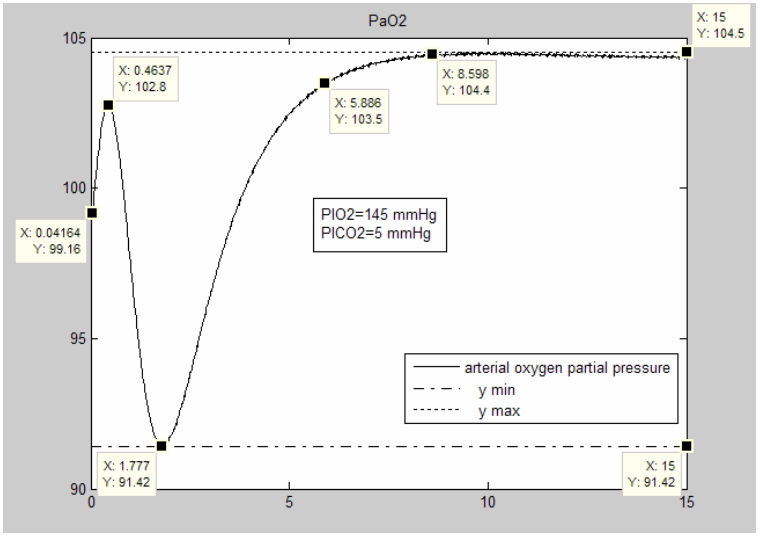

Figure 7.19 Arterial Oxygen Partial Pressure for Inspired Oxygen Partial Pressure=145 mmHg ($P_{I_{O_2}} = 145 mmHg$)

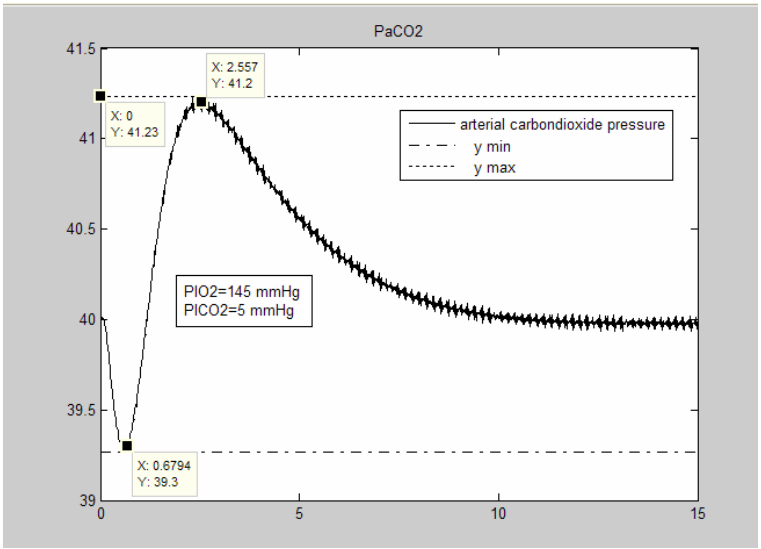

Figure 7.20 Arterial Carbon Dioxide Partial Pressure for Inspired Oxygen Partial Pressure=145 mmHg ($P_{I_{O_2}} = 145 mmHg$)

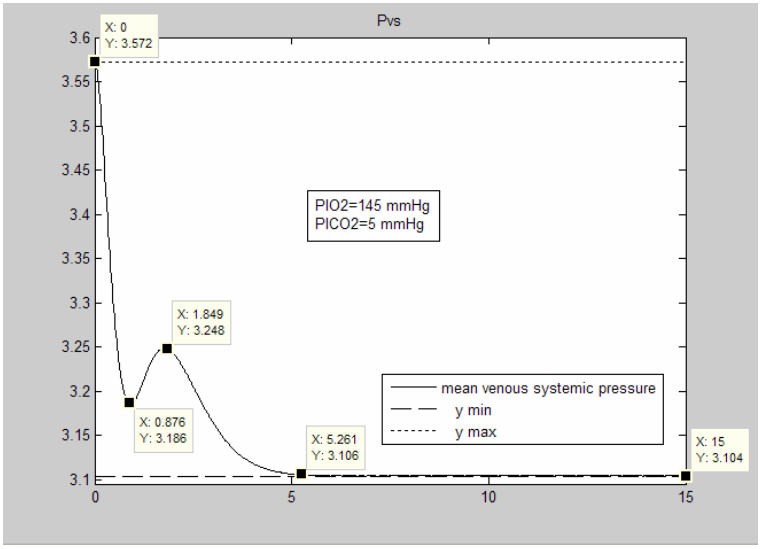

Figure 7.21 Mean Venous Systemic Pressure for Inspired Oxygen Partial Pressure=145 mmHg

($P_{I_{O_2}} = 145 mmHg$)

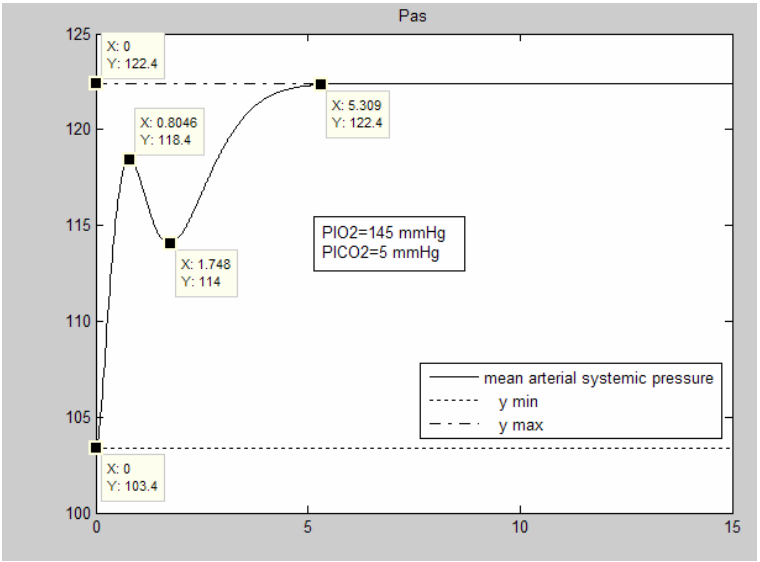

Figure 7.22 Mean Arterial Systemic Pressure for Inspired Oxygen Partial Pressure=145 mmHg ($P_{I_{O_2}} = 145 mmHg$)

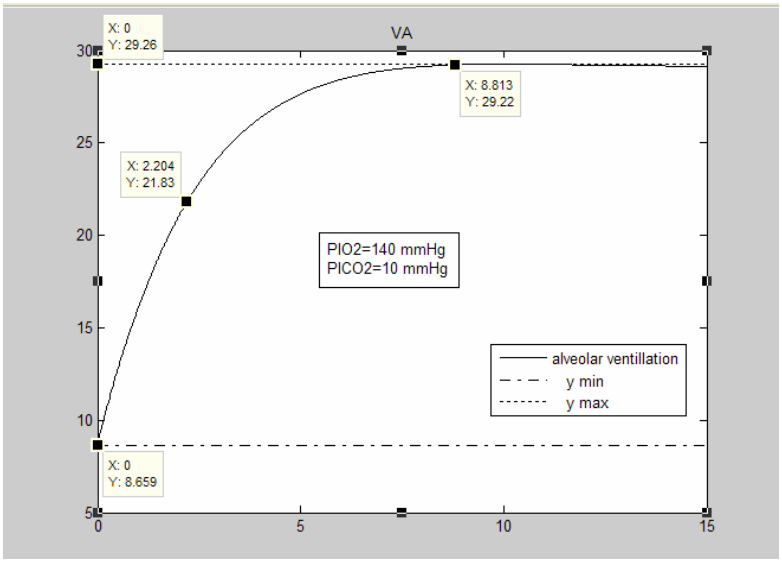

Figure 7.23 Alveolar Ventilation for Inspired Oxygen Partial Pressure=140 mmHg

($P_{I_{O_2}} = 140 mmHg$)

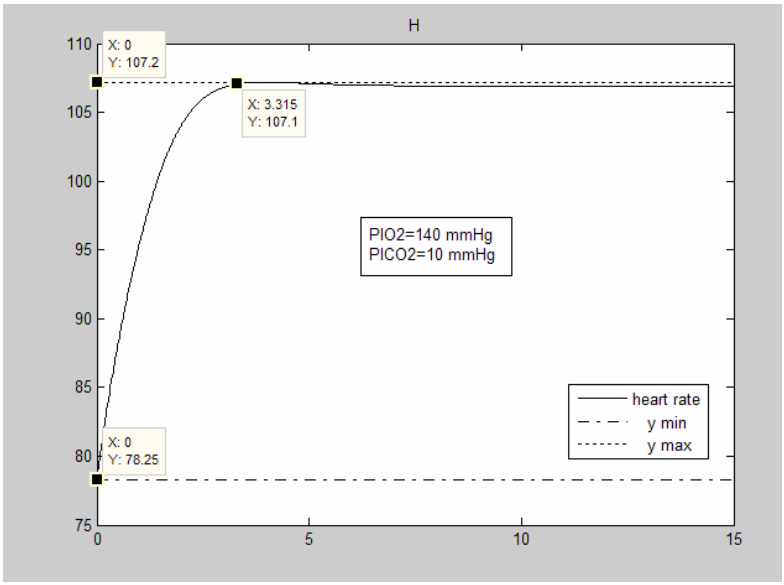

Figure 7.24 Heart Rate for Inspired Oxygen Partial Pressure=140 mmHg ($P_{I_{O_2}} = 140 mmHg$)

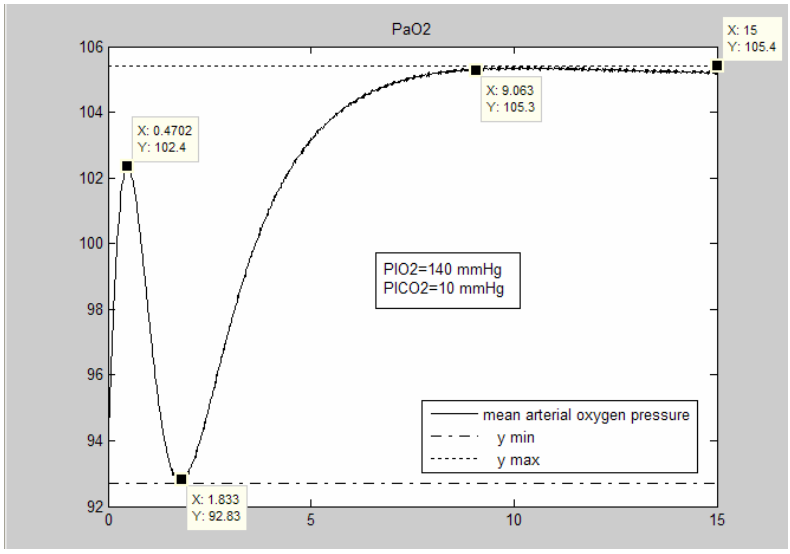

Figure 7.25 Arterial Oxygen Partial Pressure for Inspired Oxygen Partial Pressure=140 mmHg ($P_{I_{O_2}} = 140 mmHg$)

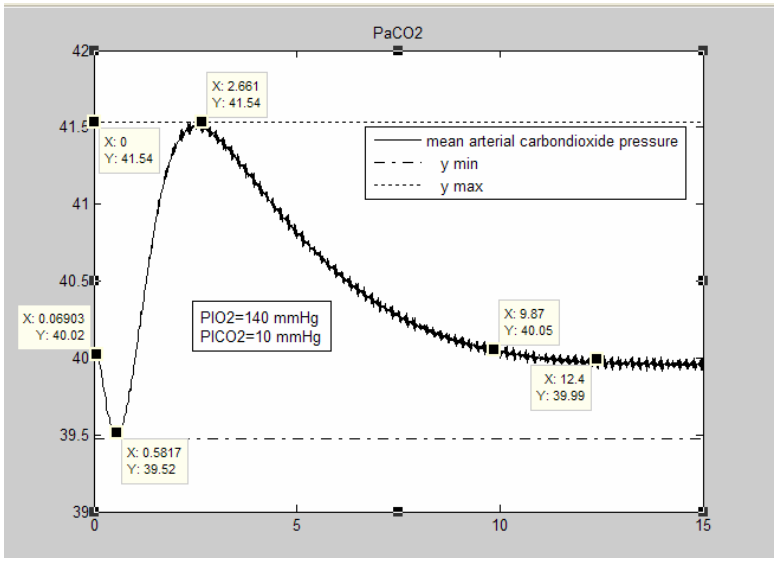

Figure 7.26 Arterial Carbon Dioxide Partial Pressure for Inspired Oxygen Partial Pressure=140 mmHg ($P_{I_{O_2}} = 140 mmHg$)

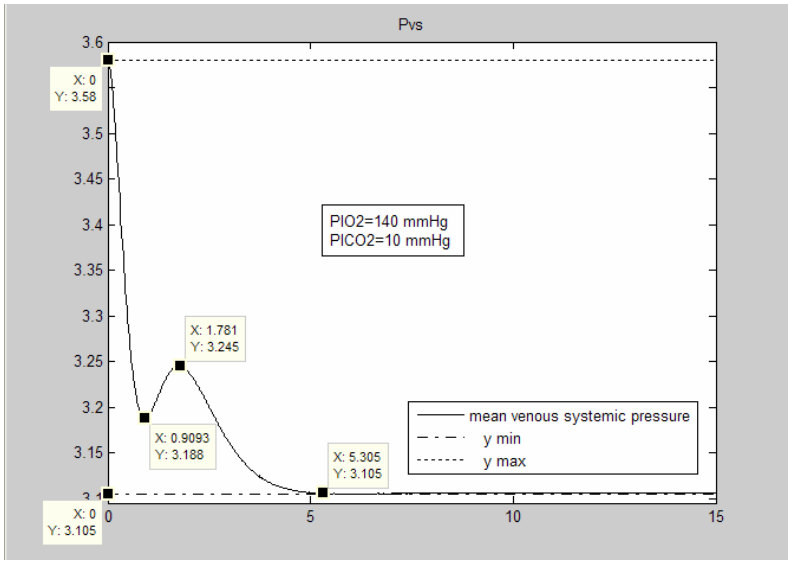

Figure 7.27 Mean Venous Systemic Pressure for Inspired Oxygen Partial Pressure=140 mmHg

($P_{I_{O_2}} = 140 mmHg$)

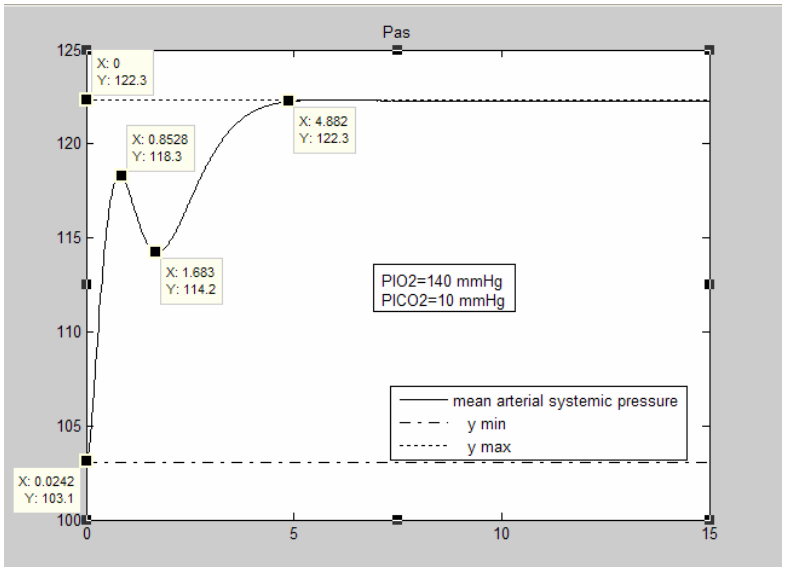

Figure 7.28 Mean Arterial Systemic Pressure for Inspired Oxygen Partial Pressure=140 mmHg ($P_{I_{O_2}} = 140 mmHg$)

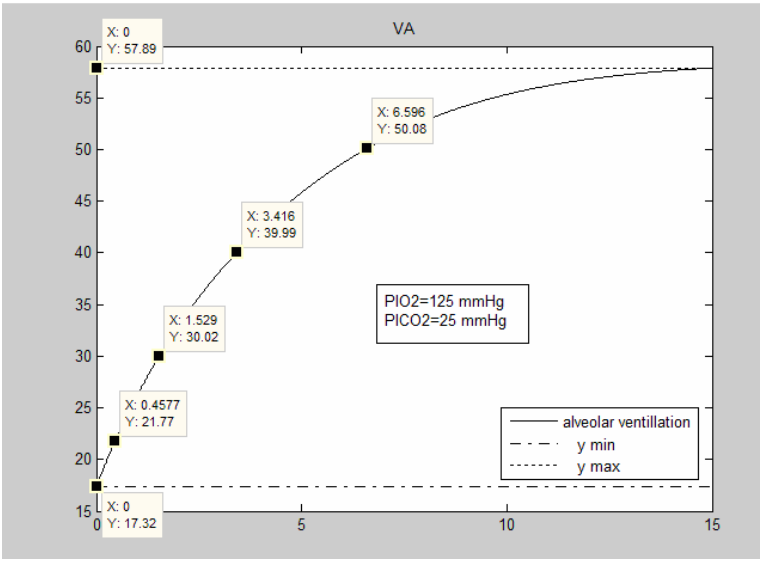

Figure 7.29 Alveolar Ventilation for Inspired Oxygen Partial Pressure=125 mmHg

($P_{I_{O_2}} = 125 mmHg$)

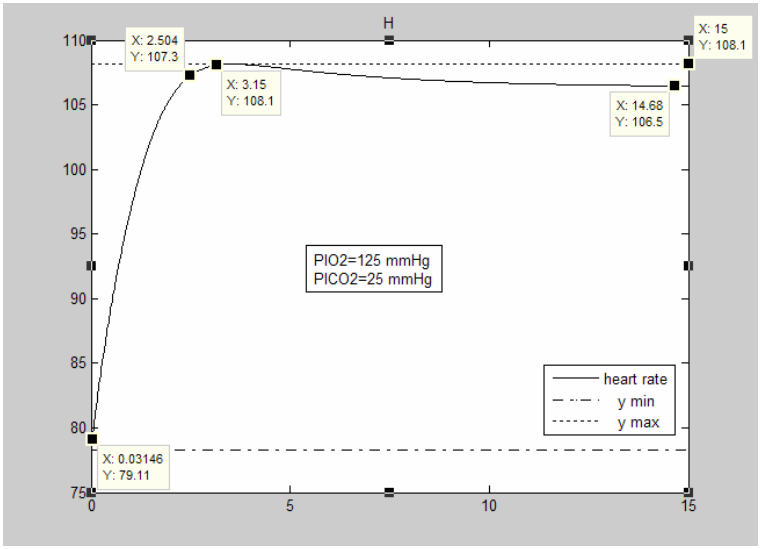

Figure 7.30 Heart Rate for Inspired Oxygen Partial Pressure=125 mmHg ($P_{I_{O_2}} = 125 mmHg$)

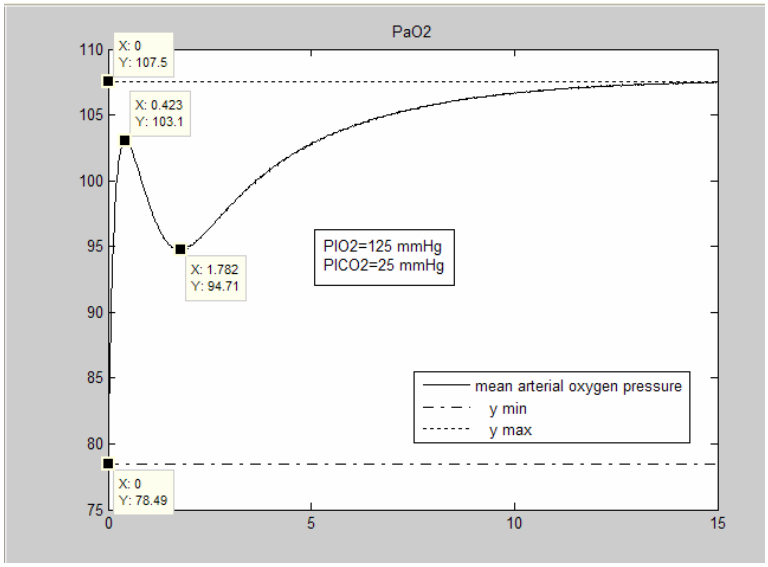

Figure 7.31 Mean Arterial Oxygen Pressure for Inspired Oxygen Partial Pressure=125 mmHg

($P_{I_{O_2}} = 125 mmHg$)

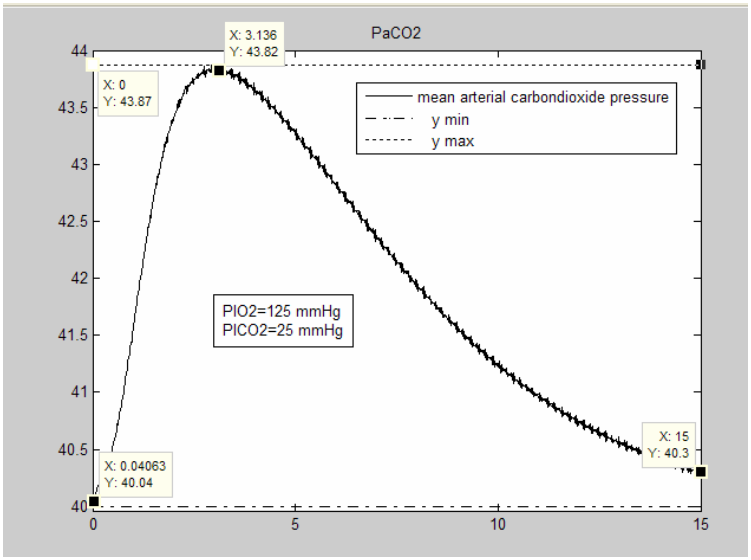

Figure 7.32 Mean Arterial Carbon Dioxide Pressure for Inspired Oxygen Partial Pressure=125 mmHg ($P_{I_{O_2}} = 125 mmHg$)

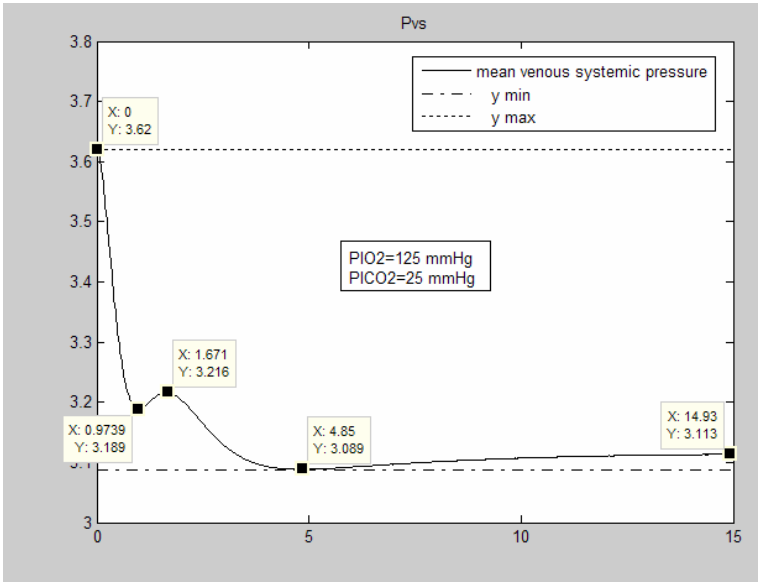

Figure 7.33 Mean Venous Systemic Pressure for Inspired Oxygen Partial Pressure=125 mmHg

($P_{I_{O_2}} = 125mmHg$)

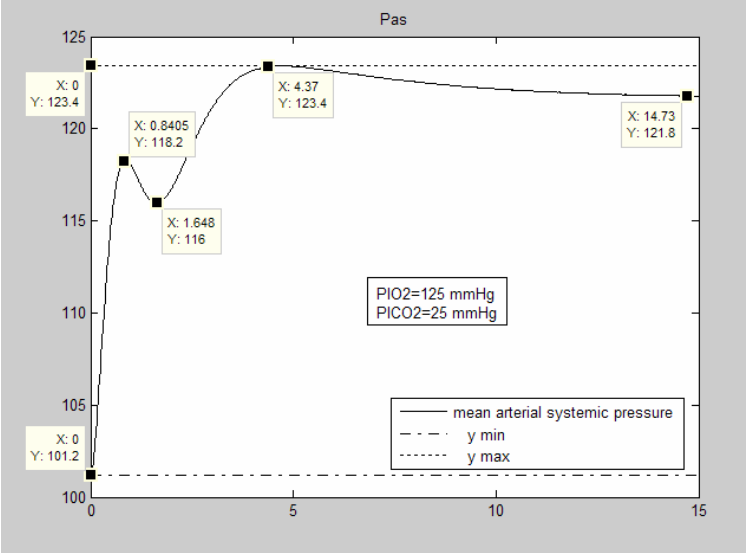

Figure 7.34 Mean Arterial Systemic Pressure for Inspired Oxygen Partial Pressure=125 mmHg ($P_{I_{O_2}} = 125mmHg$) P_{as}

7.4.3. Effects of Changes in Pulmonary Resistance Dynamics

Several simulations have been done to study the effects of the pulmonary resistance dynamics. In the first case, the time constant for pulmonary resistance has been increased and the results were observed. The expected behavior is, the larger τ_p, the smaller is the decrease of pulmonary resistance and hence the smaller the initial increase of pulmonary blood flow. This in turn implies smaller changes of mean blood pressures at the onset of exercise [27]. The simulations match well with the expected behavior as can be seen in Figure 7.35, Figure 7.36, Figure 7.37, Figure 7.38.

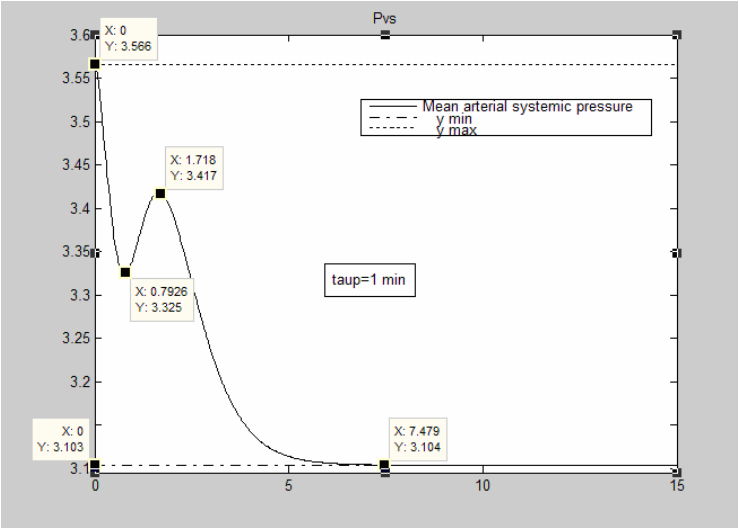

Figure 7.35 Mean Venous Systemic Pressure at Pulmonary Time Constant =1min

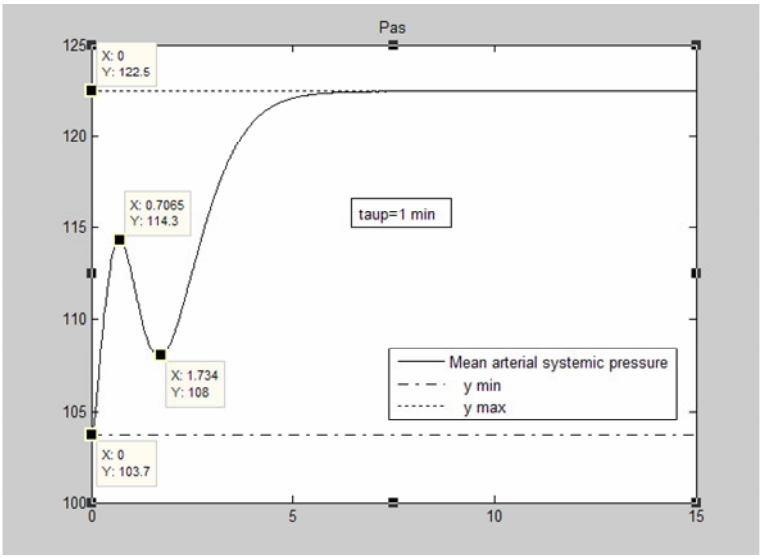

Figure 7.36 Mean Arterial Systemic Pressure at Pulmonary Time Constant =1min

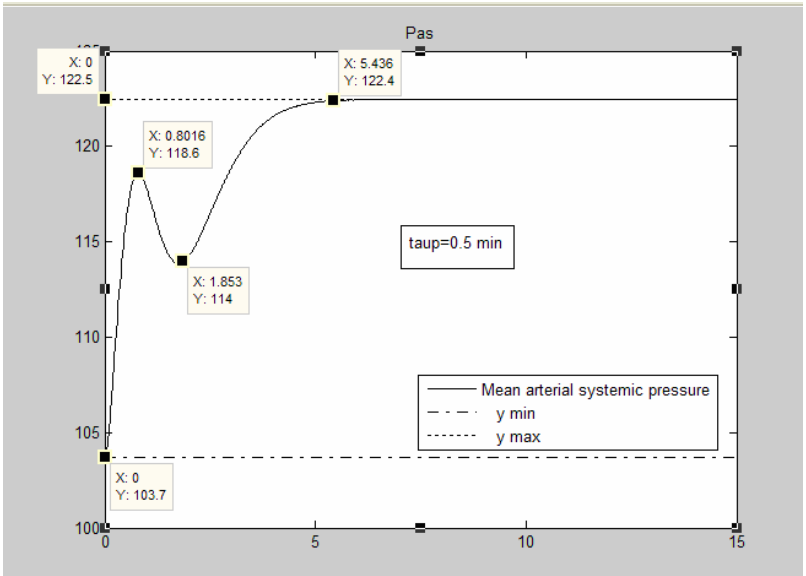

Figure 7.37 Mean Arterial Systemic Pressure at Pulmonary Time Constant =0.5min

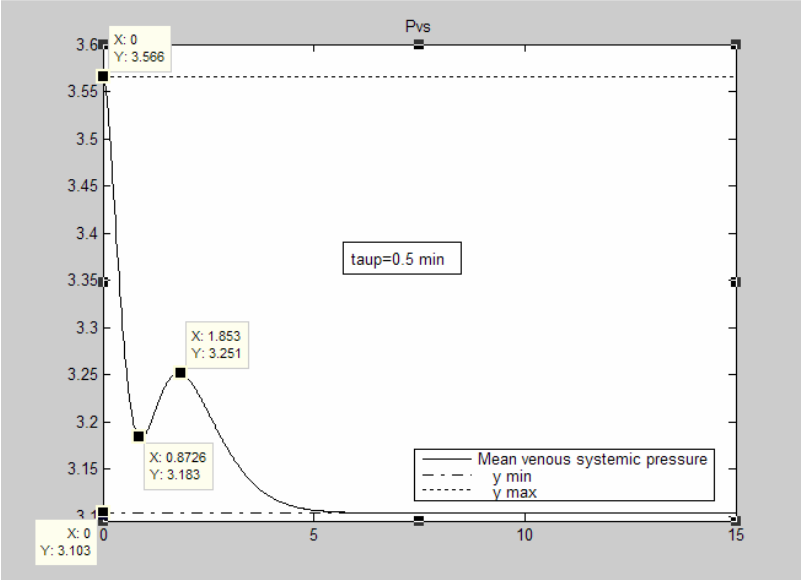

Figure 7.38 Mean Venous Systemic Pressure at Pulmonary Time Constant =0.5min

Another simulation is made to see the effects of a drastic fall in time constant that would cause the pulmonary blood flow to increase too fast. Such an increase would cause $P_{a_{CO_2}}$ to rather increase than decrease at the onset of exercise since the CO_2 brought by the pulmonary flow to the lungs would now be too high to be removed by respiration [27]. This increase in $P_{a_{CO_2}}$ would also be accompanied by an initial decrease in $P_{a_{O_2}}$. These effects can be seen in Figure 7.39 and Figure 7.40.

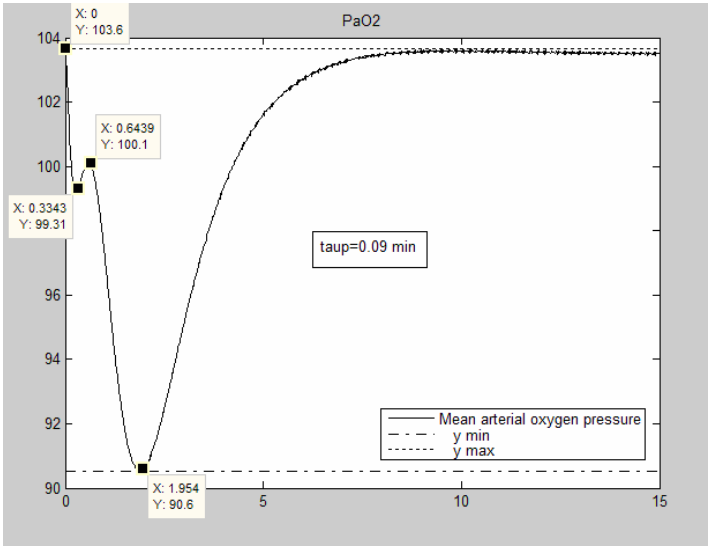

Figure 7.39 Mean Arterial Oxygen Pressure with Pulmonary Time Constant=0.09min

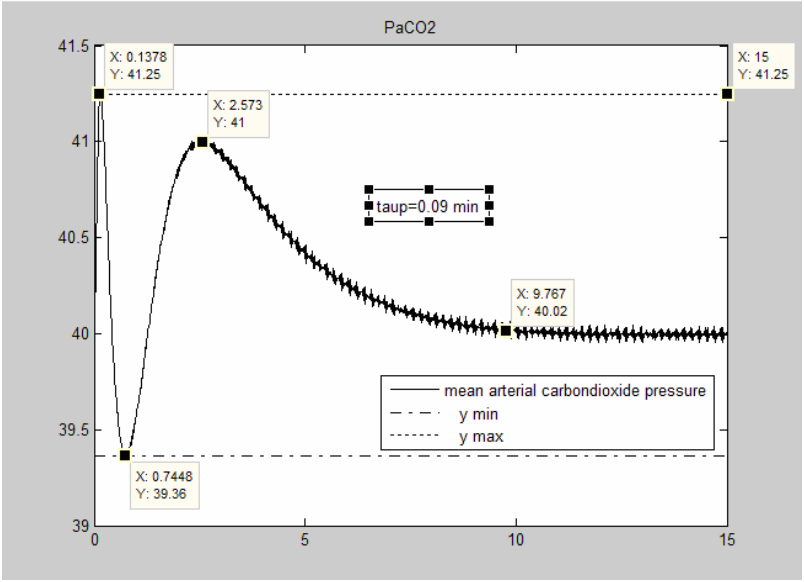

Figure 7.40 Mean Arterial Carbon Dioxide Pressure with Pulmonary Time Constant=0.09min

CHAPTER 8

CONCLUSION AND FUTURE WORK

In this thesis study, models of cardiopulmonary system [27], airway mechanics [30] and gas exchange [32] that preexisted in literature have been reviewed, modified and combined. Work done throughout this study can be summarized as below:

- Firstly, the model presented in [27] has been implemented. A graphical user interface has been prepared for it. Standalone working MATLAB models for airway mechanics [30] and gas exchange [32] has been implemented and integrated to the previous system. Another graphical user interface has been prepared for the final implementation.
- Combined model has been validated by making dynamic cycle ergometer tests at Baskent University, Pulmonary Function Laboratory. The tests have been held on two subjects. One of them had to be discarded from the experiment due to incorrect data readings. The second data set matched well with the model generated data.
- Simulations have been done to show that the model makes reasonable predictions for several scenarios like oxygen deficiency and excess carbon dioxide or influence of dynamics of pulmonary resistance. The model predictions for exercise testing under normal conditions have been interpreted.

Results show that this combined model can be used for education purposes in medical schools or by physiology students to gain an understanding of the

cardiopulmonary interactions. Although it is an approximate model with several assumptions in its derivation it still gives a good match with experimental data and simulation predictions.

As a future work the approximations can be refined and new modules can be added to the model in order to give a more exact view of the ongoing events in the cardiovascular and respiratory systems. It can be modified to model different diseases like emphysema, COPD (chronic obstructive pulmonary disease) or effects of cures on the treatment of diseases, i.e. lung volume reduction surgery or lobectomy for emphysema, lung cancer etc. Such a modeling effort needs extremely tedious work and should be made in coordination with clinicians.

The model can be worked on numerous other cases that can be created and simulated. One such case is the effect of increasing workloads on cardiopulmonary variables. More complex cases can be generated and tried out by the computer model.

The experimental validation by cycle ergometer tests can be extended for a larger number of subjects to increase reliability of the model. ABG (analysis of blood gases) can also be performed to check real data with model outputs if the laboratory resources and capabilities allow. Other types of constant workload ergometer tests can be done to compare the effect of the ergometer on exercise test results. (See [63] for an example of how one can make constant workload experiments with a treadmill ergometer.)

It has been observed that the combined model implementation has a very long execution time due to model complexity and data storage. As future work it can be coded in another language like C for time efficiency.

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APPENDIX A

PYHSICAL BACKGROUND

A1. Water Vapor

Water vapor is liquid at normal temperatures unlike the other respiratory gases. The maximum partial pressure of water in a wet gas at a given temperature is equal to the vapor pressure of water at that temperature. When the partial pressure of water in a wet gas is equal to its maximum value at the existing temperature, it is said to be saturated. If vapor is in contact with an excess of liquid, then saturation is insured. Thus, in the lung or wet spirometer where an ample amount of water is always present, the partial pressure of water vapor equals the vapor pressure of water and is a function of temperature alone.

Since temperature and water vapor pressure both influence gas volume, their effects must be considered in any measurement of volume. Thus, if there is a difference in temperature between the measurement apparatus and gas volume of interest, the measured volume must be corrected.

When lung volumes at body temperature are measured with a wet spirometer at room temperature, measured volumes must be corrected to BTPS conditions (body temperature, pressure saturated).Thus if a wet spirometer volume V_1 is measured at temperature T_1(^{o}C), barometric pressure B(mmHg), and water vapor pressure $P_1(H2O)$, then the volume V_{BTPS} is

$$V_{BTPS} = \frac{V_1 \times (B - P_1(H_2O)) \times (273 + 37)}{(B - 47) \times (273 + T_1)}, \quad \text{A.1}$$

where $P_1(H2O)$ is the vapor pressure of water at temperature T_1. The constant 273 is used to convert ^{o}C to ^{o}K.

When the number of gas molecules is of primary interest, volumes are expressed at standard temperature (0^{o}C), standard pressure (760 mmHg), and dry (STPD). Oxygen consumption, carbon dioxide production and diffusing capacity are examples where STPD units are used. Similarly as above, if volume V_1 is measured at temperature T_1, barometric pressure B, and saturated water vapor, then the volume V_{STPD} is

$$V_{STPD} = \frac{V_1 \times (B - P_1(H_2O)) \times 273}{760 \times (273 + T_1)}. \quad \text{A.2}$$

Volumes expressed in BTPS and STPD can be converted to each other using the relation

$$\frac{V_{STPD}}{V_{BTPS}} = \frac{273}{760} \frac{(B - 47)}{(273 + 37)}. \quad \text{A.3}$$

A2. Unit Conversions

Blood pressure is almost always measured in millimeters of mercury *(mmHg)* since mercury manometer is conventionally being used as the standard reference for measuring blood pressure.

Occasionally, pressure is measured in centimeters of water cm H_2O. 10 cm H_2O is the pressure needed to raise a column of water to height of 10 cm.

Density of mercury is 1.36 times that of water and 10 mm is equal to 1cm. This yield,

$$1mmHg = 1.36\ cm\ H_2O. \qquad \text{A.4}$$

A3. Ideal Gas Law

Experimentally, it has been found that all gases behave essentially in the same way provided temperatures are not too low and pressures are not too high. Thus, the volume, V, occupied by a mass m of any kind of gas depends on the pressure, P, to which the gas is subjected, and on its temperature, T. This interrelationship is neatly summarized by the empirical equation of state of an ideal gas:

$$PV = nRT. \qquad \text{A.5}$$

The quantity, n, refers to the mass in terms of the number of moles (n=m/M, M=molecular weight) and R is the universal gas constant. In physiology, volumes are commonly expressed in liters, pressures in millimeters of mercury or centimeters of water, and temperatures in degrees centigrade or Kelvin. In this system of units

$$R = 62.37 \frac{liter.mmHg}{mole.^{o}K}, \qquad \text{A.6}$$

if pressure is measured in millimeters of mercury.

All gases deviate from the ideal gas behavior especially at high pressures. However, over the physiological range of pressures, most gases can be adequately described by Equation A.5. For a fixed mass (or a fixed number of moles) and a constant temperature, Equation A.5. becomes,

$$PV = constant. \qquad \text{A.7}$$

The observation that the product of pressure and volume of a fixed mass of gas at constant temperature is constant was first made by Robert Boyle in 1660. This equation has many applications in respiratory mechanics.

APPENDIX B

GLOSSARY FOR NOTATION

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
a	slope of the relationship between heart rate and metabolic rate	l_{STPD}^{-1}
α_l	coefficient of S_l in the differential equation for σ_l	min^{-2}
α_r	coefficient of S_r in the differential equation for σ_r	min^{-2}
A_c	offset for collapsible airways recoil pressure	cmH_2O
A_{cw}	constant	-
A_l	lung recoil pressure scaling parameter	cmH_2O
A_{pesk}	$R_s = A_{pesk} C_{v_{O_2}}$	$mmHg.min.l^{-1}$
A_{pesk}^r	steady state value of A_{pesk} during rest	$mmHg.min.l^{-1}$
A_{pesk}^e	steady state value of A_{pesk} during exercise	$mmHg.min.l^{-1}$
A_s	small airways resistance scaling parameter	$cmH_2O.sec.l^{-1}$
A_u	offset for upper airways resistance	$cmH_2O.sec.l^{-1}$
b	constant relating heart rate and metabolic rate	min^{-1}
B_c	collapsible airways recoil pressure scaling parameter	cmH_2O
B_c'	collapsible airways recoil pressure scaling parameter	cmH_2O
B_{cw}	constant	-
B_l	offset for lung recoil pressure	cmH_2O

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
B_s	offset for small airways resistance	$cmH_2O.sec.l^{-1}$
β_l	coefficient of h in the differential equation for σ_l	$mmHg.min.l^{-1}$
β_r	coefficient of h1 in the differential equation for σ_r	$mmHg.min.l^{-1}$
c	factor converting from STPD to BTPS conditions, c = 1.21	-
$C_{a_{CO_2}}$	concentration of bound and dissolved CO_2 in arterial blood	$l_{STPD}.l^{-1}$
$C_{a_{O_2}}$	concentration of bound and dissolved O_2 in arterial blood	$l_{STPD}.l^{-1}$
C_{ap}	compliance of the arterial part of the pulmonary circuit	$l.mmHg^{-1}$
C_{as}	compliance of the arterial part of the systemic circuit	$l.mmHg^{-1}$
$C_{B_{CO_2}}$	concentration of bound and dissolved CO_2 in brain tissue	$l_{STPD}.l^{-1}$
C_{CO_2}	general symbol for carbon dioxide concentration	$l_{STPD}.l^{-1}$
C_{cw}	chest wall compliance	$l^{-1}.cmH_2O$
C_l	compliance of the relaxed left ventricle	$l.mmHg^{-1}$
C_{ls}	a static, non linear compliance used to model elastic recoil of the lung	$l^{-1}.cmH_2O$
C_{O_2}	general symbol for oxygen concentration	$l_{STPD}.l^{-1}$
C_r	compliance of the relaxed right ventricle	$l.mmHg^{-1}$
$C_{T_{CO_2}}$	concentration of bound and dissolved CO_2 in lumped body tissue	$l_{STPD}.l^{-1}$
$C_{vB_{CO_2}}$	concentration of bound and dissolved CO_2 in the venous blood leaving the brain tissue	$l_{STPD}.l^{-1}$
$C_{vB_{O_2}}$	concentration of bound and dissolved O_2 in lumped body tissue	$l_{STPD}.l^{-1}$

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
$C_{v_{CO_2}}$	concentration of bound and dissolved CO_2 in the mixed venous blood entering the lungs	$l_{STPD}.l^{-1}$
C_{ve}	viscoelastic compliance of lung	$l^{-1}.cmH_2O$
$C_{v_{O_2}}$	concentration of bound and dissolved O_2 in the mixed venous blood entering the lungs	$l_{STPD}.l^{-1}$
C_{vp}	compliance of the venous part of the pulmonary circuit	$l.mmHg^{-1}$
C_{vs}	compliance of the venous part of the systemic circuit	$l.mmHg^{-1}$
$F_{A_{CO_2}}$	fractional concentration of CO_2 in the alveolar gas mixture	-
$F_{A_{O_2}}$	fractional concentration of O_2 in the alveolar gas mixture	-
F_B	blood flow perfusing the brain tissue compartment	$l.min^{-1}$
F_{B_0}	cerebral blood flow for $P_{a_{CO_2}} = 40$	$l.min^{-1}$
$F_{I_{CO_2}}$	fractional concentration of CO_2 in the inspired gas mixture	-
$F_{I_{O_2}}$	fractional concentration of O_2 in the inspired gas mixture	-
F_p	blood flow perfusing the lung compartment	$l.min^{-1}$
F_s	blood flow perfusing the tissue compartment	$l.min^{-1}$
H	heart rate	min^{-1}
G_c	central controller gain factor	$l.(min.mmHg)^{-1}$
G_p	peripheral controller gain factor	$l.(min.mmHg)^{-1}$
γ_l	coefficient of σ_l in the differential equation for σ_l	min^{-1}
γ_r	coefficient of σ_r in the differential equation for σ_r	min^{-1}
I_c	constant for central drive of ventilation	$mmHg$

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
I_p	constant for peripheral drive of ventilation	$mmHg$
K_1	constant for the O_2 dissociation curve	$l_{STPD}.l^{-1}$
K_2	constant for the O_2 dissociation curve	$mmHg^{-1}$
K_{CO_2}	slope of the physiological CO_2 dissociation curve	$l_{STPD}.(l.mmHg)^{-1}$
k_{CO_2}	constant for the physiological CO_2 dissociation curve	$l_{STPD}.l^{-1}$
κ	duration of the systole $= \kappa.\sqrt{duration\_of\_heart\_cycle}$	$sec^{1/2}$
K_c	collapsible airways resistance scaling parameter	$cmH_2O.sec.l^{-1}$
K_l	lung recoil pressure scaling parameter	l^{-1}
K_s	small airways resistance scaling parameter	-
K_u	upper airways resistance scaling parameter	$cmH_2O.sec^2.l^{-2}$
$MR_{B_{CO_2}}$	metabolic rate of CO_2 production in brain tissue	$l_{STPD}.min^{-1}$
$MR^r_{co_2}$	steady state metabolic CO_2 production rate during rest	$l_{STPD}.min^{-1}$
$MR^e_{co_2}$	steady state metabolic CO_2 production rate during exercise	$l_{STPD}.min^{-1}$
$MR^e_{o_2}$	steady state metabolic O_2 consumption rate during exercise	$l_{STPD}.min^{-1}$
$MR^r_{o_2}$	steady state metabolic O_2 consumption rate during rest	$l_{STPD}.min^{-1}$
P_a	ambient pressure	$mmHg$
$P_{a_{CO_2}}$	partial pressure of CO_2 in arterial blood	$mmHg$
$P_{a_{O_2}}$	partial pressure of O_2 in arterial blood	$mmHg$
P_A	alveolar pressure	cmH_2O
$P_{A_{CO_2}}$	partial pressure of CO_2 in alveolar air	$mmHg$

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
$P_{A_{O_2}}$	partial pressure of O_2 in alveolar air	$mmHg$
P_{ap}	mean blood pressure in the venous region of the pulmonary circuit	$mmHg$
P_{as}	mean blood pressure in the arterial region of the systemic circuit	$mmHg$
P_{atm}	external atmospheric pressure	$mmHg$
$P_{atm_{CO_2}}$	atmospheric CO_2 pressure	$mmHg$
$P_{atm_{O_2}}$	atmospheric CO_2 pressure	$mmHg$
P_C	collapsible airways pressure	cmH_2O
$P_{C_{O_2}}$	O_2 pressure across collapsible airways	$mmHg$
$P_{C_{CO_2}}$	CO_2 pressure across collapsible airways	$mmHg$
P_{cw}	chest wall recoil pressure	cmH_2O
P_{CO_2}	general symbol for partial pressure of CO_2	$mmHg$
P_D	pressure in the lung dead space	cmH_2O
$P_{D_{O_2}}$	O_2 pressure across dead space	$mmHg$
$P_{D_{CO_2}}$	CO_2 pressure across dead space	$mmHg$
$P_{I_{CO_2}}$	partial pressure of CO_2 in inspired air	$mmHg$
$P_{I_{O_2}}$	partial pressure of O_2 in inspired air	$mmHg$
P_{O_2}	general symbol for partial pressure of O_2	$mmHg$
P_{pl}	pleural pressure	cmH_2O
P_{stp}	standard pressure	$mmHg$
P_{tm}	transmural pressure across pleural space & collapsible airways	

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
$P_{v_{CO_2}}$	partial pressure of CO_2 in mixed venous blood entering the lungs	$mmHg$
P_{ve}	viscoelastic pressure	cmH_2O
$P_{v_{O_2}}$	partial pressure of O_2 in mixed venous blood entering the lungs	$mmHg$
P_{vs}	mean blood pressure in the venous region of the systemic circuit	$mmHg$
q_{as}	weighting factor of P_{as} in the cost functional	$mmHg^{-2}$
q_c	weighting factor of $P_{a_{CO_2}}$ in the cost functional	$mmHg^{-2}$
q_o	weighting factor of $P_{a_{O_2}}$ in the cost functional	$mmHg^{-2}$
q_1	weighting factor of u1 in the cost functional	min^4
q_2	weighting factor of u2 in the cost functional	$min^4.l_{BTPS}^{-2}$
$\dot{Q}_{CA}$	airflow from collapsible airways to alveolar region	$ml.sec^{-1}$
$\dot{Q}_{DC}$	airflow from upper airways to collapsible airways	$ml.sec^{-1}$
$\dot{Q}_{ED}$	airflow from environment to upper airways	$ml.sec^{-1}$
Q_l	left cardiac output	$l.min^{-1}$
Q_r	right cardiac output	$l.min^{-1}$
Q_{tot}	total gas exchange of all species from the alveolar region to the blood in the capillary across the alveolar capillary barrier	$ml.sec^{-1}$
$\dot{Q}_{VE}$	airflow through viscoelastic kelvin body	$ml.sec^{-1}$
R_c	resistance of collapsible airways	$cmH_2O.sec.l^{-1}$
R_l	viscous resistance of the left ventricle	$mmHg.sec.l^{-1}$
R_r	viscous resistance of the right ventricle	$mmHg.sec.l^{-1}$

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
R_p^r	steady state value of pulmonary resistance during rest	$mmHg.min.l^{-1}$
R_p^e	steady state value of pulmonary resistance during exercise	$mmHg.min.l^{-1}$
R_{pl}	resistance in the peripheral region of the pulmonary circuit	$mmHg.min.l^{-1}$
RQ	respiratory quotient of the chemical reactions in the tissues	-
R_s	peripheral resistance in the systemic circuit	$mmHg.min.l^{-1}$
R_{sm}	resistance of small airways	$cmH_2O.sec.l^{-1}$
R_{ve}	resistance of lung viscoelastance	$cmH_2O.sec.l^{-1}$
R_u	resistance of upper airways	$cmH_2O.sec.l^{-1}$
ρ	constant relating imposed workload and metabolic rate	$l.(min.Watt)^{-1}$
S_l	contractility of the left ventricle	$mmHg$
S_r	contractility of the right ventricle	$mmHg$
t_d	duration of the diastole	sec
σ_l	derivative of S_l	$mmHg.min^{-1}$
σ_r	derivative of S_r	$mmHg.min^{-1}$
τ_a	time constant of mro2	min
τ_p	time constant of rp1	min
τ_s	time constant of A_{pesk}	min
u_1	control function, $u_1 = \dot{H}$	min^{-2}
u_2	control function, $u_2 = \dot{V}_A$	$l_{BTPS}.min^{-2}$
V_A	Alveolar gas volume	l_{BTPS} ,l
$V_{A_{O_2}}$	effective O_2 storage volume of the lung compartment	l_{BTPS}

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
$V_{A_{CO_2}}$	effective CO_2 storage volume of the lung compartment	l_{BTPS}
V_{ap}	blood volume in pulmonary arterial compartment	l
V_{as}	blood volume in systemic arterial compartment	l
$\dot{V}_{A_0}$	airflow detected by the flow transducer at mouthpiece	$ml.sec^{-1}$
$\dot{V}_{av}$	alveolar ventilation	$l_{BTPS}.min^{-1}$
$\ddot{V}_{av}$	time derivative of alveolar ventilation	$l_{BTPS}.min^{-2}$
$V_{B_{CO_2}}$	effective brain tissue storage volume for CO_2	l
V_c	volume of collapsible airways	l
V_{cmax}	collapsible airways resistance parameter	l
V_{cw}	chest wall volume	l
V_d^l	end-diastolic volume of the left ventricle	l
V_d^r	end-diastolic volume of the right ventricle	l
V_D	dead space	l
$\dot{V}_D$	dead space ventilation	$l_{BTPS}.min^{-1}$
$\dot{V}_E$	total ventilation	$l_{BTPS}.min^{-1}$
V_0	total blood volume	l
V_r^l	rest volume of the left ventricle	l
V_r^r	rest volume of the right ventricle	l
V_{star}	small airways resistance parameter	l
V_{str}^l	stroke volume of the left ventricle	l
V_{str}^r	stroke volume of the right ventricle	l
V_T	tidal volume	l

Table B.1.Glossary for Notation

SYMBOL	DESCRIPTION	UNIT
$V_{T_{O_2}}$	effective tissue storage volume for O_2	l
$V_{T_{CO_2}}$	effective tissue storage volume for CO_2	l
V_{ve}	lung viscoelastic volume	l
V_{vp}	blood volume in pulmonary venous compartment	l
V_{vs}	blood volume in systemic venous compartment	l
W	imposed workload	*Watt*

APPENDIX C

NUMERICAL VALUES FROM LITERATURE

The numerical values collected from literature, are obtained by different methods, such as experimental measurements, empirical estimation, or parameter fitting. They are average values under resting conditions.

Most of the values not given here can be found in the papers by Kappel and Peer [17], [18], Kappel et al. [19], and Lafer [20]. The sources of the values given here can be looked up from [27] and [30].

Table C.1 Numerical Values from Literature

SYMBOL	VALUE FROM LITERATURE	UNIT
A_c		cmH_2O
	7.09	cmH_2O
	8.27	cmH_2O
	9.39	cmH_2O
	10.67	cmH_2O
A_{cw}	1.4	-
	4.4	-
A_l		cmH_2O
	0.2	cmH_2O
	0.04	cmH_2O
	0.1	cmH_2O
	0.57	cmH_2O

Table C.1 Numerical Values from Literature

SYMBOL	VALUE FROM LITERATURE	UNIT
A_s	2.2 2.8 2.47 5.47	$cmH_2O.sec.l^{-1}$
A_u	0.34 0.31	$cmH_2O.sec.l^{-1}$ $cmH_2O.sec.l^{-1}$
B_c	37.3 66.8 94.9 127.0	cmH_2O cmH_2O cmH_2O cmH_2O
B_c'	3.73 6.69 9.50 12.7	cmH_2O cmH_2O cmH_2O cmH_2O
B_{cw}	-3.5	cmH_2O
B_l	-0.5 1.0 1.5 0.0	cmH_2O cmH_2O cmH_2O cmH_2O
B_s	0.02	$cmH_2O.sec.l^{-1}$
$C_{a_{CO_2}}$	0.493	$l_{STPD}.l^{-1}$
$C_{a_{O_2}}$	0.197	$l_{STPD}.l^{-1}$
$C_{v_{CO_2}}$	0.535	$l_{STPD}.l^{-1}$
C_{ve}	0.5	$l^{-1}.cmH_2O$

Table C.1 Numerical Values from Literature

SYMBOL	VALUE FROM LITERATURE	UNIT
$C_{v_{O_2}}$	0.147	$l_{STPD}.l^{-1}$
F_B	0.5 0.75 12-15 % of resting cardiac output	$l.(min.kg\_brain\_tissue)^{-1}$ $l.min^{-1}$ $l.min^{-1}$
G_c	1.440 3.2	$l.(min.mmHg)^{-1}$ $l.(min.mmHg)^{-1}$
G_p	30.240 26.5	$l.(min.mmHg)^{-1}$ $l.(min.mmHg)^{-1}$
H	70	min^{-1}
I_c	35.5 45.0	$mmHg$ $mmHg$
I_p	35.5 38.0	$mmHg$ $mmHg$
K_1	0.2	$l_{STPD}.l^{-1}$
K_2	0.046 0.05	$mmHg^{-1}$
K_c	0.21 0.49 0.50 0.24	$cmH_2O.sec.l^{-1}$ $cmH_2O.sec.l^{-1}$ $cmH_2O.sec.l^{-1}$ $cmH_2O.sec.l^{-1}$
K_{CO_2}	0.0065 0.0057	$l_{STPD}.(l.mmHg)^{-1}$ $l_{STPD}.(l.mmHg)^{-1}$
k_{CO_2}	0.244	$l_{STPD}.l^{-1}$

Table C.1 Numerical Values from Literature

SYMBOL	VALUE FROM LITERATURE	UNIT
K_l	1.0	l^{-1}
	0.8	l^{-1}
K_s	-10.9	-
	-9.9	-
	-6.5	-
	-5.13	-
K_u		$cmH_2O.sec^2.l^{-2}$
	0.46	$cmH_2O.sec^2.l^{-2}$
	0.40	$cmH_2O.sec^2.l^{-2}$
	0.32	
	0.20	$cmH_2O.sec^2.l^{-2}$
$MR_{B_{CO_2}}$	0.042	$l_{STPD}.min^{-1}$
	0.031	$l_{STPD}.(min.kg\_brain\_tissue)^{-1}$
	0.054	$l_{STPD}.min^{-1}$
MR_{co_2}	0.21	$l_{STPD}.min^{-1}$
	0.26	$l_{STPD}.min^{-1}$
MR_{o_2}	0.26	$l_{STPD}.min^{-1}$
	0.31	$l_{STPD}.min^{-1}$
$P_{a_{CO_2}}$	40	$mmHg$
$P_{a_{O_2}}$	95	$mmHg$
	90	$mmHg$
P_{ap}	12	$mmHg$
P_{as}	100	$mmHg$
P_{atm}	760	$mmHg$
$P_{C_{CO_2}}$	22.21	$mmHg$

Table C.1 Numerical Values from Literature

SYMBOL	VALUE FROM LITERATURE	UNIT
$P_{C_{O_2}}$	123.87	$mmHg$
$P_{D_{CO_2}}$	13.68	$mmHg$
$P_{D_{O_2}}$	133.9	$mmHg$
$P_{H_2O\_Tbody}$	47	$mmHg$
$P_{I_{CO_2}}$	0	$mmHg$
$P_{I_{O_2}}$	150	$mmHg$
$P_{v\,CO_2}$	45 46	$mmHg$ $mmHg$
$P_{v\,O_2}$	40	$mmHg$
P_{vp}	5	$mmHg$
P_{vs}	2-4	$mmHg$
$Q_l = Q_r =$ $F_p = F_s$	6 6.2 5	$l.min^{-1}$ $l.min^{-1}$ $l.min^{-1}$
R_p	0.965	$mmHg.min.l^{-1}$
R_s	20.	$mmHg.min.l^{-1}$
R_{ve}	1.0	$cmH_2O.sec.l^{-1}$
RQ	1.4 0.88 0.81	- - -
V_0	5	l
V_A	3.12	l

Table C.1 Numerical Values from Literature

SYMBOL	VALUE FROM LITERATURE	UNIT
$V_{A_{CO_2}}$	3.2	l_{BTPS}
	3.0	l_{BTPS}
$V_{A_{O_2}}$	2.5	l_{BTPS}
	3.0	l_{BTPS}
	0.5	l_{BTPS}
$\dot{V}_{av}$	4.038	$l_{BTPS}.min^{-1}$
	5.6	$l_{BTPS}.min^{-1}$
$V_{B_{CO_2}}$	0.9	l
	1.0	l
	1.1	l
V_c	0.08	l
$V_{C_{max}}$	0.185	l
	0.125	l
	0.165	l
	0.101	l
V_{cw}	2.25	l
$\dot{V}_D$	2.4	$l_{BTPS}.min^{-1}$
	2.28	$l_{BTPS}.min^{-1}$
$\dot{V}_E$	8	$l_{BTPS}.min^{-1}$
V_{str}^{l}	0.070	l
V_T	0.5	l
$V_{T_{CO_2}}$	15	l
$V_{T_{O_2}}$	6	l
V_{ve}	-0.08	l

Table C.1 Numerical Values from Literature

SYMBOL	VALUE FROM LITERATURE	UNIT
	5.3	l
	10.3	l
	8.41	l
V^*	7.37	l

APPENDIX D

EXERCISE TEST DATA

D1. Test Data and Graphics for Subject 1

BASKENT ÜNIVERSITESI

Solunum Fonksiyon Testleri

Soyad-Ad: Subject 1
Prot. No: 362700
Tarih: 19/08/06
Biomedikal Teknikeri : E. ERDEM

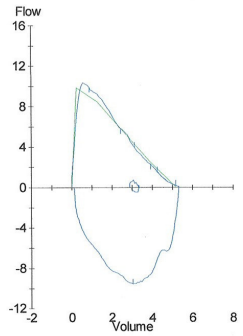
Yas: 32 Boy(cm): 180 Kilo(kg): 72.0 Cinsiyet: Male Irk: Caucasian

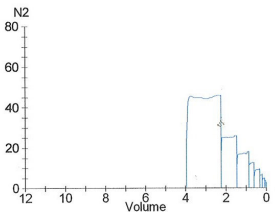
Standart Spirometri

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Chg
FVC	Liters	5.20	5.33	103		
FEV1	Liters	4.32	4.30	99		
FEV1/FVC	%		81			
FEF25-75%	L/sec	4.82	4.06	84		
FEF50%	L/sec	5.48	5.22	95		
FEF75-85%	L/sec		1.36			
FEF200-1200	L/sec		10.29			
PEF	L/sec	9.83	10.35	105		
PIF	L/sec		9.57			
MVV	L/min		118			
FIF50%	L/sec		9.47			
FEF/FIF50			0.55			
FEV1/SVC	%		78			

Akciger Volümleri

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
TLC	Liters	7.30	7.22	99			
VC	Liters	5.43	5.49	101			
IC	Liters		3.63				
FRC N2	Liters	3.41	3.59	105			
ERV	Liters		1.86				
RV	Liters	1.83	1.73	94			
RV/TLC	%	26	24				





Yorum:

Dr.Gaye ULUBAY

BASKENT ÜNIVERSITESI
SFT LABORATUVARI

Kardiyopulmoner Egzersiz Testi Özeti

Isim: Subject 1
Protokol No: 362700
Tarih: 19/08/06
Yas: 32 Irk: Caucasian
Boy: 180 Kilo: 72.0

	Beklenen	Ölçülen	% Beklenen
FVC (L)	5.20	5.33	103
FEV1 (L)	4.32	4.30	99
MVV (L)		118	

Istirahat HR (bpm): 71 SpO2: 92 SPB(mmHg): DPB (mmHg):

Kardiyovasküler cevap	Beklenen	Ölçülen	% Beklenen
VO2 (ml/kg/min)	42.4	46.8	110
VO2 (l/min)	3.176	3.369	106
VCO2 (l/min)		3.630	
Work (Watts)	245	223	91
Anaerobic Threshold (AT)(l/min)	> 1.270	2.752	
AT (% Predicted Max VO2)	> 40%	87	
Heart Rate (bpm)	180	70	(39)
O2 Pulse (ml/beat)	17.6	48.1	(274)
Systolic Blood Pressure (Max)	190		
Diastolic Blood Pressure (Max)	85-105		
Heart Rate Reserve (bpm)	<15	-67	
Pik solunum cevabi			
VE Max (l/min) BTPS	136.3	119.7	88
Tidal Volume (VT) (L)	3.039	3.365	111
Respiratory Rate (RR)	<50	31	
Breathing Reserve (%)	20-40	-1	
Gaz degisim cevabi			
End Tidal CO2 (Peak PetCO2)			
End Tidal O2 (Peak PetO2)			
VE/VO2 @ AT			
VE/VCO2 @ AT			
VD/VT (Est) @ Rest	0.30	0.17	(55)
VD/VT (Est) Peak	0.18	0.05	(28)
Respiratory Quotient (RQ)(Peak)	1.1-1.3	1.08	
SpO2 (O2 Sat--Pulse Ox) @ Peak	96	93	

Kalibrasyon

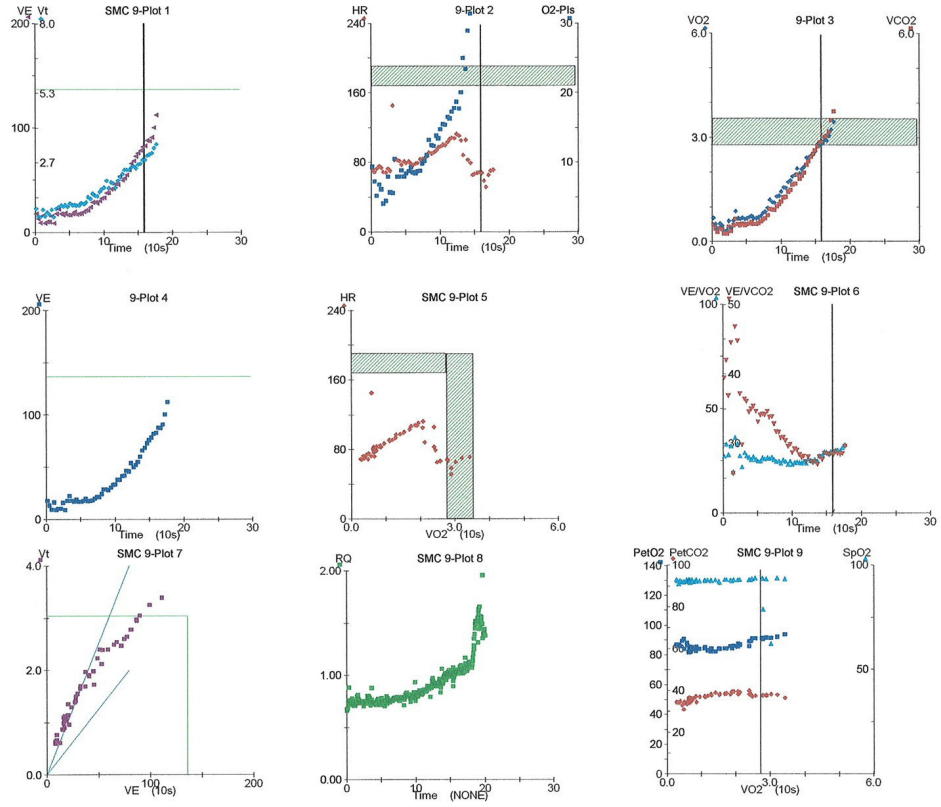
Akim kal. Pred Volume: 3.00 Expire Avg: 3.00 Inspire Avg: 2.94

Gaz kal.	Cal1 O2	Cal 1 CO2	Cal 2 O2	Cal 2 CO2	Ambient O2	Ambient CO2
Beklenen	16.00	4.00	26.00	0.00		
Ölçülen	16.06	4.03	26.09	0.02	20.73	0.14
Geçis (msec)	0.572	0.469				
Cevap (msec)	0.120	0.085				

Kardiyopulmoner Egzersiz Testi Grafikleri: 9-Plot

Isim: Subject 1
Tarih: 19/08/06
Yas: 32

Protokol No: 362700
Boy: 71
Kilo: 158



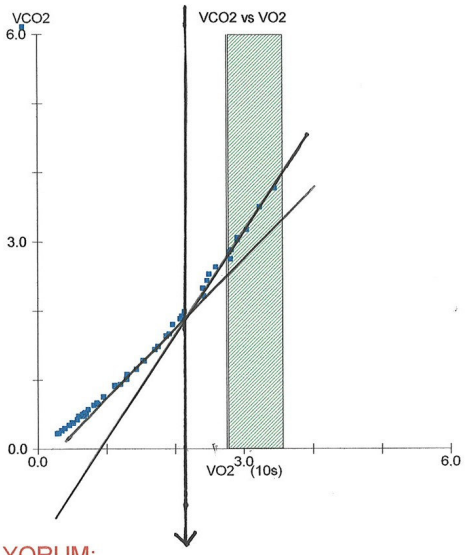
Ölçüm (pik):	Beklenen	Ölçülen	% Ölçülen	Plot #
VO2 (l/min)	3.176	3.369	106	1,3
Work Rate (Watts)	245	223	91	3
HR (bpm)	180	70	(39)	2
O2 Pulse (ml/beat)	17.6	48.1	(274)	5
Respiratory Quotient (RQ)	1.1-1.3	1.08		8
VE Max (l/min) BTPS	136.3	119.7	88	1,7
Breathing Reserve (%)	20-40	-1		1,7
AT (l/min)	1.270	2.752		1,5,6,9
Slope hesaplamasi			(Normal Range)	
VO2/Work (ml/min/watt)	10.3		8.7-11.9	3
HR/VO2kg (bpm/ml/kg)	3.8		3.0-4.0	2,5
VE/VO2 (L BTPS/L STPD)	27.5		23-26	1,6
VE/VCO2 (L BTPS/L STPD)	22.7		26-29	3

BASKENT ÜNIVERSITESI
SFT LABORATUVARI

Isim: Subject 1
Protokol No: 362700
Tarih: 19/08/06
Yas: 32 Irk: Caucasian
Boy: 180 Kilo: 72.0

Kardiyopulmoner Egzersiz Testi Sonucu

VCO2 vs VO2 (AT profili)



YORUM:

Anaerobik Threshold değerleri

AT VO_2 = 2.100 L /dk

AT HR = 120

AT VE = 53

AT RQ = 0,90.

Doktor: Dr.Gaye ULUBAY

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
Test Stage	Baseline								
00:00:00		0,435	6	0,292	0,67	8,2	11	70	6,2
00:00:04		0,432	6	0,285	0,66	7,8	16	72	6
00:00:08		0,432	6	0,288	0,67	8,9	16	72	6
00:00:13		0,487	6,8	0,33	0,68	15,4	11	72	6,8
00:00:15		1,373	19,1	1,004	0,73	23,5	44	72	19,1
00:00:20		0,198	2,7	0,174	0,88	8	36	67	3
00:00:23		0,372	5,2	0,274	0,74	8,8	20	68	5,5
00:00:25		1,648	22,9	1,176	0,71	28,4	24	68	24,2
00:00:27		0,228	3,2	0,173	0,76	8,4	31	67	3,4
00:00:32		0,563	7,8	0,419	0,74	8,7	13	70	8
00:00:36		0,492	6,8	0,365	0,74	4,4	15	72	6,8
00:00:40		0,5	6,9	0,369	0,74	6,4	14	72	6,9
00:00:45	0	0,473	6,6	0,351	0,74	5,5	13	73	6,5
00:00:49	0	0,226	3,1	0,174	0,77	4,7	16	72	3,1
00:00:53	0	0,246	3,4	0,187	0,76	7,3	15	73	3,4
00:00:56	0	0,246	3,4	0,181	0,74	7,9	16		
00:01:00	0	0,302	4,2	0,221	0,73	9,8	17	73	4,1
00:01:03		0,321	4,5	0,231	0,72	8,2	17	73	4,4
00:01:06		0,614	8,5	0,431	0,7	12,4	22	73	8,4
00:01:10		0,544	7,6	0,381	0,7	18,4	15	75	7,3
00:01:13		0,658	9,1	0,463	0,7	13	23	77	8,5
00:01:17		0,57	7,9	0,41	0,72	7,1	15	82	7
00:01:20		0,538	7,5	0,388	0,72	7,3	18	82	6,6
00:01:25		0,522	7,2	0,382	0,73	6,7	13	75	7
00:01:30		0,46	6,4	0,343	0,75	6,2	13	67	6,9
00:01:35	0	0,303	4,2	0,239	0,79	4,5	11	70	4,3
00:01:39		0,242	3,4	0,196	0,81	6,7	15	69	3,5
00:01:44		0,262	3,6	0,202	0,77	7,6	12	67	3,9
00:01:48		0,293	4,1	0,221	0,76	9,3	15	67	4,4
00:01:53	0	0,303	4,2	0,225	0,74	7,4	12	73	4,2
00:01:57	0	0,295	4,1	0,216	0,73	5,1	12	67	4,4

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:02:02		0,31	4,3	0,226	0,73	6,5	14	67	4,6
00:02:06		0,311	4,3	0,228	0,73	7	15	67	4,6
00:02:09		0,313	4,4	0,229	0,73	8,3	16	68	4,6
00:02:13		0,293	4,1	0,215	0,74	7,9	16	70	4,2
00:02:17		0,296	4,1	0,219	0,74	8,8	18	70	4,2
00:02:21		0,366	5,1	0,273	0,75	12,5	15	70	5,2
00:02:25		0,368	5,1	0,274	0,75	6,2	12	70	5,3
Test Stage - Warmup									
00:02:28		0,992	13,8	0,693	0,7	18,5	28	72	13,8
00:02:34		0,455	6,3	0,34	0,75	5,7	10	77	5,9
00:02:40		0,42	5,8	0,315	0,75	3,7	11	70	6
00:02:44	0	0,398	5,5	0,296	0,75	5,2	15	69	5,8
00:02:48	0	0,346	4,8	0,253	0,73	6,3	14	70	4,9
00:00:00		0,355	4,9	0,257	0,72	7,1	15	70	5,1
00:00:05		0,316	4,4	0,228	0,72	7,2	14	70	4,5
00:00:07		0,775	10,8	0,562	0,72	14,8	19	70	11,1
00:00:10		0,531	7,4	0,413	0,78	11,6	21		
00:00:12	0	0,647	9	0,515	0,8	14,1	23	247	2,6
00:00:16	19	0,558	7,8	0,443	0,79	11,6	18	247	2,3
00:00:19	19	0,555	7,7	0,438	0,79	12,1	18	90	6,2
00:00:23	19	0,585	8,1	0,458	0,78	12,4	18	82	7,1
00:00:26	19	0,565	7,8	0,44	0,78	11,6	15	77	7,3
00:00:30	19	0,584	8,1	0,451	0,77	11,8	17	80	7,3
00:00:34	19	0,637	8,8	0,476	0,75	12,3	16	85	7,5
00:00:37	19	0,78	10,8	0,58	0,74	14,9	18	84	9,3
00:00:38	19	2,376	33	1,683	0,71	35,7	53	85	28
00:00:41	19	0,576	8	0,419	0,73	13,4	21	82	7
00:00:45	19	0,624	8,7	0,475	0,76	13,3	18	85	7,3
00:00:49	19	0,57	7,9	0,497	0,87	12,2	15	82	7
00:00:53	19	0,529	7,3	0,387	0,73	10	15	84	6,3
00:00:56	19	0,703	9,8	0,513	0,73	12,9	17	82	8,6
00:00:59	19	0,724	10,1	0,528	0,73	13,9	17	82	8,8
00:01:03	19	0,692	9,6	0,51	0,74	13,2	18	82	8,4

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:01:07	19	0,765	10,6	0,563	0,74	14,6	17	82	9,3
00:01:10	19	0,498	6,9	0,366	0,74	9,9	15	83	6
00:01:14	19	0,622	8,6	0,452	0,73	11,7	16	82	7,6
00:01:18	19	0,654	9,1	0,472	0,72	12,3	17	83	7,9
00:01:21	19	0,679	9,4	0,486	0,71	12,4	16	79	8,6
00:01:24	19	0,695	9,6	0,5	0,72	12,7	18	80	8,7
00:01:27	19	0,79	11	0,576	0,73	14,8	19	79	10
00:01:32	19	0,635	8,8	0,474	0,75	12,6	17	80	7,9
00:01:35	19	0,741	10,3	0,554	0,75	14,5	18	77	9,6
00:01:39	19	0,611	8,5	0,462	0,76	12	15	80	7,6
00:01:42	19	0,631	8,8	0,483	0,77	13	17	73	8,6
00:01:46	19	0,619	8,6	0,476	0,77	12,6	17	75	8,3
00:01:49	19	0,594	8,3	0,455	0,77	11,7	16	79	7,5
00:01:52	19	0,492	6,8	0,363	0,74	10,3	19	82	6
00:01:55	19	0,676	9,4	0,482	0,71	12,5	19	80	8,4
00:01:59	19	0,691	9,6	0,496	0,72	12,5	15	82	8,4
00:02:04	19	0,701	9,7	0,5	0,71	12,1	16	82	8,6
00:02:08	19	0,684	9,5	0,496	0,73	12,4	15	75	9,1
00:02:13	19	0,673	9,4	0,524	0,78	12,3	11	80	8,4
00:02:16	19	0,606	8,4	0,45	0,74	11,3	16	82	7,4
00:02:20	19	0,66	9,2	0,487	0,74	12	16	79	8,4
00:02:24	19	0,692	9,6	0,506	0,73	12,4	16	81	8,5
00:02:28	19	0,709	9,8	0,516	0,73	12,6	15	82	8,6
00:02:32	19	0,485	6,7	0,357	0,73	9,7	15	80	6,1
00:02:36	19	0,877	12,2	0,621	0,71	15,5	17	80	11
00:02:41	19	0,475	6,6	0,355	0,75	9,1	11	82	5,8
00:02:43	19	0,787	10,9	0,55	0,7	13,7	20	82	9,6
00:02:48	19	0,892	12,4	0,658	0,74	15,8	17	82	10,9
00:02:51	19	0,752	10,5	0,565	0,75	14,4	18	82	9,2
00:02:53	19	0,855	11,9	0,648	0,76	16,6	20	77	11,1
00:02:57	19	0,61	8,5	0,484	0,79	12,5	18	77	7,9
00:03:00	19	0,642	8,9	0,5	0,78	12,9	18	77	8,3
Test Stage - Exercise									

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:00:00	19	0,671	9,3	0,521	0,78	13,5	18	80	8,4
00:00:03	19	0,602	8,4	0,435	0,72	11,4	17	77	7,8
00:00:06	19	0,625	8,7	0,479	0,77	12,3	16	77	8,1
00:00:10	19	0,823	11,4	0,62	0,75	14,6	17	77	10,7
00:00:14	19	0,528	7,3	0,399	0,76	10,3	15	75	7
00:00:17	19	0,671	9,3	0,501	0,75	12,8	17	78	8,6
00:00:22	19	0,6	8,3	0,443	0,74	11,8	17	77	7,8
00:00:25	19	0,637	8,8	0,475	0,75	12,3	17	75	8,5
00:00:28	19	0,679	9,4	0,51	0,75	13,4	18	78	8,7
00:00:31	19	0,601	8,4	0,452	0,75	11,9	18	80	7,5
00:00:35	19	0,696	9,7	0,527	0,76	13,3	17	77	9
00:00:39	19	0,682	9,5	0,512	0,75	12,9	16	81	8,4
00:00:43	19	0,669	9,3	0,502	0,75	12,4	15	82	8,2
00:00:46	19	0,653	9,1	0,488	0,75	12,6	16	78	8,4
00:00:50	19	0,736	10,2	0,562	0,76	13,9	16	80	9,2
00:00:54	19	0,649	9	0,497	0,77	12,6	16	77	8,4
00:00:58	19	0,743	10,3	0,572	0,77	14,2	16	80	9,3
00:01:02	19	0,633	8,8	0,493	0,78	12,7	17	80	7,9
00:01:06	37	0,642	8,9	0,5	0,78	12,9	16	82	7,8
00:01:09	37	0,721	10	0,564	0,78	14,3	18	82	8,8
00:01:12	37	0,823	11,4	0,637	0,77	15,7	19	82	10
00:01:15	37	0,723	10	0,566	0,78	14,1	18	84	8,6
00:01:19	37	0,806	11,2	0,63	0,78	15,5	19	87	9,3
00:01:22	37	0,746	10,4	0,576	0,77	14,7	19	87	8,6
00:01:25	37	1,17	16,2	0,894	0,76	20,2	19	85	13,8
00:01:28	37	0,657	9,1	0,517	0,79	13	17	84	7,8
00:01:31	37	0,677	9,4	0,524	0,77	13	17	87	7,8
00:01:34	37	0,814	11,3	0,624	0,77	15,3	19	80	10,2
00:01:39	37	0,8	11,1	0,625	0,78	15,4	18	80	10
00:01:43	37	0,716	9,9	0,554	0,77	13,3	15	87	8,2
00:01:46	37	0,753	10,5	0,565	0,75	13,2	16	84	9
00:01:50	37	0,839	11,7	0,625	0,75	14,6	16	85	9,9
00:01:54	37	1,138	15,8	0,891	0,78	20,4	13	86	13,2

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:01:58	37	0,773	10,7	0,598	0,77	14,6	17	79	9,8
00:02:01	37	0,836	11,6	0,648	0,77	15,6	17	85	9,8
00:02:04	56	0,92	12,8	0,716	0,78	16,6	18	87	10,6
00:02:07	56	0,955	13,3	0,75	0,78	18	19	83	11,5
00:02:10	56	0,794	11	0,627	0,79	15,3	18	87	9,1
00:02:15	56	0,983	13,6	0,768	0,78	17,8	18	90	10,9
00:02:18	56	0,96	13,3	0,743	0,77	17,2	19	87	11
00:02:21	56	1,251	17,4	0,972	0,78	21,8	18	87	14,4
00:02:26	56	0,574	8	0,444	0,77	10,2	12	94	6,1
00:02:28	56	1,241	17,2	0,878	0,71	20,2	21	92	13,5
00:02:32	56	1,432	19,9	1,092	0,76	24,9	21	92	15,6
00:02:35	56	1,334	18,5	1,041	0,78	23,6	19	91	14,7
00:02:38	56	1,116	15,5	0,885	0,79	20,4	18	93	12
00:02:41	56	1,272	17,7	1,026	0,81	23,3	21	90	14,1
00:02:43	56	1,292	18	1,062	0,82	24,3	21	90	14,4
00:02:47	56	1,11	15,4	0,915	0,82	21,1	19	92	12,1
00:02:50	56	0,925	12,8	0,763	0,83	17,2	18	94	9,8
00:02:53	56	1,009	14	0,806	0,8	18,5	18	89	11,3
00:02:56	56	1,161	16,1	0,929	0,8	21,2	21	86	13,5
00:02:59	56	1,213	16,9	0,973	0,8	22,6	22	89	13,6
00:03:02	56	1,176	16,3	0,94	0,8	21,5	20	93	12,6
00:03:05	56	1,152	16	0,935	0,81	21,2	20	92	12,5
00:03:07	74	1,004	13,9	0,812	0,81	18,6	21	90	11,2
00:03:11	74	1,163	16,2	0,937	0,81	21	19	92	12,6
00:03:14	74	1,222	17	0,99	0,81	22,6	20	90	13,6
00:03:17	74	0,983	13,7	0,796	0,81	18,4	19	90	10,9
00:03:20	74	1,205	16,7	0,934	0,78	20,3	19	93	13
00:03:24	74	1,035	14,4	0,8	0,77	17,6	17	95	10,9
00:03:27	74	1,168	16,2	0,87	0,74	19,1	18	88	13,3
00:03:30	74	1,388	19,3	1,075	0,77	23,7	18	92	15,1
00:03:33	74	1,418	19,7	1,095	0,77	24,2	20	95	14,9
00:03:37	74	1,263	17,5	0,997	0,79	22,1	20	92	13,7
00:03:39	74	1,377	19,1	1,081	0,79	23,8	21	95	14,5

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:03:42	74	1,394	19,4	1,104	0,79	23,4	19	97	14,4
00:03:45	74	1,439	20	1,144	0,8	25,4	19	97	14,8
00:03:49	74	1,543	21,4	1,245	0,81	27,4	20	97	15,9
00:03:51	74	1,433	19,9	1,177	0,82	26,8	21	97	14,8
00:03:54	74	1,511	21	1,249	0,83	27,6	20	97	15,6
00:03:56	74	1,178	16,4	0,98	0,83	22,3	21	97	12,1
00:04:02	74	0,727	10,1	0,675	0,93	14	11	98	7,4
00:04:05	93	1,498	20,8	1,119	0,75	23	21	97	15,4
00:04:09	93	1,601	22,2	1,259	0,79	26,7	19	97	16,5
00:04:11	93	1,583	22	1,269	0,8	27,1	20	97	16,3
00:04:14	93	1,504	20,9	1,218	0,81	26,6	20	97	15,5
00:04:18	93	1,398	19,4	1,144	0,82	24,8	19	100	14
00:04:21	93	1,258	17,5	1,015	0,81	21,7	19	100	12,6
00:04:23	93	1,39	19,3	1,103	0,79	23,4	19	100	13,9
00:04:27	93	1,743	24,2	1,392	0,8	29,7	14	100	17,4
00:04:31	93	1,475	20,5	1,205	0,82	26,6	20	99	14,9
00:04:34	93	1,553	21,6	1,293	0,83	28,1	21	100	15,5
00:04:36	93	1,457	20,2	1,214	0,83	26,7	21	102	14,3
00:04:40	93	1,698	23,6	1,413	0,83	30,5	22	101	16,8
00:04:42	93	1,566	21,8	1,315	0,84	29,1	22	100	15,7
00:04:44	93	1,576	21,9	1,334	0,85	29,5	23	97	16,2
00:04:48	93	1,463	20,3	1,239	0,85	27,3	21	99	14,8
00:04:50	93	1,554	21,6	1,308	0,84	27,9	21	102	15,2
00:04:52	93	1,545	21,5	1,292	0,84	27,6	24	102	15,1
00:04:56	93	1,502	20,9	1,226	0,82	26,5	21	102	14,7
00:04:59	93	1,476	20,5	1,204	0,82	25,6	21	102	14,5
00:05:01	93	1,597	22,2	1,289	0,81	27,1	21	97	16,5
00:05:05	93	1,562	21,7	1,275	0,82	27,3	21	99	15,8
00:05:07	111	1,597	22,2	1,32	0,83	27,6	20	102	15,7
00:05:10	111	1,823	25,3	1,499	0,82	31,4	22	104	17,5
00:05:13	111	1,855	25,8	1,568	0,85	33,7	22	101	18,4
00:05:15	111	1,742	24,2	1,482	0,85	31,7	22	102	17,1
00:05:18	111	1,699	23,6	1,448	0,85	30,3	21	107	15,9

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:05:22	111	1,712	23,8	1,464	0,86	30,6	20	107	16
00:05:24	111	1,528	21,2	1,289	0,84	26,9	20	104	14,7
00:05:27	111	1,75	24,3	1,467	0,84	30,3	21	107	16,4
00:05:29	111	1,754	24,4	1,474	0,84	30,5	21	108	16,2
00:05:33	111	1,947	27	1,635	0,84	34,4	23	107	18,2
00:05:35	111	1,636	22,7	1,389	0,85	29,4	22	107	15,3
00:05:38	111	1,996	27,7	1,672	0,84	34,8	27	109	18,3
00:05:40	111	1,785	24,8	1,517	0,85	31	23	109	16,4
00:05:43	111	1,825	25,3	1,559	0,85	32,8	23	107	17,1
00:05:46	111	1,747	24,3	1,506	0,86	31,2	24	107	16,3
00:05:47	111	2,873	39,9	2,439	0,85	48,3	32	107	26,8
00:05:49	111	1,657	23	1,438	0,87	32	33	109	15,2
00:05:51	111	1,694	23,5	1,5	0,89	32,1	25	109	15,5
00:05:53	111	1,612	22,4	1,438	0,89	30,3	24	109	14,8
00:05:55	111	2,069	28,7	1,79	0,87	36,9	42	109	19
00:05:57	111	1,928	26,8	1,687	0,88	34,7	25	110	17,5
00:06:00	111	1,595	22,2	1,378	0,86	28,9	23	107	14,9
00:06:03	111	1,671	23,2	1,454	0,87	29,8	22	107	15,6
00:06:06	130	1,846	25,6	1,597	0,86	32,8	25	107	17,3
00:06:08	130	2,101	29,2	1,83	0,87	37,4	26	107	19,6
00:06:11	130	1,964	27,3	1,754	0,89	36,1	25	107	18,4
00:06:13	130	1,733	24,1	1,547	0,89	32,7	24	107	16,2
00:06:18	130	1,334	18,5	1,177	0,88	22,1	12	110	12,1
00:06:20	130	2,525	35,1	1,99	0,79	38,4	27	109	23,2
00:06:23	130	2,297	31,9	1,998	0,87	41,2	23	112	20,5
00:06:25	130	2,093	29,1	1,848	0,88	38,1	23	112	18,7
00:06:28	130	1,943	27	1,73	0,89	35,7	23	113	17,2
00:06:31	130	2,082	28,9	1,875	0,9	38,4	26	112	18,6
00:06:31	130	3,426	47,6	3,031	0,88	60,7	40	112	30,6
00:06:34	130	1,803	25	1,711	0,95	37,9	24	112	16,1
00:06:37	130	1,724	23,9	1,67	0,97	36,5	24	112	15,4
00:06:39	130	1,642	22,8	1,548	0,94	31,8	21	112	14,7
00:06:43	130	1,921	26,7	1,754	0,91	35,1	21	112	17,1

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:06:46	130	2,005	27,8	1,856	0,93	38,5	18	112	17,9
00:06:48	130	1,925	26,7	1,755	0,91	34,6	22	107	18
00:06:50	130	1,859	25,8	1,66	0,89	33	22	109	17,1
00:06:54	130	2,013	28	1,832	0,91	37,8	20	111	18,1
00:06:56	130	2,247	31,2	2,054	0,91	42,5	25	112	20,1
00:06:59	130	1,812	25,2	1,675	0,92	34,9	24	112	16,2
00:07:02	130	2,022	28,1	1,849	0,91	36,9	23	111	18,2
00:07:04	130	1,946	27	1,742	0,9	34	22	111	17,5
00:07:08	148	2,104	29,2	1,928	0,92	40,1	18	112	18,8
00:07:11	149	2,026	28,1	1,821	0,9	36,5	22	111	18,3
00:07:13	149	2,274	31,6	2,022	0,89	40,9	24	112	20,3
00:07:15	149	2,116	29,4	1,918	0,91	39,8	22	112	18,9
00:07:19	149	2,002	27,8	1,812	0,9	36,5	22	84	23,8
00:07:21	149	2,163	30	1,952	0,9	39,5	23	85	25,4
00:07:23	149	2,146	29,8	1,938	0,9	39,4	23	88	24,4
00:07:26	149	2,226	30,9	2,038	0,92	41,1	23	87	25,6
00:07:29	149	2,125	29,5	1,943	0,91	39,9	23	87	24,4
00:07:32	149	2,355	32,7	2,16	0,92	43,4	24	87	27,1
00:07:34	149	2,226	30,9	2,057	0,92	41,5	24	92	24,2
00:07:36	149	2,197	30,5	2,044	0,93	41,4	24		
00:07:40	149	2,095	29,1	2,004	0,96	41,1	20		
00:07:43	149	1,242	17,3	1,17	0,94	23,9	18		
00:07:44	149	2,757	38,3	2,279	0,83	43,8	30	117	23,6
00:07:47	149	2,883	40	2,53	0,88	49,8	25	121	23,8
00:07:49	149	2,385	33,1	2,18	0,91	45,2	25	121	19,7
00:07:52	149	2,391	33,2	2,236	0,94	45,6	25	121	19,8
00:07:55	149	2,008	27,9	1,882	0,94	37,4	23	117	17,2
00:07:57	149	2,512	34,9	2,328	0,93	45,6	25	79	31,8
00:08:00	149	1,843	25,6	1,947	1,06	39,1	19	83	22,2
00:08:02	149	2,421	33,6	2,207	0,91	44,7	27	82	29,5
00:08:04	167	2,437	33,8	2,249	0,92	45,1	25	82	29,7
00:08:07	167	2,307	32	2,139	0,93	44,6	28	82	28,1
00:08:09	167	2,604	36,2	2,466	0,95	51,3	27	82	31,8

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:08:12	167	2,243	31,2	2,179	0,97	46,9	27	82	27,4
00:08:13	167	2,313	32,1	2,26	0,98	47,6	26	84	27,5
00:08:17	167	2,299	31,9	2,259	0,98	46,5	24	85	27,1
00:08:18	167	2,464	34,2	2,42	0,98	50,8	26	85	29
00:08:20	167	2,465	34,2	2,419	0,98	50,7	27	83	29,7
00:08:23	167	2,355	32,7	2,342	0,99	50,4	27	82	28,7
00:08:25	167	2,419	33,6	2,422	1	51,2	27	82	29,5
00:08:28	167	2,567	35,7	2,572	1	54,2	27	82	31,3
00:08:29	167	2,548	35,4	2,574	1,01	55,5	28	85	30
00:08:32	167	1,457	20,2	1,407	0,97	24,9	23	85	17,1
00:08:34	167	2,937	40,8	2,781	0,95	54,2	29	82	35,8
00:08:37	167	2,65	36,8	2,604	0,98	55,3	25	75	35,3
00:08:39	167	2,394	33,2	2,382	0,99	49,7	25	72	33,2
00:08:41	167	2,574	35,7	2,521	0,98	52,4	27	68	37,8
00:08:44	167	2,615	36,3	2,578	0,99	53,6	28	65	40,2
00:08:45	167	2,437	33,8	2,433	1	52,3	28	65	37,5
00:08:48	167	2,432	33,8	2,451	1,01	50,9	29	65	37,4
00:08:49	167	2,414	33,5	2,362	0,98	48	29	65	37,1
00:08:52	167	2,824	39,2	2,813	1	58,3	30	66	42,8
00:08:54	167	2,569	35,7	2,631	1,02	57	26	65	39,5
00:08:56	167	2,743	38,1	2,824	1,03	62,6	36	66	41,6
00:08:58	167	2,47	34,3	2,548	1,03	56,3	32	65	38
00:09:00	167	2,182	30,3	2,273	1,04	49,2	28	64	34,1
00:09:01	167	2,359	32,8	2,386	1,01	50,2	29	65	36,3
00:09:04	167	2,818	39,1	2,831	1	60,3	32	65	43,4
00:09:06	186	2,85	39,6	2,887	1,01	62,8	32	65	43,8
00:09:08	186	2,493	34,6	2,539	1,02	54,6	29	65	38,3
00:09:10	186	2,461	34,2	2,508	1,02	53,9	29	65	37,9
00:09:12	186	2,462	34,2	2,523	1,02	54,4	28	65	37,9
00:09:14	186	2,608	36,2	2,636	1,01	56,2	30	67	38,9
00:09:16	186	2,536	35,2	2,624	1,03	55,9	28	69	36,8
00:09:19	186	2,518	35	2,536	1,01	51,9	27	67	37,6
00:09:20	186	2,58	35,8	2,584	1	53,1	27	67	38,5

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:09:23	186	2,644	36,7	2,595	0,98	52,2	27	67	39,5
00:09:24	186	2,621	36,4	2,594	0,99	54,4	30	68	38,6
00:09:27	186	2,623	36,4	2,58	0,98	53,3	28	68	38,6
00:09:29	186	2,723	37,8	2,67	0,98	57	29	68	40
00:09:31	186	2,737	38	2,77	1,01	59,7	29	68	40,2
00:09:33	186	3,005	41,7	3,059	1,02	67,1	33	68	44,2
00:09:36	186	1,201	16,7	1,284	1,07	28,6	17	67	17,9
00:09:38	186	3,993	55,5	3,543	0,89	65,1	38	68	58,7
00:09:39	186	3,619	50,3	3,39	0,94	68	31	67	54
00:09:42	186	3,121	43,3	3,049	0,98	65,6	31	68	45,9
00:09:43	186	2,684	37,3	2,702	1,01	57,2	28	68	39,5
00:09:46	186	2,574	35,7	2,561	1	53,7	28	69	37,3
00:09:47	186	2,725	37,8	2,753	1,01	59,4	32	67	40,7
00:09:50	186	2,872	39,9	2,955	1,03	62	30	69	41,6
00:09:52	186	2,674	37,1	2,714	1,01	56,3	28	68	39,3
00:09:54	186	3,101	43,1	3,105	1	65,1	29	70	44,3
00:09:57	186	2,688	37,3	2,772	1,03	60,6	28	68	39,5
00:09:58	186	2,88	40	3,023	1,05	64,4	30	68	42,3
00:10:01	186	2,672	37,1	2,798	1,05	59	29	67	39,9
00:10:02	186	2,664	37	2,736	1,03	57,4	29	68	39,2
00:10:05	186	2,84	39,4	2,893	1,02	59,7	29	67	42,4
00:10:07	204	2,652	36,8	2,722	1,03	58,1	29	68	39
00:10:08	204	2,853	39,6	2,911	1,02	60,2	28		
00:10:11	204	2,759	38,3	2,796	1,01	58,5	29		
00:10:12	204	3,013	41,8	3,064	1,02	66,2	31		
00:10:15	204	2,805	39	2,897	1,03	62,7	33		
00:10:17	204	2,915	40,5	2,958	1,02	62,5	32	68	42,9
00:10:19	204	2,895	40,2	2,977	1,03	62,7	28	67	43,2
00:10:20	204	2,615	36,3	2,659	1,02	56,8	27	67	39
00:10:23	204	2,892	40,2	2,946	1,02	62,3	28		
00:10:24	204	2,849	39,6	2,896	1,02	61,3	30		
00:10:27	204	2,854	39,6	2,903	1,02	61,5	29		
00:10:29	204	2,715	37,7	2,76	1,02	57,8	30		

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:10:31	204	3,174	44,1	3,22	1,01	68,2	32		
00:10:32	204	3,155	43,8	3,31	1,05	73,2	31	60	52,6
00:10:35	204	2,983	41,4	3,208	1,08	70,8	29	73	40,9
00:10:36	204	2,708	37,6	2,835	1,05	61,9	29	72	37,6
00:10:39	204	2,915	40,5	3,047	1,05	63,2	29	48	60,7
00:10:41	204	2,975	41,3	3,119	1,05	66,1	27	45	66,1
00:10:43	204	2,987	41,5	3,18	1,06	68,2	30	48	62,2
00:10:45	204	2,898	40,2	3,077	1,06	67,2	30	50	58
00:10:48	204	2,77	38,5	3,019	1,09	65	26	50	55,4
00:10:49	204	2,936	40,8	3,102	1,06	65,6	30	53	55,4
00:10:52	204	3,032	42,1	3,14	1,04	66,6	29	52	58,3
00:10:54	204	3,037	42,2	3,184	1,05	67,5	31	53	57,3
00:10:56	204	2,849	39,6	2,999	1,05	64,9	30		
00:10:57	204	2,433	33,8	2,579	1,06	53,8	26		
00:11:00	204	3,036	42,2	3,078	1,01	62,7	30		
00:11:01	204	3,212	44,6	3,25	1,01	67,6	31		
00:11:04	204	3,189	44,3	3,282	1,03	69,4	31		
00:11:05	223	3,046	42,3	3,175	1,04	67,8	31		
00:11:08	223	3,055	42,4	3,156	1,03	66,7	30		
00:11:09	223	2,839	39,4	2,947	1,04	62,6	28		
00:11:12	223	2,984	41,4	3,046	1,02	63,7	30		
00:11:14	223	3,327	46,2	3,49	1,05	73,9	29		
00:11:16	223	2,812	39,1	3,001	1,07	63,3	25		
00:11:18	223	2,764	38,4	2,868	1,04	60,6	30	51	54,2
00:11:20	223	3,717	51,6	3,827	1,03	77,1	34	72	51,6
00:11:22	223	2,918	40,5	3,07	1,05	67,1	30	73	40
00:11:24	223	2,912	40,4	3,38	1,16	70,6	28	71	41
00:11:25	223	3,671	51	3,995	1,09	86,5	39	73	50,3
00:11:27	223	3,33	46,2	3,682	1,11	79,3	35	72	46,2
00:11:30	223	3,133	43,5	3,454	1,1	73,9	32	72	43,5
00:11:31	223	3,11	43,2	3,371	1,08	70,9	30	72	43,2
00:11:34	223	3,391	47,1	3,639	1,07	76,8	30	73	46,5
00:11:35	223	3,088	42,9	3,293	1,07	68,6	27	67	46,1

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:11:38	223	3,462	48,1	3,678	1,06	78,5	30	70	49,5
00:11:40	223	3,05	42,4	3,257	1,07	68,2	26	67	45,5
00:11:42	223	3,201	44,5	3,321	1,04	69,5	31	67	47,8
00:11:44	223	3,56	49,5	3,742	1,05	77,4	30	67	53,1
00:11:46	223	3,266	45,4	3,453	1,06	72,8	30	70	46,7
00:11:47	223	3,21	44,6	3,453	1,08	76,6	31	72	44,6
00:11:50	223	3,658	50,8	3,98	1,09	87,4	34	72	50,8
00:11:52	223	3,311	46	3,625	1,09	81,3	34	73	45,4
00:11:53	223	3,292	45,7	3,621	1,1	81,2	34	72	45,7
00:11:55	223	3,57	49,6	4	1,12	88,1	34	72	49,6
00:11:57	223	3,365	46,7	3,751	1,11	80,8	32	72	46,7
00:11:59	223	3,298	45,8	3,576	1,08	79,9	36	70	47,1
00:12:00	223	3,747	52	4,14	1,1	91,7	34	73	51,3
00:12:02	223	3,63	50,4	3,987	1,1	90,5	37	72	50,4
00:12:04	223	3,611	50,1	4,036	1,12	89,8	35	72	50,1
00:12:05	241	3,254	45,2	3,559	1,09	79,1	32	72	45,2
00:12:08	242	3,327	46,2	3,668	1,1	78,7	31	75	44,4
Test Stage-Recovery									
00:00:00	242	3,439	47,8	3,732	1,09	83,4	35	75	45,9
00:00:01	242	3,873	53,8	4,268	1,1	96,8	37	70	55,3
00:00:03	242	3,608	50,1	4,029	1,12	92	36	70	51,5
00:00:05	242	3,384	47	3,754	1,11	85,2	35	73	46,4
00:00:07	241	3,129	43,5	3,503	1,12	78,9	34	72	43,5
00:00:09	181	2,819	39,1	3,114	1,1	65,8	29	73	38,6
00:00:12	158	2,614	36,3	2,886	1,1	56,7	23	72	36,3
00:00:13	116	3,391	47,1	3,62	1,07	72,7	30		
00:00:16	62	3,02	41,9	3,292	1,09	68,9	28		
00:00:17	19	3,142	43,6	3,425	1,09	73,1	31		
00:00:19	19	3,211	44,6	3,547	1,1	76	33		
00:00:22	19	3,167	44	3,593	1,13	79	34		
00:00:23	19	2,77	38,5	3,237	1,17	69	30		
00:00:26	19	2,592	36	3,099	1,2	65,7	28		
00:00:27	19	2,578	35,8	3,119	1,21	65	29		

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:00:30	19	2,722	37,8	3,376	1,24	71	31		
00:00:32	19	2,417	33,6	3,086	1,28	63,5	28		
00:00:33	19	2,306	32	3,099	1,34	65,7	27	73	31,6
00:00:36	19	2,147	29,8	2,975	1,39	63,6	29	72	29,8
00:00:38	19	2,212	30,7	3,186	1,44	68,2	29	72	30,7
00:00:40	19	1,972	27,4	2,93	1,49	65,9	28	70	28,2
00:00:43	19	1,698	23,6	2,565	1,51	57,3	26	70	24,3
00:00:45	19	1,705	23,7	2,554	1,5	55,3	24	70	24,4
00:00:47	19	1,626	22,6	2,412	1,48	51	24	70	23,2
00:00:50	19	1,664	23,1	2,467	1,48	52,8	25		
00:00:52	19	1,503	20,9	2,278	1,52	50,9	24		
00:00:55	19	1,674	23,2	2,508	1,5	55,6	28		
00:00:57	19	1,541	21,4	2,329	1,51	53,1	26		
00:00:59	19	1,401	19,5	2,122	1,51	48	24		
00:01:02	19	1,461	20,3	2,221	1,52	50,6	26		
00:01:04	19	1,296	18	2,002	1,54	47,3	22	247	5,2
00:01:07	19	1,884	26,2	2,467	1,31	58,7	29	248	7,6
00:01:09	19	1,425	19,8	2,202	1,55	53,5	27	247	5,8
00:01:10	19	1,446	20,1	2,289	1,58	56	28	247	5,9
00:01:13	19	1,43	19,9	2,312	1,62	57,5	30		
00:01:14	19	1,25	17,4	2,033	1,63	50,9	29		
00:01:17	19	1,353	18,8	2,2	1,63	54,8	30		
00:01:20	19	0,706	9,8	1,166	1,65	30,2	19		
00:01:22	19	1,523	21,1	2,191	1,44	51	31		
00:01:24	19	1,388	19,3	2,046	1,47	50,1	26		
00:01:27	19	1,308	18,2	1,92	1,47	47	29		
00:01:28	19	1,364	18,9	2,058	1,51	52,9	29		
00:01:31	19	1,277	17,7	1,967	1,54	51,2	30		
00:01:32	19	1,046	14,5	1,631	1,56	43,3	28		
00:01:34	19	1,112	15,4	1,727	1,55	44	26		
00:01:37	19	1,072	14,9	1,656	1,55	42	26		
00:01:39	19	1,025	14,2	1,553	1,51	39,9	25		
00:01:42	19	1,125	15,6	1,67	1,48	41,5	25		

Table D-1 Exercise Test Data for Subject 1

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE(STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg/min	L/min		L/min	BPM	BPM	mL/Beat
00:01:44	19	1,11	15,4	1,654	1,49	41,8	24		
00:01:47	19	0,558	7,8	1,09	1,95	24	17		
00:01:50	19	1,103	15,3	1,484	1,35	37,5	25		
00:01:52	19	1,191	16,5	1,658	1,39	41,4	26		
00:01:55	19	1,082	15	1,494	1,38	36,5	28		
00:01:57	19	1,257	17,5	1,73	1,38	45,1	30		
00:01:59	19	1,386	19,2	1,922	1,39	50	33		
00:02:00	19	1,08	15	1,51	1,4	41,3	30		
00:02:02	19	1,03	14,3	1,483	1,44	41,7	29		
00:02:05	19	0,948	13,2	1,362	1,44	36,4	24		
00:02:07	19	0,984	13,7	1,368	1,39	35,7	23		
00:02:10	19	1,044	14,5	1,434	1,37	38,1	24		

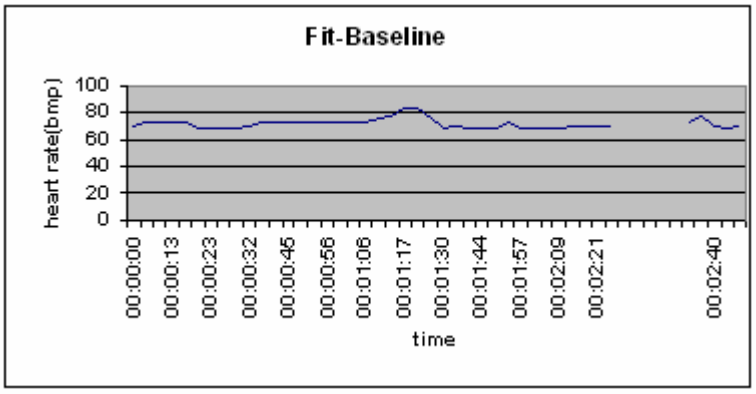


Figure D.1.1 Baseline Data for Subject 1

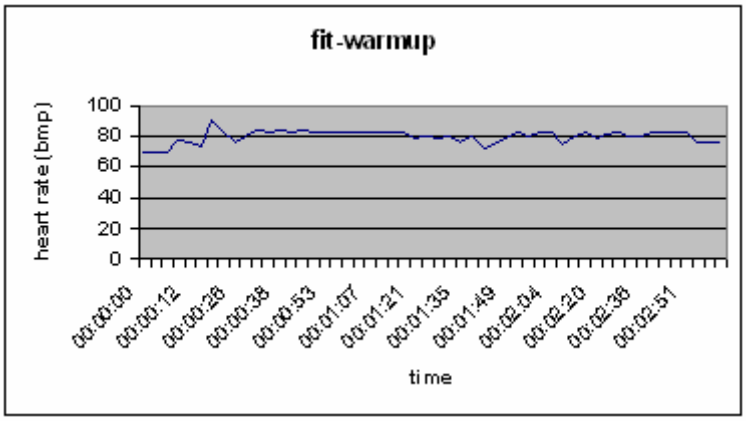


Figure D.1.2 Warmup Data for Subject 1

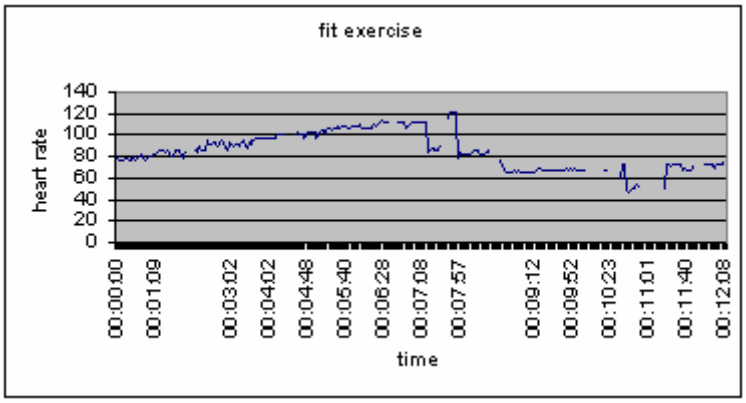


Figure D.1.3 Exercise Data for Subject 1

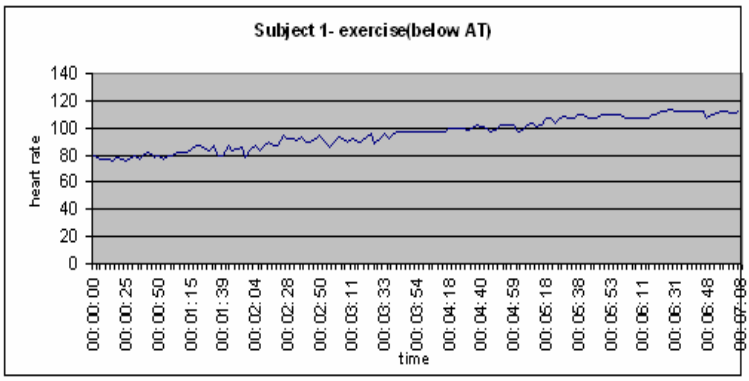


Figure D.1.4 Exercise Data Under Anaerobic Threshold for Subject 1

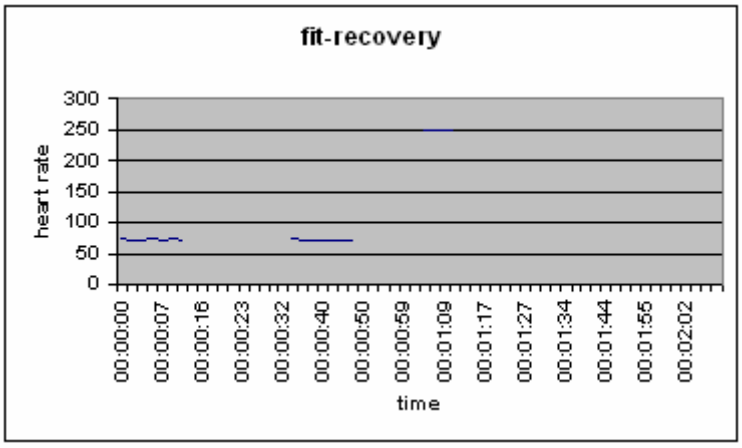


Figure D.1.5 Recovery Data for Subject 1

D.2 Test Data and Graphics for Subject 2

BASKENT ÜNIVERSITESI

Solunum Fonksiyon Testleri

Soyad-Ad: Subject 2
Prot. No: 2
Tarih: 19/08/06
Biomedikal Teknikeri : E. ERDEM

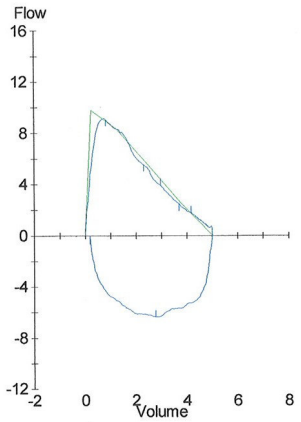
Yas: 24 Boy(cm): 174 Kilo(kg): 67.0 Cinsiyet: Male Irk: Caucasian

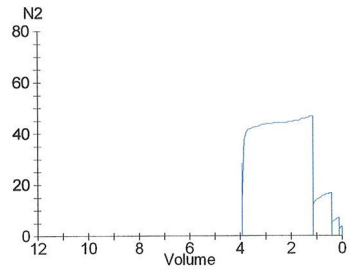
Standart Spirometri

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Chg
FVC	Liters	5.03	5.02	100		
FEV1	Liters	4.27	4.20	98		
FEV1/FVC	%	83	84			
FEF25-75%	L/sec	5.00	4.09	82		
FEF50%	L/sec	5.47	5.07	93		
FEF75-85%	L/sec		1.79			
FEF200-1200	L/sec		8.73			
PEF	L/sec	9.76	9.09	93		
PIF	L/sec		6.37			
MVV	L/min		106			
FIF50%	L/sec		6.31			
FEF/FIF50			0.80			
FEV1/SVC	%		82			

Akciger Volümleri

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
TLC	Liters	6.82	7.06	103			
VC	Liters	5.26	5.11	97			
IC	Liters		2.80				
FRC N2	Liters	3.21	(4.26)	(133)			
ERV	Liters		2.31				
RV	Liters	1.60	1.96	122			
RV/TLC	%	24	28				





Yorum:

Dr.Gaye ULUBAY

BASKENT ÜNIVERSITESI
SFT LABORATUVARI

Kardiyopulmoner Egzersiz Testi Özeti

Isim: Subject 2
Protokol No: 36270
Tarih: 19/08/06
Yas: 24 Irk: Caucasian
Boy: 174 Kilo: 67.0

	Beklenen	Ölçülen	% Beklenen
FVC (L)	5.03	5.02	100
FEV1 (L)	4.27	4.20	98
MVV (L)		106	

Istirahat HR (bpm): 110 SpO2: 78 SPB(mmHg): DPB (mmHg):

Kardiyovasküler cevap	Beklenen	Ölçülen	% Beklenen
VO2 (ml/kg/min)	46.8	22.2	(47)
VO2 (l/min)	3.432	1.487	(43)
VCO2 (l/min)		1.811	
Work (Watts)	232	93	(40)
Anaerobic Threshold (AT)(l/min)	> 1.373	1.429	
AT (% Predicted Max VO2)	> 40%	42	
Heart Rate (bpm)	187	169	(90)
O2 Pulse (ml/beat)	15.5	8.8	(57)
Systolic Blood Pressure (Max)	187		
Diastolic Blood Pressure (Max)	85-105		
Heart Rate Reserve (bpm)	<15	9	
Pik solunum cevabi			
VE Max (l/min) BTPS	133.7	54.4	41
Tidal Volume (VT) (L)	2.780	1.812	65
Respiratory Rate (RR)	<50	26	
Breathing Reserve (%)	20-40	49	
Gaz degisim cevabi			
End Tidal CO2 (Peak PetCO2)			
End Tidal O2 (Peak PetO2)			
VE/VO2 @ AT			
VE/VCO2 @ AT			
VD/VT (Est) @ Rest	0.30	0.23	76
VD/VT (Est) Peak	0.18	0.10	(58)
Respiratory Quotient (RQ)(Peak)	1.1-1.3	1.22	
SpO2 (O2 Sat--Pulse Ox) @ Peak	96	93	

Kalibrasyon

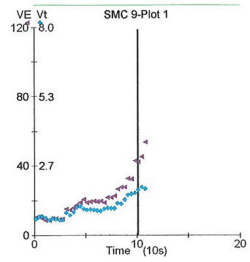
Akim kal. Pred Volume: 3.00 Expire Avg: 3.00 Inspire Avg: 2.94

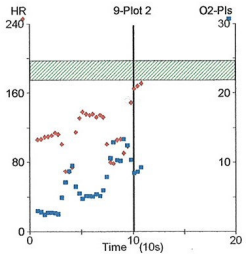
Gaz kal.	Cal1 O2	Cal 1 CO2	Cal 2 O2	Cal 2 CO2	Ambient O2	Ambient CO2
Beklenen	16.00	4.00	26.00	0.00		
Ölçülen	16.04	4.03	26.06	0.00	20.70	0.10
Geçis (msec)	0.575	0.473				
Cevap (msec)	0.115	0.087				

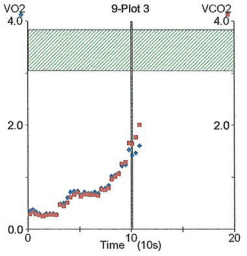
Kardiyopulmoner Egzersiz Testi Grafikleri: 9-Plot

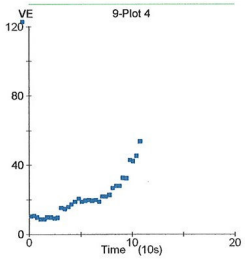
Isim: Subject 2
Tarih: 19/08/06
Yas: 24

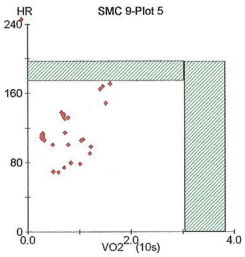
Protokol No: 36270
Boy: 69
Kilo: 147

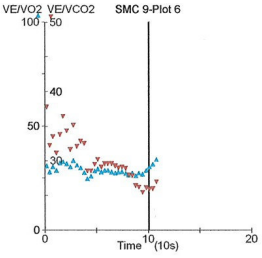


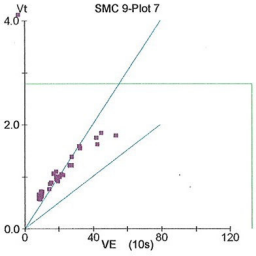


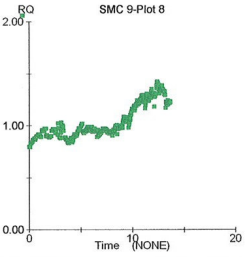


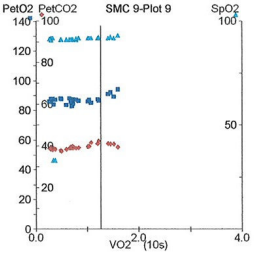












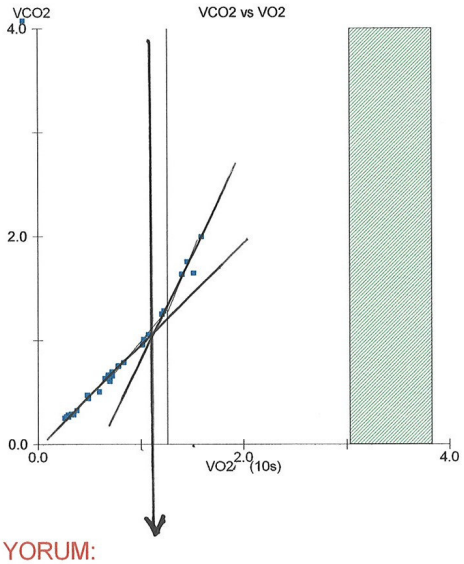
Ölçüm (pik):	Beklenen	Ölçülen	% Ölçülen	Plot #
VO2 (l/min)	3.432	1.487	(43)	1,3
Work Rate (Watts)	232	93	(40)	3
HR (bpm)	187	169	(90)	2
O2 Pulse (ml/beat)	15.5	8.8	(57)	5
Respiratory Quotient (RQ)	1.1-1.3	1.22		8
VE Max (l/min) BTPS	133.7	54.4	41	1,7
Breathing Reserve (%)	20-40	49		1.7
AT (l/min)	1.373	1.429		1,5,6,9
Slope hesaplamasi			(Normal Range)	
VO2/Work (ml/min/watt)	10.3		8.7-11.9	3
HR/VO2kg (bpm/ml/kg)	3.8		3.0-4.0	2,5
VE/VO2 (L BTPS/L STPD)	27.5		23-26	1,6
VE/VCO2 (L BTPS/L STPD)	21.8		26-29	3

BASKENT ÜNIVERSITESI
SFT LABORATUVARI

Isim: Subject 2
Protokol No: 36270
Tarih: 19/08/06
Yas: 24 Irk: Caucasian
Boy: 174 Kilo: 67.0

Kardiyopulmoner Egzersiz Testi Sonucu

VCO2 vs VO2 (AT profili)



YORUM:

AT VO2 = 1.186 L/dk
AT HR = 107 → 140
AT RQ = 1.03.
AT VE = 23.5 L/dk

Doktor: Dr.Gaye ULUBAY

Table D-2 Exercise Test Data for Subject 2

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE (STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg /min	L/min		L/min	BPM	BPM	mL /Beat
Test Stage	Baseline								
00:00:00		0,384	5,7	0,304	0,79	7,2	15		
00:00:04		0,398	5,9	0,316	0,79	7,3	15		
00:00:07		0,163	2,4	0,129	0,79	4,9	21		
00:00:10		0,347	5,2	0,288	0,83	8,1	17		
00:00:14		0,397	5,9	0,329	0,83	9,2	16		
00:00:18		0,361	5,4	0,304	0,84	8,9	16		
00:00:22		0,379	5,7	0,323	0,85	9,9	16		
00:00:26	0	0,359	5,4	0,309	0,86	5,8	13		
00:00:30		0,394	5,9	0,343	0,87	8,2	15		
00:00:35		0,386	5,8	0,332	0,86	6,8	13		
00:00:39		0,353	5,3	0,308	0,87	6,5	15		
00:00:43		0,334	5	0,298	0,89	7,6	15		
00:00:47		0,308	4,6	0,277	0,9	7,2	15	109	2,8
00:00:51		0,305	4,5	0,276	0,91	5,5	15	107	2,8
00:00:56		0,315	4,7	0,286	0,91	9,2	11	102	3,1
00:01:03		0,298	4,5	0,27	0,91	4,3	9	109	2,7
00:01:07		0,307	4,6	0,274	0,89	6,8	15	109	2,8
00:01:11		0,287	4,3	0,255	0,89	5,1	14	107	2,7
00:01:15		0,265	4	0,252	0,95	6,2	16	107	2,5
00:01:19		0,277	4,1	0,261	0,94	6,4	14	109	
00:01:23		0,243	3,6	0,23	0,95	5,6	14	112	2,2
00:01:27		0,268	4	0,253	0,94	7,7	17	112	2,4
00:01:31		0,256	3,8	0,247	0,97	5,9	13	109	2,3
00:01:36		0,257	3,8	0,249	0,97	5	14	105	2,4
00:01:39		0,285	4,3	0,256	0,9	7,6	16	107	2,7
00:01:44		0,281	4,2	0,253	0,9	6,2	13	112	2,5
00:01:48		0,301	4,5	0,268	0,89	7,7	16	114	2,6
00:01:51		0,303	4,5	0,27	0,89	8,1	16	110	2,8
00:01:55		0,309	4,6	0,272	0,88	6,5	15	109	2,8
00:02:00		0,314	4,7	0,278	0,89	5,9	15	107	2,9
00:02:05		0,295	4,4	0,264	0,9	5,7	12	107	2,8
00:02:08		0,294	4,4	0,265	0,9	6,6	17	109	2,7
00:02:11		0,291	4,3	0,275	0,95	8,3	20	117	2,5
00:02:15		0,295	4,4	0,279	0,95	8,3	15	114	2,6
00:02:19		0,297	4,4	0,286	0,96	7,4	16	112	2,7
00:02:23		0,3	4,5	0,288	0,96	6,6	15	115	2,6
00:02:27		0,299	4,5	0,287	0,96	6	15	113	2,6
00:02:30		0,302	4,5	0,29	0,96	6,9	16	114	2,6
00:02:34		0,285	4,2	0,265	0,93	5,8	15	115	2,5
00:02:38		0,272	4,1	0,254	0,93	7,2	16	114	2,4
00:02:46		0,263	3,9	0,239	0,91	6,2	16	112	2,3
00:02:49	0	0,23	3,4	0,234	1,02	5,8	15	112	2,1

Table D-2 Exercise Test Data for Subject 2

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE (STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg /min	L/min		L/min	BPM	BPM	mL /Beat
Test Stage	Warmup								
00:00:00	0	0,225	3,4	0,219	0,97	5,7	16	112	2
00:00:04	0	0,444	6,6	0,393	0,88	9,4	16	109	4,1
00:00:07	0	0,525	7,8	0,462	0,88	11	19	109	4,8
00:00:11	0	0,567	8,5	0,528	0,93	11,9	16	109	5,2
00:00:14	19	0,441	6,6	0,452	1,03	10,7	18	109	4
00:00:18	19	0,461	6,9	0,45	0,98	10,9	17	114	4
00:00:21	19	0,434	6,5	0,433	1	10,9	18	82	5,3
00:00:25	19	0,498	7,4	0,491	0,99	11,3	19	74	6,7
00:00:28	19	0,362	5,4	0,342	0,95	8,9	20	70	5,2
00:00:35	19	0,507	7,6	0,447	0,88	10,6	19	67	7,6
00:00:38	19	0,567	8,5	0,499	0,88	11,5	17	67	8,5
00:00:41	19	0,532	7,9	0,459	0,86	11,2	20	68	7,8
00:00:44	19	0,654	9,8	0,565	0,86	12,9	19	73	9
00:00:47	19	0,62	9,3	0,536	0,86	12,1	17	69	9
00:00:51	19	0,767	11,5	0,648	0,85	14,5	20	65	11,8
00:00:53	19	0,577	8,6	0,48	0,83	11,5	22	68	8,5
00:00:55	19	0,261	3,9	0,218	0,84	7,8	32	69	3,8
00:00:58	19	0,655	9,8	0,541	0,83	11,6	17	69	9,5
00:01:02	19	0,672	10	0,564	0,84	12,2	14	70	9,6
00:01:07	19	0,757	11,3	0,64	0,85	13,8	16	70	10,8
00:01:12	19	0,361	5,4	0,317	0,88	7,5	11	73	4,9
00:01:15	19	0,798	11,9	0,694	0,87	13,2	19	77	10,4
00:01:19	19	0,766	11,4	0,643	0,84	13,5	17	72	10,6
00:01:22	19	0,761	11,4	0,65	0,85	13,7	16	77	9,9
00:01:26	19	0,697	10,4	0,62	0,89	12,9	17	80	8,7
00:01:30	19	0,686	10,2	0,625	0,91	13	15	97	7,1
00:01:33	19	0,722	10,8	0,643	0,89	13,5	16	114	6,3
00:01:37	19	0,696	10,4	0,627	0,9	13,2	16	129	5,4
00:01:41	19	0,777	11,6	0,702	0,9	15,1	19	131	5,9
00:01:44	19	0,795	11,9	0,731	0,92	15,7	19	133	6
00:01:46	19	0,677	10,1	0,63	0,93	14,2	22	134	5,1
00:01:49	19	0,648	9,7	0,609	0,94	13,6	21	126	5,1
00:01:52	19	0,676	10,1	0,641	0,95	13,9	20	131	5,2
00:01:55	19	0,715	10,7	0,681	0,95	14,8	20	133	5,4
00:01:58	19	0,719	10,7	0,699	0,97	15,4	19	129	5,6
00:02:01	19	0,725	10,8	0,705	0,97	15,4	20	131	5,5
00:02:04	19	0,881	13,1	0,855	0,97	18,3	22	134	6,6
00:02:07	19	0,819	12,2	0,811	0,99	17,5	20	134	6,1
00:02:10	19	0,67	10	0,668	1	15,3	20	138	4,9
00:02:14	19	0,289	4,3	0,293	1,01	7,5	15	141	2,1
00:02:17	19	0,752	11,2	0,708	0,94	14,5	20	142	5,3

Table D-2 Exercise Test Data for Subject 2

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE (STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg /min	L/min		L/min	BPM	BPM	mL /Beat
00:02:20	19	0,624	9,3	0,586	0,94	12,9	20	139	4,5
00:02:23	19	0,729	10,9	0,675	0,93	14,8	20	138	5,3
00:02:26	19	0,709	10,6	0,659	0,93	14,3	20	136	5,2
00:02:29	19	0,706	10,5	0,668	0,95	14,3	19	136	5,2
00:02:33	19	0,738	11	0,698	0,95	14,8	17	136	5,4
00:02:35	19	0,648	9,7	0,608	0,94	13,1	21	137	4,7
00:02:38	19	0,747	11,1	0,711	0,95	15,2	19	136	5,5
00:02:41	19	0,707	10,5	0,676	0,96	14,7	19	136	5,2
00:02:45	19	0,639	9,5	0,619	0,97	13,9	21	137	4,7
00:02:48	19	0,714	10,7	0,702	0,98	14,9	20	133	5,4
00:02:51	19	0,611	9,1	0,599	0,98	13,3	19	134	4,6
00:02:53	19	0,682	10,2	0,658	0,96	14,7	20	134	5,1
00:02:57	19	0,617	9,2	0,59	0,96	13,3	21	136	4,5
00:02:59	19	0,743	11,1	0,704	0,95	15,2	21	136	5,5
Test Stage	Exercise								
00:00:00	19	0,691	10,3	0,658	0,95	14,4	20	136	5,1
00:00:03	19	0,731	10,9	0,696	0,95	15,1	20	137	5,3
00:00:07	19	0,608	9,1	0,594	0,98	13,3	20	136	4,5
00:00:09	19	0,72	10,7	0,706	0,98	15,3	20	134	5,4
00:00:12	19	0,558	8,3	0,524	0,94	12,3	23	139	4
00:00:14	19	0,711	10,6	0,679	0,96	14,9	20	139	5,1
00:00:18	19	0,665	9,9	0,629	0,95	13,8	21	136	4,9
00:00:21	19	0,71	10,6	0,677	0,95	14,5	19	132	5,4
00:00:23	19	0,696	10,4	0,661	0,95	14,1	21	134	5,2
00:00:26	19	0,661	9,9	0,639	0,97	14,2	19	134	4,9
00:00:30	19	0,647	9,7	0,608	0,94	13,4	21	126	5,1
00:00:32	19	0,729	10,9	0,692	0,95	15	21	127	5,7
00:00:35	19	0,713	10,6	0,669	0,94	14,5	21	132	5,4
00:00:39	19	0,611	9,1	0,58	0,95	12,7	17	134	4,6
00:00:41	19	0,803	12	0,713	0,89	16	30	136	5,9
00:00:45	19	0,472	7	0,448	0,95	9,8	14	139	3,4
00:00:48	19	0,746	11,1	0,671	0,9	13,9	18	136	5,5
00:00:51	19	0,594	8,9	0,539	0,91	12,4	21	134	4,4
00:00:55	19	0,964	14,4	0,88	0,91	18,7	21	134	7,2
00:00:58	19	0,709	10,6	0,669	0,94	14,3	17	133	5,3
00:01:01	19	0,678	10,1	0,64	0,94	13,6	18	134	5,1
00:01:03	19	0,683	10,2	0,635	0,93	14,1	22	134	5,1
00:01:07	19	0,807	12	0,761	0,94	16,1	21	131	6,2
00:01:10	37	0,735	11	0,697	0,95	15	21	133	5,5
00:01:12	37	0,843	12,6	0,816	0,97	17,5	21	135	6,2
00:01:16	37	0,799	11,9	0,763	0,95	16,7	23	134	6
00:01:18	37	0,746	11,1	0,717	0,96	15,6	20	137	5,4
00:01:21	37	0,836	12,5	0,793	0,95	16,6	20	129	6,5

Table D-2 Exercise Test Data for Subject 2

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE (STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg /min	L/min		L/min	BPM	BPM	mL /Beat
00:01:24	37	0,768	11,5	0,743	0,97	15,9	20	111	6,9
00:01:27	37	0,781	11,7	0,754	0,96	16,9	22	107	7,3
00:01:30	37	0,663	9,9	0,639	0,96	14,5	21	109	6,1
00:01:32	37	0,806	12	0,773	0,96	16,5	23	112	7,2
00:01:36	37	0,771	11,5	0,734	0,95	15,6	19	98	7,9
00:01:39	37	0,793	11,8	0,746	0,94	15,8	20	91	8,7
00:01:41	37	0,829	12,4	0,773	0,93	16,7	22	85	9,8
00:01:44	37	0,857	12,8	0,798	0,93	17,1	22	82	10,4
00:01:47	37	0,87	13	0,808	0,93	16,7	21	82	10,6
00:01:50	37	0,805	12	0,744	0,92	15,9	22	80	10,1
00:01:52	37	0,866	12,9	0,807	0,93	17,1	20	80	10,8
00:01:56	37	0,726	10,8	0,686	0,94	14,9	21	80	9,1
00:01:58	37	0,851	12,7	0,8	0,94	17,3	21	77	11,1
00:02:00	37	0,703	10,5	0,652	0,93	14,8	26	77	9,1
00:02:03	37	1,04	15,5	0,972	0,93	20,5	24	77	13,5
00:02:06	37	0,79	11,8	0,727	0,92	15,4	21	78	10,1
00:02:08	56	0,913	13,6	0,825	0,9	17	20	77	11,9
00:02:12	56	1,133	16,9	1,054	0,93	21,6	20	77	14,7
00:02:15	56	0,873	13	0,832	0,95	17,8	21	77	11,3
00:02:17	56	1,108	16,5	1,037	0,94	20,7	21	80	13,9
00:02:20	56	1,159	17,3	1,099	0,95	22,5	24	80	14,5
00:02:22	56	1,037	15,5	0,995	0,96	21,4	24	82	12,6
00:02:24	56	1,2	17,9	1,166	0,97	24,2	25	82	14,6
00:02:28	56	0,906	13,5	0,898	0,99	18,8	21	85	10,7
00:02:30	56	1,164	17,4	1,139	0,98	24,2	28	84	13,9
00:02:33	56	0,644	9,6	0,646	1	13,9	16	102	6,3
00:02:36	56	1,513	22,6	1,378	0,91	26,7	29	110	13,8
00:02:38	56	0,959	14,3	0,923	0,96	18,7	21	127	7,6
00:02:41	56	0,964	14,4	0,94	0,98	19,2	21	133	7,2
00:02:44	56	1,043	15,6	1,008	0,97	20,4	23	136	7,7
00:02:47	56	1,067	15,9	1,032	0,97	20,6	21	109	9,8
00:02:50	56	1,102	16,4	1,081	0,98	21,1	19	107	10,3
00:02:53	56	1,074	16	1,047	0,98	20,7	20	107	10
00:02:56	56	0,969	14,5	0,94	0,97	18,9	24	107	9,1
00:02:58	56	1,247	18,6	1,215	0,97	22,9	22	99	12,6
00:03:02	56	0,938	14	0,933	1	18,1	16	97	9,7
00:03:05	56	1,269	18,9	1,237	0,97	23,3	22	97	13,1
00:03:07	74	1,432	21,4	1,412	0,99	26,6	24	87	16,5
00:03:10	74	1,277	19,1	1,319	1,03	25,9	20	87	14,7
00:03:13	74	1,234	18,4	1,291	1,05	25,5	23	87	14,2
00:03:16	74	1,062	15,9	1,149	1,08	23,3	20	90	11,8
00:03:19	74	1,111	16,6	1,18	1,06	22,8	21	92	12,1
00:03:22	74	1,084	16,2	1,154	1,07	22,3	18	97	11,2
00:03:25	74	1,186	17,7	1,227	1,03	23,5	21	95	12,5

Table D-2 Exercise Test Data for Subject 2

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE (STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg /min	L/min		L/min	BPM	BPM	mL /Beat
00:03:28	74	1,232	18,4	1,281	1,04	24,4	21	97	12,7
00:03:30	74	1,33	19,9	1,378	1,04	26,4	23	104	12,8
00:03:33	74	1,148	17,1	1,235	1,08	23,5	18	101	11,4
00:03:37	74	1,27	19	1,344	1,06	24,9	21	96	13,2
00:03:41	74	0,662	9,9	0,709	1,07	14	15	94	7
00:03:43	74	1,751	26,1	1,71	0,98	30,1	24	99	17,7
00:03:46	74	1,459	21,8	1,473	1,01	28,1	25	127	11,5
00:03:48	74	1,621	24,2	1,665	1,03	31	24	146	11,1
00:03:50	74	1,569	23,4	1,647	1,05	31,7	26	149	10,5
00:03:52	74	1,489	22,2	1,592	1,07	32,2	33	153	9,7
00:03:54	74	1,61	24	1,77	1,1	35	30	153	10,5
00:03:56	74	1,45	21,6	1,607	1,11	32,1	31	156	9,3
00:03:58	74	1,521	22,7	1,71	1,12	33,7	28	158	9,6
00:04:01	74	1,484	22,1	1,688	1,14	33,3	24	163	9,1
00:04:03	74	1,35	20,2	1,565	1,16	30	22	163	8,3
00:04:05	74	1,336	19,9	1,545	1,16	29,5	24	164	8,1
00:04:09	93	1,452	21,7	1,684	1,16	32,4	23	163	8,9
00:04:10	93	1,456	21,7	1,688	1,16	33	25	163	8,9
00:04:14	93	1,361	20,3	1,6	1,18	31,9	25	165	8,2
00:04:16	93	1,058	15,8	1,255	1,19	24,1	20	168	6,3
00:04:18	93	1,577	23,5	1,801	1,14	32,9	25	168	9,4
00:04:21	93	1,497	22,3	1,75	1,17	33,9	25	168	8,9
00:04:24	93	1,406	21	1,676	1,19	32,4	22	169	8,3
00:04:27	93	1,53	22,8	1,815	1,19	34,3	25	169	9,1
00:04:29	93	1,361	20,3	1,628	1,2	32,4	24	168	8,1
00:04:31	93	1,589	23,7	1,917	1,21	36,1	24	168	9,5
00:04:34	93	1,368	20,4	1,691	1,24	33,9	25	168	8,1
00:04:36	93	1,315	19,6	1,613	1,23	30,8	25	169	7,8
00:04:39	93	1,721	25,7	2,072	1,2	39,2	26	168	10,2
00:04:41	93	1,34	20	1,625	1,21	31,9	24	171	7,8
00:04:43	93	1,427	21,3	1,726	1,21	33	27	170	8,4
00:04:45	93	1,694	25,3	2,066	1,22	39,9	26	170	10
00:04:48	93	1,552	23,2	1,916	1,23	38,4	30	170	9,1
00:04:49	93	1,497	22,3	1,86	1,24	37,4	30	170	8,8
00:04:52	93	1,583	23,6	1,973	1,25	39,2	32	171	9,3
00:04:53	93	1,697	25,3	2,109	1,24	42,3	31	173	9,8
00:04:56	93	1,61	24	2,021	1,26	40,7	31	173	9,3
00:04:57	93	1,6	23,9	2,004	1,25	40,3	31	173	9,3
00:04:59	93	1,534	22,9	1,935	1,26	39,1	31	173	8,9
00:05:01	93	1,58	23,6	2,029	1,28	41,5	32	173	9,1
00:05:03	93	1,507	22,5	1,941	1,29	39,4	32	173	8,7
00:05:04	93	1,529	22,8	1,965	1,28	39,8	34	173	8,8
00:05:06	93	1,579	23,6	2,013	1,27	42,3	36	174	9,1
00:05:08	111	1,521	22,7	1,929	1,27	39,6	32	173	8,8

Table D-2 Exercise Test Data for Subject 2

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE (STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg /min	L/min		L/min	BPM	BPM	mL /Beat
00:05:10	111	1,47	21,9	1,87	1,27	39,2	35	176	8,4
00:05:12	111	1,609	24	2,014	1,25	40,3	35	178	9
00:05:13	111	1,65	24,6	2,02	1,22	39,5	32	177	9,3
00:05:16	111	1,605	24	1,994	1,24	40,3	33	178	9
00:05:17	111	0,874	13	1,113	1,27	24,4	28	178	4,9
Test Stage	Recover y								
00:00:00	111	1,916	28,6	2,231	1,16	43	34	178	10,8
00:00:02	111	2,049	30,6	2,454	1,2	46	35	178	11,5
00:00:03	111	2,036	30,4	2,499	1,23	50,2	36	178	11,4
00:00:06	111	1,481	22,1	1,874	1,27	38,1	30	178	
00:00:07	111	1,701	25,4	2,143	1,26	43,1	34	178	9,6
00:00:09	56	1,433	21,4	1,85	1,29	38	32	175	8,2
00:00:11	19	1,3	19,4	1,693	1,3	34,2	28	175	7,4
00:00:14	19	1,446	21,6	1,836	1,27	35,5	27	173	8,4
00:00:16	19	1,376	20,5	1,721	1,25	32,7	25	174	7,9
00:00:18	19	1,438	21,5	1,793	1,25	34,1	27	171	8,4
00:00:20	19	1,538	23	1,898	1,23	36,5	31	171	9
00:00:22	19	1,417	21,1	1,753	1,24	33,5	29	170	8,3
00:00:24	19	1,493	22,3	1,867	1,25	36,3	28	173	8,6
00:00:27	19	1,303	19,4	1,654	1,27	33	28	173	7,5
00:00:29	19	1,409	21	1,79	1,27	33,8	26	173	8,1
00:00:31	19	1,317	19,7	1,666	1,26	32,7	30	173	7,6
00:00:33	19	1,319	19,7	1,681	1,27	32,8	30	172	7,7
00:00:35	19	1,348	20,1	1,742	1,29	35,8	34	173	7,8
00:00:36	19	1,368	20,4	1,806	1,32	37,1	34	173	7,9
00:00:38	19	1,283	19,1	1,713	1,34	35	30	173	7,4
00:00:40	19	0,918	13,7	1,236	1,35	26,4	29	171	5,4
00:00:43	19	1,183	17,7	1,54	1,3	29,4	26	169	7
00:00:45	19	1,308	19,5	1,697	1,3	32,3	26	168	7,8
00:00:47	19	1,251	18,7	1,62	1,3	31,4	24	169	7,4
00:00:51	19	0,774	11,6	1,013	1,31	19,3	16	163	4,7
00:00:54	19	1,245	18,6	1,464	1,18	27	23	163	7,6
00:00:56	19	1,09	16,3	1,384	1,27	26,3	22	163	6,7
00:00:59	19	1,029	15,4	1,32	1,28	25,6	23	158	6,5
00:01:02	19	1,131	16,9	1,475	1,3	29,2	25	158	7,2
00:01:04	19	1,013	15,1	1,375	1,36	27,5	23	157	6,5
00:01:06	19	0,972	14,5	1,341	1,38	27,7	23	158	6,2
00:01:10	19	0,935	14	1,319	1,41	26,8	22	158	5,9
00:01:12	19	0,908	13,5	1,286	1,42	26,1	22	159	5,7
00:01:15	19	0,707	10,6	0,996	1,41	21,4	23	156	4,5
00:01:17	19	0,744	11,1	1,033	1,39	21,3	23	156	4,8
00:01:20	19	1,001	14,9	1,345	1,34	26,9	23	153	6,5
00:01:23	19	1,122	16,8	1,469	1,31	29,7	25	153	7,3

Table D-2 Exercise Test Data for Subject 2

Time Sec	Work	VO2	VO2/kg	VCO2	RQ	VE (STPD)	RR	HR	O2 Pulse
HH:MM	Watts	L/min	mL/kg /min	L/min		L/min	BPM	BPM	mL /Beat
00:01:25	19	1,033	15,4	1,359	1,31	29,5	25	153	6,8
00:01:28	19	0,935	14	1,248	1,34	27,5	24	155	6
00:01:30	19	0,947	14,1	1,275	1,35	28,4	24	155	6,1
00:01:32	19	0,856	12,8	1,164	1,36	26,3	25	157	5,5
00:01:35	19	0,929	13,9	1,273	1,37	28	25	155	6
00:01:37	19	0,949	14,2	1,304	1,37	29,5	25	153	6,2
00:01:39	19	0,808	12,1	1,116	1,38	25,4	24	154	5,2
00:01:42	19	0,881	13,1	1,187	1,35	26,9	27	154	5,7
00:01:44	19	0,953	14,2	1,281	1,34	29,4	27	154	6,2
00:01:46	19	0,895	13,4	1,189	1,33	27,5	26	153	5,8
00:01:48	19	0,844	12,6	1,121	1,33	26	26	153	5,5
00:01:51	19	0,863	12,9	1,144	1,33	27,1	29	154	5,6
00:01:53	19	0,639	9,5	0,844	1,32	21,1	28	153	4,2
00:01:55	19	0,848	12,7	1,098	1,3	25,2	27	153	5,5
00:01:58	19	0,727	10,9	0,936	1,29	21	22	154	4,7
00:02:00	19	0,776	11,6	0,905	1,17	20,7	36	154	5
00:02:01	19	0,879	13,1	1,075	1,22	23,9	29	151	5,8
00:02:03	19	0,743	11,1	0,903	1,22	20,9	27	153	4,9
00:02:06	19	0,885	13,2	1,068	1,21	24,1	28	151	5,9
00:02:08	19	0,84	12,5	1,006	1,2	23,1	28	151	5,6
00:02:11	19	0,882	13,2	1,06	1,2	24,1	25	148	6
00:02:13	19	0,735	11	0,909	1,24	21	24	149	4,9
00:02:15	19	0,822	12,3	0,99	1,2	23,3	29	148	5,6
00:02:17	19	0,837	12,5	1,019	1,22	23,4	27	149	5,6
00:02:20	19	0,836	12,5	1,013	1,21	23,1	26	149	5,6
00:02:22	19	0,792	11,8	0,962	1,21	21,5	23	149	5,3
00:02:25	19	0,786	11,7	0,965	1,23	21,2	21	148	5,3
00:02:28		0,658	9,8	0,805	1,22	17,7	21		

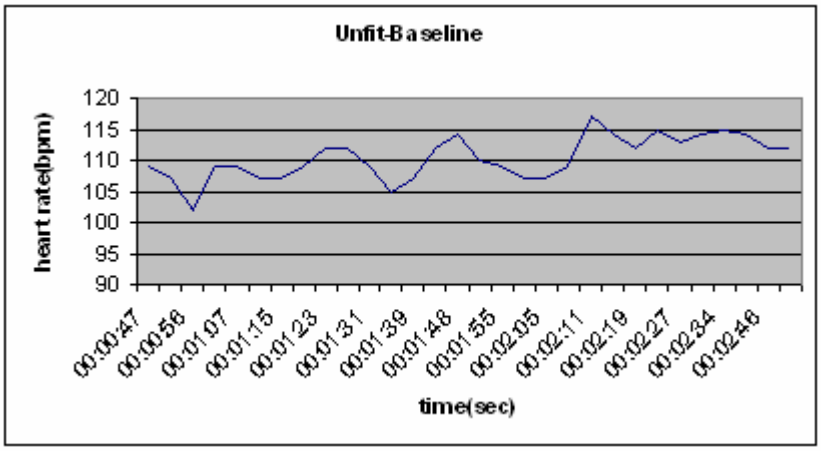


Figure D.1.6 Baseline Data for Subject 2

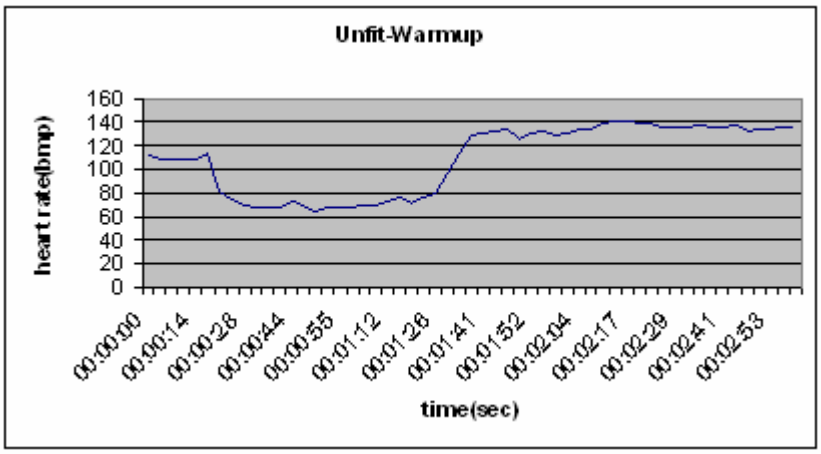


Figure D.1.7 Warmup Data for Subject 2

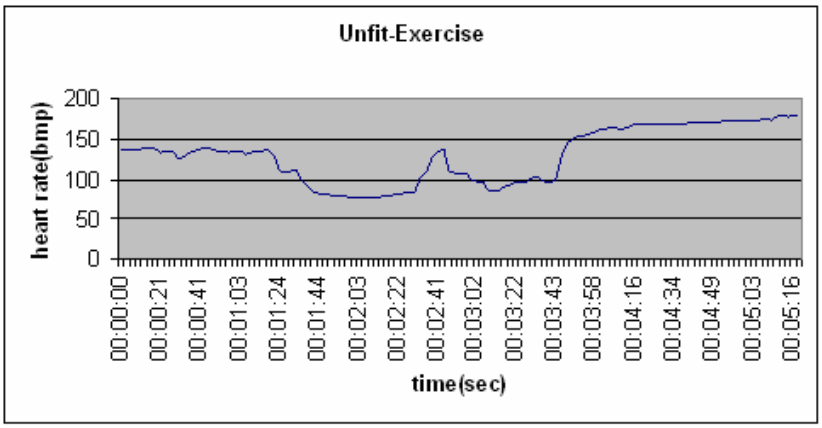


Figure D.1.8 Exercise Data for Subject 2

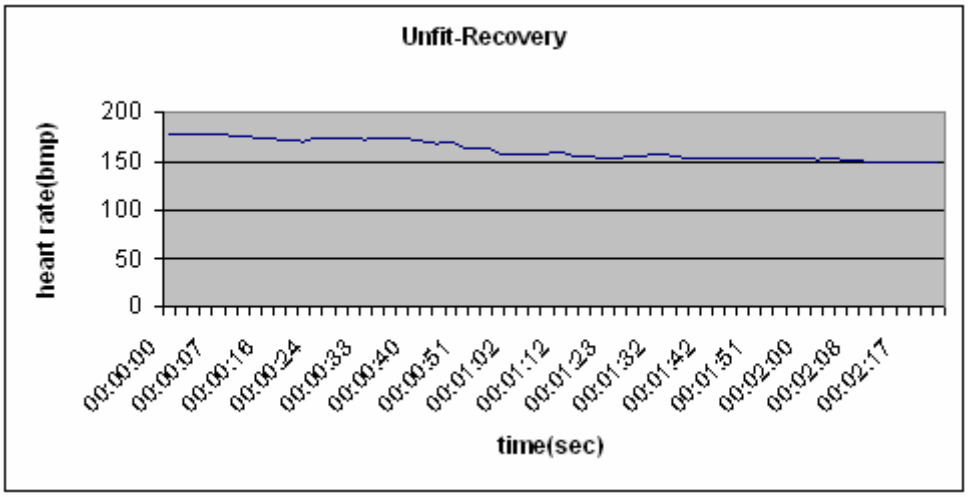


Figure D.1.9 Recovery Data for Subject 2