ABSTRACT

THE INFLUENCE OF EXERCISE ON OXYGEN UPTAKE IN MILD HYPERTENSION

by
Matthew Joseph Herban

The amount of oxygen used by muscle cells increase with exercise. The two body systems that influence the amount of oxygen delivered are the cardiovascular system and the pulmonary system. Two groups of patients were studied, those that were mildly hypertensive (but are not taking prescription medication for hypertension) and the control or normal group. The two groups exercised on a bicycle ergometer. Work rate was increased in steps (multiples of thirty watts) until anaerobic threshold (as measured by an ear oximeter) was reached. Heart rate, blood pressure, oxygen uptake and carbon dioxide production were measured during exercise. Their data were then fitted to a mathematical model developed by Kyuichi Niizeki, Tatsushisa Takahashi, and Yoshimi Miyamoto. The model consisted of three compartments (the lungs, muscle tissue involved in exercise, and the inactive tissues and organs). The assumptions made for the model are: (1) that the dynamic responses of pulmonary blood flow and the muscle VO_2 obey first-order kinetics; (2) the ratio of blood flow in the muscle compartment to total cardiac output was assumed to increase linearly with work rate; (3) the muscle compartment and the inactive tissue compartment were assumed to be connected in parallel to the lung compartment and perfused by separate regional circulations. The model is able

to predict the volume of oxygen consumed by the cells as a function of time during incremental step exercise.

THE INFLUENCE OF EXERCISE ON OXYGEN UPTAKE IN MILD HYPERTENSION

by
Matthew Joseph Herban

A Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Biomedical Engineering

Department of Biomedical Engineering

August 2003

APPROVAL PAGE

THE INFLUENCE
OF EXERCISE ON OXYGEN UPTAKE
IN MILD HYPERTENSION

Matthew Joseph Herban

8/8/03

Dr. Arthur Ritter, Thesis Advisor — Date
Associate Professor of Pharmacology and Physiology,
University of Medicine and Dentistry – New Jersey Medical School

8/7/03

Dr. David Kristol, Committee Member — Date
Professor of Biomedical Engineering, NJIT

08/12/03

Dr. Peter Engler, Committee Member — Date
Professor Emeritus of Biomedical Engineering, NJIT

BIOGRAPHICAL SKETCH

Author: Matthew Joseph Herban

Degree: Master of Science

Date: August 2003

Date of Birth:

Place of Birth:

Undergraduate and Graduate Education:

- Master of Science in Biomedical Engineering,
  New Jersey Institute of Technology, Newark, NJ, 2003

- Bachelor of Science in Engineering Science,
  New Jersey Institute of Technology, Newark, NJ, 1998

Major: Biomedical Engineering

This thesis is dedicated to my family
for their love and encouragement.

ACKNOWLEDGMENT

I would like to express my sincere appreciation to my advisor, Dr. Arthur Ritter, who not only served as my thesis advisor, but who also offered an endless supply of support, encouragement and reassurance. I would also like to thank Dr. David Kristol and Dr. Peter Engler for being active and accommodating members of my thesis committee.

I deeply appreciate the support given by Dr. Michael Gutkin and Cynthia Procaccio for providing the data used in the study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS

Q	Blood Flow
VO_2	Oxygen Uptake
RBC	Red Blood Cell
Fe^{2+}	Iron ion
CO	Cardiac Output
SV	Stroke Volume
HR	Heart Rate
BP	Blood Pressure
MAP	Mean Arterial Blood Pressure
TPR	Total Peripheral Resistance
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
pO_2	Partial Pressure of Oxygen
pCO_2	Partial Pressure of Carbon Dioxide
Hb	Hemoglobin
$J_{a,x}$	Mass Flux
$-D_{AB}$	Diffusion Coefficient
dC_A/dx	Concentration Gradient
P	Permeability Coefficient
$VO_{2m}(t)$	Oxygen Consumption in the Active Muscles
$VO_{2t}(t)$	Oxygen Consumption in the Inactive Muscles

LIST OF SYMBOLS
(Continued)

$Q_m(t)$	Blood Flow in the Active Muscles
$Q_t(t)$	Blood Flow in the Inactive Muscles
C_{ao2}	Concentration of Arterial Oxygen
C_{vo2}	Concentration of Venous Oxygen
$CvO_{2m}(t)$	Concentration of Venous Oxygen Leaving the Active Muscles
$CvO_{2t}(t)$	Concentration of Venous Oxygen Leaving the Inactive Muscles
VO_{2max}	Maximum Oxygen Consumption
WR	Work Rate
$[La^-]$	Blood Lactate Concentration
DPG	Diphosphoglyceride
ADP	Adenosine Diphosphate
ATP	Adenosine Triphosphate
F_m	Distribution Ratio of Blood in the Active Muscles
τ	Time Constant

CHAPTER 1

INTRODUCTION

1.1 Objective

The objective of this thesis is to analyze oxygen uptake during exercise on a bicycle ergometer using a mathematical model. The experimental data was obtained in the exercise physiology laboratory of Michael Gutkin, M.D., on normotensive and mildly hypertensive patients that Dr. Gutkin was treating in his clinical practice.

Many authors have modeled Pulmonary Oxygen Uptake (VO_2) dynamics during a stepwise increase in work rate using bicycle ergometers (2,3,4,7,9,12,16,28,29). These models show that pulmonary VO_2 response has an early linear rise followed by a predominant exponential rise to a new steady state. The exponential rise reflects muscle VO_2 dynamics. There is evidence that suggests that pulmonary VO_2 kinetics can be influenced by the perfusion kinetics of exercising legs.

The model chosen for analysis of the experimental data was developed by Kyuichi Niizeki, Tatsuhisa Takahashi, and Yoshimi Miyamoto. This was one of the few models that were published with enough information to recreate. It differentiate itself from the others by analyzing the relationships between the metabolic kinetics of muscle and inactive tissues and the changes of VO_2 during non-steady state exercise using a three compartment mathematical model (lungs, exercising muscles and other organs and tissues).

1.2 Background

Muscles consume more oxygen during exercise than at rest. As a result, changes must take place in the cardiovascular and pulmonary systems to accommodate the demand for more oxygen in muscle tissues. The cardiovascular system is made up of the blood, heart, and blood vessels and the pulmonary system consists of the lungs and supporting ductwork.

Blood transports oxygen from the lungs to the cells of the body and carbon dioxide from the cells to the lungs. Blood also regulates pH through buffers, which can influence the ability of the red blood cell (RBC) to carry oxygen. As blood passes through the lungs, hemoglobin inside RBCs combine with oxygen to form oxyhemoglobin. A hemoglobin molecule consists of a protein called globin. This protein is composed of four polypeptides chains (two alpha and two beta), plus four nonprotein pigments called hemes. Each of these hemes contains an iron (Fe2+) that can combine reversibly with one oxygen molecule. The oxygen is transported in this state to other tissues of the body. In the tissues, the iron-oxygen reaction reverses. Hemoglobin releases oxygen, which diffuses into the interstitial fluid and from there into cells.

The heart is a pump that is regulated by the nervous and endocrine systems. Since the heart has autorhythmic fibers, it is able to beat independently. Its operation is related to events occurring in the rest of the body. All body cells must receive a certain amount of oxygenated blood each minute to maintain health and life. When cells are very active, as during exercise, they need faster delivery of oxygen by the blood. During rest periods, cellular need is reduced,

and the workload of the heart decreases. To keep up with the changing workload, the heart changes its Cardiac Output (CO). CO is the amount of blood ejected from the left ventricle into the aorta each minute. Cardiac output is determined by the volume of blood pumped by the ventricle per beat (SV) and the number of heartbeats per minute (HR).

$$CO = SV * HR \tag{1.1}$$

In a resting adult, the stroke volume averages 70 ml/beat and heart rate of 75 beats/min. This gives an average CO of 5.25 l/min and this value is close to the total blood volume. The entire blood supply flows through the pulmonary and systemic circulations about once a minute. During mild exercise SV may increase to 110 ml/beat and HR to 100 beats/min, doubling the resting CO. There are two other factors that influence CO: blood pressure (BP) and resistance (the force of friction as blood moves along blood vessels). Blood flows from regions of higher pressure to lower pressure. The greater the pressure difference the greater the flow. The higher the resistance the lower the flow. Thus:

$$CO = MAP/TPR \tag{1.2}$$

Where MAP is mean arterial blood pressure and TPR is total peripheral resistance.

$$MAP=DBP+(SBP-DBP)/3 \tag{1.3}$$

BP is the pressure exerted by the blood on the wall of a blood vessel and is generated by contraction of the ventricles. In the aorta of a resting, young adult, BP rises to about 120 mm Hg during systole (contraction) and drops to about 80 mm Hg during diastole (relaxation). If CO rises due to an increase in SV or HR then blood pressure rises so long as resistance remains constant.

The pulmonary circulation carries deoxygenated blood from the right ventricle to the air sacs of the lungs and returns oxygenated blood from the lungs to the left atrium. Deoxygenated blood enters the pulmonary artery from the right ventricle. The pulmonary artery then branches out into the large pulmonary arteries which further divide and subdivide. The smallest subdivisions, called capillaries wrap around the alveoli in the lungs. Carbon dioxide passes from the RBCs in the pulmonary capillaries into the alveoli and oxygen diffuses from the alveoli into the blood.

Respiration is divided into external and internal respiration. External respiration is the exchange of oxygen and carbon dioxide between the alveoli of the lungs and the pulmonary blood capillaries. It results in the conversion of deoxygenated blood coming from the heart to oxygenated blood returning to the heart. Several factors can change the rate of external respiration: partial pressure difference between the alveolar pO_2 and pO_2 in the veins, surface area for gas exchange (alveolar-capillary membranes), diffusion distance (total thickness of the alveolar-capillary membranes), and breathing rate and depth.

The exchange between tissue blood capillaries and tissue cells is called cellular respiration. It results in the conversion of oxygenated blood into

deoxygenated blood. In a healthy human, oxygenated blood entering tissue capillaries has a pO_2 of 105 mm Hg, whereas tissue cells have an average pO_2 of 40 mm Hg. This pressure gradient causes oxygen to diffuse from the oxygenated blood through interstitial fluid and into tissue cells. At rest, approximately 25% of the available oxygen in oxygenated blood actually enters the tissue cells. This amount is sufficient to support the needs of resting cells. During exercise, more oxygen diffuses from the blood into active cells. While oxygen diffuses from the tissue blood capillaries into tissue cells, carbon dioxide diffuses in the opposite direction. The average pCO_2 of the tissue cells is 45 mm Hg and tissue capillary oxygenated blood is 40mm Hg. As a result, carbon dioxide diffuses from tissue cells through interstitial fluid into the deoxygenated blood. The deoxygenated blood now returns to the heart. From here, it is pumped to the lungs for another cycle of external respiration.

Although pO_2 is the most important factor that determines the percent of saturated hemoglobin, several other factors influence the affinity of hemoglobin (Hb) for oxygen, (the strength of hemoglobin-oxygen bonding). Metabolically active cells need oxygen and produce acids, CO_2, and heat as by-products. Much of the CO_2 is temporarily taken up by hemoglobin and converted to carbonic acid. Carbonic acid then dissociates into hydrogen ions and bicarbonate ions. The reaction is catalyzed by the enzyme Carbonic Anhydrase, which is present in red blood cells but not in plasma. As hydrogen ion concentration increases, pH decreases. Low pH can also result from Lactic acid, a by-product of anaerobic metabolism within muscles. Higher temperatures resulting from

active muscles can also decrease Hb - O_2 affinity. Evidence also supports that certain chemicals can decrease Hb - O_2 affinity. 2,3 Diphosphoglyceride (2,3 DPG) formed by red blood cells during anaerobic glycolysis (breakdown of glucose for energy) lowers the affinity of Hb for oxygen. 2,3 DPG can be stimulated by higher altitudes and hormones such as Epinephrine, Norepinephrine, Testosterone, Human Growth Hormone, and Thyroxine.

CHAPTER 2

ANALYSIS OF AEROBIC AND ANAEROBIC ATP GENERATION

It has been observed that when a normal individual is subjected to progressively increasing workloads and is allowed sufficient time for recovery between each increment of work, a linear relation between workload and oxygen uptake takes place until the maximal oxygen uptake per unit time is reached. The mechanics of oxygen uptake, before VO_{2max} appears to be simple diffusion, where the main circulatory determinants must be cardiac output and arteriovenous oxygen difference (14,15).

Fick's first law of diffusion:

$$j_{A,x} = -D_{AB}\, dC_A/dx \tag{2.1}$$

Mass flux $j_{A,x}$ is equal to the concentration gradient dC_A/dx multiplied by the binary diffusion coefficient D_{AB}. The integrated form of this equation becomes:

$$j_A = P\Delta C \tag{2.2}$$

where ΔC is the concentration difference across the membrane and P is the permeability coefficient. Applying Equation 2.2 to oxygen consumption by the active muscle tissues yields the equation:

$$VO_{2m}(t) = Q_m(t) \cdot [C_{ao2} - C_{VO2m}(t)] \tag{2.3}$$

The arteriovenous oxygen difference is determined by the difference between the oxygen content in the arterial blood and minimal oxygen content in mixed venous blood. The maintenance of arterial oxygen tension during heavy exercise demonstrates that pulmonary factors, ventilatory or diffusive do not limit oxygen transport in normal subjects (14).

Workload can usually be increased past VO_{2max} but ordinarily oxygen uptake levels off or declines (VO_2 slow component). Studies have shown that the volume of carbon dioxide produced outweighs the volume of O_2 produced when these workloads are reached. As a result the body can be considered a bioenergetic system that adjusts two mechanisms of energy production (aerobic and anaerobic) in response to a mechanical stimulus (i.e. cycle ergometer). It is assumed that during incremental exercise VO_2 is a good indicator of the energy production released from aerobic sources and that the net accumulation of Lactic Acid in the blood is quantitatively related to the overall net energy production from anaerobic sources that is independent of the Phosphocreatine energy system. In a study by Yano, Yunoki, and Ogata, blood lactate levels begin to rise at 50-70% of VO_{2max} (6,29).

The mechanisms responsible for increased arterial blood lactate concentration ($[La^-]$) during muscular exercise in humans remain controversial, especially with respect to whether the change in blood $[La^-]$ evidences threshold behavior as a function of work rate and whole-body oxygen uptake; and whether such a threshold is a result of anaerobic glycolosis. One piece of evidence which

is often cited as an indicator that tissue anaerobiosis is not normally a cause of increased blood [La^-] is that the partial pressure of O_2 (pO_2) of the venous blood from the contracting muscles in subjects exercising at VO_{2max} is 15-20 mm Hg. This is more than an order of magnitude greater than critical pO_2 below which mitochondria O_2 consumption begins to diminish and tissue anaerobiosis begins. This view fails to take into account local variability of tissue pO_2, which depends on relative distributions of VO_2 and blood flow within the muscle (27).

John Severinghaus showed that during work, increasing ADP – driven glycolosis raises muscle cytosolic and venous pyruvate and therefore lactate resulting from cytochrome reduction as O_2 pressure falls causing an accumulation of each metabolite in the citric acid cycle. The mass effect is a concentration gradient dependence of rate in each enzyme step, particularly at Pyruvate dehydrogenase (PDH). In steady heavy exercise, rising arterial lactate reduces the output of muscle lactate and thus reduces anaerobic ATP generation, suggesting that ATP production could be forced to be completely aerobic up to VO_{2max} by lactate infusion (23).

Several factors have been considered as possible mediators of the VO_2 slow component: temperature of the body and muscles, energy cost of ventilatory and cardiac work, auxiliary muscle work, circulatory catecholamines level, blood lactate accumulation and muscle pH changes, muscle fibres energetic or recruitment profile. Since the primary origin of the VO_2 slow component is apparently in the exercising limbs, this reduces substantially the number of candidate mediators above. In particular the recruitment of type II muscle fibres,

that produce lactate more readily than type I muscle fibres, is currently the most acceptable explanation for the VO_2 slow component phenomenon. The lower pH associated with the lactic acid production might shift the O_2 – Hb saturation curve to the right, thereby facilitating the unloading of O_2 at the capillary level during heavy exercise (Bohr Effect). Higher altitudes can reduce the Bohr Effect (8,19,20,23).

Body mass alone could account for 78% of the variance in oxygen uptake during exercise (24), Data from species of various sizes have demonstrated that oxygen uptake is proportional to body mass. These findings show that work is proportional to muscle mass and body weight (14).

A fast start to exercise may help to speed VO_2 kinetics, but it also has the potential to cause premature fatigue. It is known that disturbances in muscle pH become greater as the intensity of exercise increases. Therefore, greater disturbances in muscle pH resulting from a fast start may impair supramaximal performance by inhibiting anaerobic glycolosis and/or interference with muscle contractile processes. It has also been suggested that a reduction in muscle pH resulting from a fast start may impair performance by a loss of technique that may accompany fatigue (5).

Rossiter, Ward, Kowalchuk, Howe, Griffiths, and Whipp showed that the slow component of VO_2 can was related to the fatigue process by measuring blood flow and arterio-venous O_2 content difference across an exercising limb. They showed that the VO_2 slow component was significantly associated with limb QO_2, suggesting 86% of the slow component of VO_2 arose in the exercising

muscle and anaerobiosis can result from dynamics of cardiac output, asymmetries of intramuscular pH, feedfoward control of QO_2, and asymmetric kinetics of respiratory control mechanisms. The assumption is that constant work requires constant ATP production (1,12,22).

Modesti, Olivo, Pestelli, Guarnaccia, Gensini, Malfanti, and Serneri studied hypertensives. It has been observed that they reached the anaerobic threshold earlier with a normal cardiac response. They also performed the largest portion of the exercise test in anaerobiosis. Evidence seems to indicate that cardiovascular response to exercise in hypertensives is influenced by abnormalities of the peripheral circulation rather than by central mechanisms. The reasoning behind this is that in hypertension the increase in blood flow to the exercising muscle is reduced, resulting in the observed reduction in O_2 consumption. Hypertensives experience a lower blood perfusion of the exercising muscle than controls despite an increased systemic blood pressure response. This pattern is mainly due to abnormalities of the vasomotor tone, with lower response to vasodilatory stimuli and a relatively higher increase in peripheral vascular resistance than in controls (17).

Individuals with a slow heart rate response to the onset of exercise also have a slow VO_2 response. Patients with congestive heart failure adapt to exercise more slowly because of their slow VO_2 kinetics. These patients with congestive heart failure also show interesting modifications in peripheral blood flow response. They release less nitric oxide and have lower blood flow to exercising skeletal muscle, but this response is improved with training (11).

Other studies have been done to determine whether or not training has an effect on oxygen consumption. High intensity exercise (higher than 80% of maximum heart rate) shows an improvement of VO_{2max} over time. The VO_{2max} increase suggests an increase in maximal cardiac output and/or an increased maximal oxygen extraction in response to training (10,13,26).

Age too, seems to be a factor in VO_2. It has been observed that older men tend to have lower oxygen uptake. Leg blood flow, leg vascular conductance and femoral venous O_2 saturation were 20-30% lower in older men at each work rate as work was increased. The high ventilatory demand associated with large muscle mass exercise could explain the reduction in leg blood flow (21).

CHAPTER 3

MATERIALS AND METHODS

The mathematical model proposed by Kyuichi Niizeki, Tatsuhisa Takahashi, and Yoshimi Miyamoto was recreated using Vissim. Refer to Appendix A for the modeling equations. The model starts with the hypothesis that the redistribution of blood flow is responsible for changes in pulmonary VO_2 during ramp exercise and is comprised of three compartments, lungs, exercising muscles, and inactive tissues. It is assumed that the active and inactive compartments are connected in parallel with the lung compartment and have separate regional circulations. A lumped gas exchange site for each compartment is assumed as well. Figure 3.1 illustrates the compartments and blood flows.

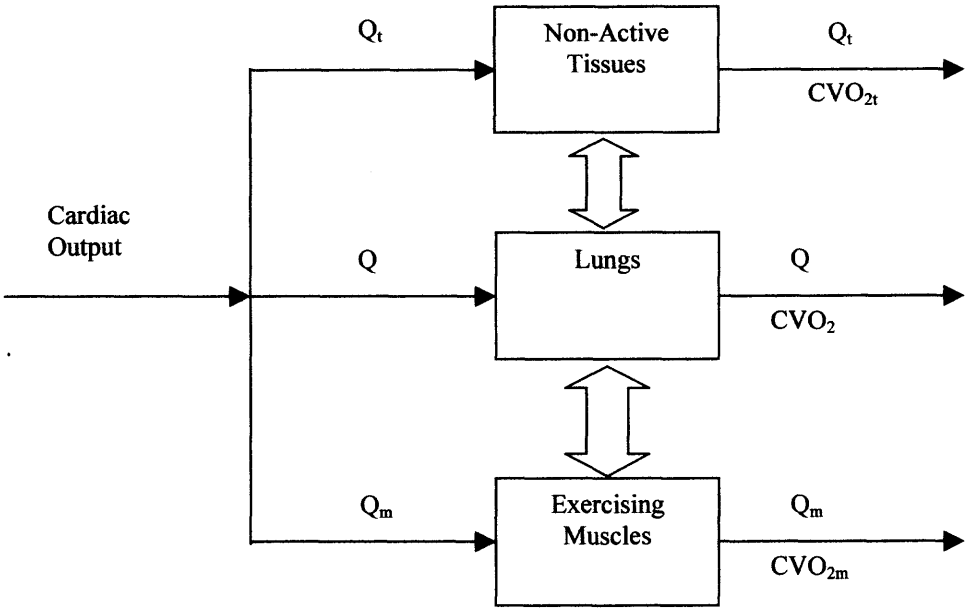

Figure 3.1 General mass / flow diagram used to develop modeling equations. The diagram shows three separate compartments used in the transfer of oxygen and the blood flow into and out of those compartments. The single line arrows represent the blood flow and the concentrations of oxygen. The double arrows represent the gas exchange between the three compartments.

Kyuichi, Takahashi, and Miyamoto used the C language to program the solution to one set of model differential equations and all calculations were performed on a SUN SPARCstation (SUN Microsystems). Responses of VO_2 to moderate exercise with workload profiles were simulated from 30 to 100 W. These responses were compared with experimental data to prove validity of the model. The study group consisted of seven young healthy male subjects that exercised using a bicycle ergometer (Lode 300) in the upright position. A baseline value of 30 W was used instead of 0 W because work rate loaded by an ergometer may not be linear from 0 to 30 W. Results from the Vissim version are similar to the C

language results. Refer to Appendix A for modeling equations and respective graph results (Figures B.1, B.2, B.3, B.4, and B.5) from Vissim. As work rate intensifies, blood flowing to the active muscles increases, while the blood flow to the viscera and the inactive muscles decreases. Most literature documents that 15-20% of the total blood flow perfuses the muscle compartment at rest and 80-85% perfuses the muscle compartment during heavy exercise. This model assumes that the ratio of blood flow in the muscle compartment to total cardiac output increases as a linear function of work rate during submaximal exercise (<150W).

$$F_m = K_f \cdot WR + 0.2 \qquad (3.1)$$

F_m is the redistribution ratio for the muscle compartment. WR is the work rate and K_f is the slope of Fm-WR relationship. K_f was set to 0.004. The redistribution ratio for the inactive tissue compartment is expressed as $1-F_m$, so the sum of the blood flow through the inactive tissue compartment and the muscle compartment is equal to the cardiac output.

The redistribution of blood flow during exercise seems to occur as a result of both an increase in the local release of vasodilatory substances from the working muscles and an increase in vascular sympathetic tone. It has been observed that $F_m(t)$ (distribution ratio in the muscle compartment as a function of time) can be predicted by a 1^{st} order exponential equation at the onset of

exercise, where t_f is the time delay and F_{mb} and F_{ms} are the redistribution ratios in the muscle compartments for baseline and steady state work rates.

$$F_m(t) = F_{mb} + (F_{ms} - F_{mb}) \times [1 - \exp(-t/t_f)] \quad (3.2)$$

From this equation, and knowing cardiac output with respect to different work rates (baseline and steady state), $Q_m(t)$ (blood flow to the muscle compartment as a function of time) can be solved for by the following equation.

$$Q_m(t) = F_m(t) \cdot \{Q_b + (Q_s - Q_b) \times [1 - \exp(-t/t_Q)]\} \quad (3.3)$$

Equation 3.3 is similar to Equation 3.2 since it too can be predicted by a 1st order exponential equation at the onset of exercise. After solving for $Q_m(t)$, the relationship between VO_{2mc} (volume of oxygen consumed in the muscle compartment)and O_2 content in blood leaving muscle compartment can be expressed by the following equation.

$$V_m \frac{dCvO_{2\,m}(t)}{dt} = -VO_{2\,mc}(t) + Q_{m}(t) \cdot [C_{ao2} - C_{vO2m}(t)] \quad (3.4)$$

CaO_2 and V_m are the arterial O_2 content and the effective volume of the muscle tissue compartment. At steady state Equation 3.4 is identical with Fick's equation. The authors of the model made an initial estimate of 10 liters for V_m. They did so by assuming that the active muscle mass was 15 kg with a water

content of ~70%. VO_{2tc}, which is the volume of oxygen in the tissue cells, was assumed to be constant regardless of work rate.

$$VO_{2tc} = CaO_2 * Q_t \tag{3.5}$$

The factors governing the volume of O_2 in the tissue compartment are the concentration of oxygen and cardiac output. Venous blood O_2 content was calculated using a similar equation to Equation 3.4.

$$V_t \frac{dCvO_{2t}(t)}{dt} = -VO_{2tc} + Q_t(t) \cdot [C_{ao2} - C_{VO2t}(t)] \tag{3.6}$$

V_t is effective volume of tissue other than working muscles. Both simulations (Vissim and C) used fourth-order Runge-Kutta technique to solve Equations 3.4 and 3.6.

The rate of VO_2 in the muscle compartment can be determined using Fick's principle.

$$VO_{2m}(t) = Q_m(t) \cdot [C_{ao2} - C_{VO2m}(t)] \tag{3.7}$$

For this model, CaO_2 was assumed to remain constant at 20 vol %, (which is defined as a flow weighted average). The authors of the model used 10 liters for the volume of their muscle compartment and 2 liters for their tissue compartment. They also used transport delays from the muscle compartment to the lungs and

from the inactive tissue to the lungs that was added to Equations 3.2 and 3.3. These delays depend on vascular volumes and regional blood flow rates. Since Vissim is limited in the amount of equation blocks used in the simulation, these delays were accommodated by adjusting the volume by a factor of 15. The values of τ_m, τ_q, and τ_f were also adjusted to fit the rate of change that was documented in the paper. The model proposed in C language used 10, 40, and 10 secs for values of τ_m, τ_q, and τ_f respectively. The ΔQ in the model is 4.2 L/min. ΔVO_{2mc} was given as 0.7 L/min and ΔF_m as 0.28. The values for τ_m, τ_q, and τ_f were found by fitting the respective equations into the rates of change. An example of how τ_q affects the equation for Q is shown in Figure B.6. As the value of τ_q increases the slope of the line decreases, slowing the time it takes Q to reach steady state. This carries over to the oxygen uptake equations causing a delay there as well. The same affect on VO_2 is observed when τ_m and τ_f is increased. All other parameters followed the model proposed by Kyuichi Niizeki, Tatsuhisa Takahashi, and Yoshimi Miyamoto. The parameters used in the model are listed in the Table 3.1.

TABLE 3.1 Parameters, values and units used in modeling oxygen consumption.

Parameters	Units	C - Language Model Default Values	Vissim Model Default Values
CaO_2	Vol %	20.0	20.0
V_m	Liters	10	150
V_t	Liters	2	30
V_{ML}	ML	1,300	NA
V_{TL}	ML	500	NA
K_f	NA	0.004	0.004
τ_m	S	10	60
τ_q	S	40	60
τ_f	S	10	60
Q (30 W)	L/min	7.5	7.5
Q_m (30 W)	L/min	2.4	2.4
Q_t (30 W)	L/min	5.1	5.1
VO_2 (30 W)	L/min	0.55	0.55
VO_{2m} (30 W)	L/min	0.20	0.20
VO_{2t} (30 W)	L/min	0.35	0.35
F_m	NA	0.32	0.32
ΔQ	L/min	4.2	4.2
ΔVO_{2mc}	L/min	0.7	0.7
ΔF_m	NA	0.28	0.28

CHAPTER 4

RESULTS AND DISCUSSION

After the model was successfully recreated on Vissim, Dr. Michael Gutkin's data was used to see if the model would fit the experimental data. Dr Gutkin's sample group consisted of 33 normal and 49 mildly hypertensive adults that were not taking any medication to lower their blood pressure. These patients were subjected to a bicycle ergometer at an increasing work rate (2 minute intervals at 30 watt increments). He measured pulse, systolic and diastolic blood pressure, O_2 consumption, and CO_2 production. Data for O_2 consumption from the two sample groups that Dr. Gutkin observed and the predicted values for O_2 consumption using the Vissim Model are listed in Tables 4.1 and 4.2.

TABLE 4.1 Oxygen consumption vs. work rate in 33 normal adults, modeled in Vissim and observed data.

Statistics of VO_2 from the Normals Modeled in Vissim								
Watts	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**
Mean	0.518265	1.000765	1.295152	1.608857	1.973647	2.341833	2.678	3.153
Standard Error	0.013868	0.00861	0.010869	0.021982	0.023587	0.052931	8E-307	8E-307
Median	0.5135	1.009	1.293	1.6145	1.981	2.338	2.678	3.153
Mode	0.591	1.036	1.353	1.607				
Standard Deviation	0.080862	0.050204	0.062437	0.116318	0.097252	0.129654		
Sample Variance	0.006539	0.00252	0.003898	0.01353	0.009458	0.01681		
Kurtosis	2.225083	2.641739	-0.55325	1.796326	-0.18245	-0.75684		
Skewness	-0.71775	-1.11249	-0.08027	-0.95912	-0.0174	0.202667		
Range	0.408	0.25	0.238	0.548	0.36	0.355	0	0
Minimum	0.253	0.832	1.172	1.28	1.782	2.174	2.678	3.153
Maximum	0.661	1.082	1.41	1.828	2.142	2.529	2.678	3.153
Sum	17.621	34.026	42.74	45.048	33.552	14.051	2.678	3.153
Count	33	33	32	27	17	6	1	1
Confidence Level(95.0%)	0.028214	0.017517	0.022139	0.045104	0.050002	0.136063		
Statistics of VO_2 from the Normals Observed by Dr. Gutkin								
Watts	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**
Mean	0.736242	0.989455	1.316156	1.636556	2.050882	2.449333	2.706	3.147
Standard Error	0.036263	0.038547	0.040338	0.062532	0.049369	0.089341	8E-307	8E-307
Median	0.721	0.937	1.316	1.617	2.096	2.3995	2.706	3.147
Mode		0.923	1.359		2.238			
Standard Deviation	0.208314	0.221438	0.228185	0.324928	0.203553	0.21884		
Sample Variance	0.043395	0.049035	0.052069	0.105578	0.041434	0.047891		
Kurtosis	1.558906	0.864532	0.477707	-0.10285	-0.63864	2.986721		
Skewness	-0.63715	0.108781	0.072297	-0.26113	-0.61864	1.593546		
Range	1.036	1.081	1.097	1.226	0.666	0.62	0	0
Minimum	0.091	0.405	0.788	0.996	1.663	2.238	2.706	3.147
Maximum	1.127	1.486	1.885	2.222	2.329	2.858	2.706	3.147
Sum	24.296	32.652	42.117	44.187	34.865	14.696	2.706	3.147
Count	33	33	32	27	17	6	1	1
Confidence Level(95.0%)	0.073865	0.078519	0.08227	0.128537	0.104657	0.229658		

TABLE 4.2 Oxygen consumption vs. work rate in 49 mildly hypertensive adults, modeled in Vissim and observed data.

Statistics of VO_2 from the Hypertensives Modeled in Vissim							
Watts	**30**	**60**	**90**	**120**	**150**	**180**	**210**
Mean	0.554735	0.999776	1.314133	1.6796	1.915966	2.327778	2.5618
Standard Error	0.013061	0.00878	0.015531	0.02121	0.025556	0.036398	0.051688
Median	0.561	1.014	1.323	1.695	1.933	2.3445	2.546
Mode	0.561	1.001	1.423	1.711	1.845		
Standard Deviation	0.091425	0.061463	0.104184	0.125479	0.137624	0.154424	0.115578
Sample Variance	0.008359	0.003778	0.010854	0.015745	0.01894	0.023847	0.013358
Kurtosis	0.366427	17.02602	3.592139	0.790269	-0.68056	-0.87032	-0.42452
Skewness	0.014166	-3.58051	-1.34472	-0.46438	-0.17272	-0.07894	0.343986
Range	0.441	0.382	0.561	0.575	0.519	0.514	0.301
Minimum	0.351	0.671	0.921	1.354	1.634	2.089	2.421
Maximum	0.792	1.053	1.482	1.929	2.153	2.603	2.722
Sum	27.182	48.989	59.136	58.786	55.563	41.9	12.809
Count	49	47	43	33	29	18	5
Confidence Level(95.0%)	0.02626	0.017654	0.0313	0.043103	0.052349	0.076794	0.143509
Statistics of VO_2 from the Hypertensives Observed by Dr. Gutkin							
Watts	**30**	**60**	**90**	**120**	**150**	**180**	**210**
Mean	0.723551	1.006723	1.328767	1.704424	1.973517	2.339222	2.63
Standard Error	0.031889	0.033826	0.042254	0.037544	0.055185	0.04767	0.109135
Median	0.775	1.05	1.362	1.701	2.02	2.335	2.677
Mode	0.961	1.091	1.177	1.437	1.873		
Standard Deviation	0.223226	0.231896	0.277081	0.215673	0.297182	0.202248	0.244033
Sample Variance	0.04983	0.053776	0.076774	0.046515	0.088317	0.040904	0.059552
Kurtosis	0.436828	3.202126	1.943679	3.914705	1.473443	-0.42086	3.831765
Skewness	-0.29046	-1.16938	-1.30817	-1.02772	-0.83658	-0.32554	-1.90074
Range	1.057	1.239	1.294	1.166	1.352	0.765	0.6
Minimum	0.186	0.129	0.415	0.944	1.216	1.926	2.207
Maximum	1.243	1.368	1.709	2.11	2.568	2.691	2.807
Sum	35.454	47.316	57.137	56.246	57.232	42.106	13.15
Count	49	47	43	33	29	18	5
Confidence Level(95.0%)	0.064118	0.068087	0.085273	0.076474	0.113042	0.100576	0.303007

The model proposed by Kyuichi Niizeki, Tatsuhisa Takahashi, and Yoshimi Miyamoto, was used to fit Dr. Gutkin's experimental data. Refer to Appendix A for the modeling equations. The parameters used are listed in Tables 4.3 and 4.4.

TABLE 4.3 Parameters used in modeling normal adults using Vissim.

Watts	F_{mb}	F_{ms}	VO_{2mcb}	$Vo_{2mc(wr)}$	Q_b	Q_s	V_m	V_t	τ_m	τ_q	τ_f	CaO_2
30-60	0.30	0.40	0.2	0.5	7.04	8.36	150	30	60	60	60	23
60-90	0.40	0.50	0.5	0.8	8.36	9.96	150	30	60	60	60	23
90-120	0.50	0.60	0.8	1.1	9.96	11.54	150	30	60	60	60	23
120-150	0.60	0.70	1.1	1.4	11.54	13.80	150	30	60	60	60	23
150-180	0.70	0.80	1.4	1.7	13.80	15.77	150	30	60	60	60	23
180-210	0.80	0.90	1.7	2.0	15.77	17.00	150	30	60	60	60	23
210-240	0.90	1.00	2.0	2.3	17.00	19.50	150	30	60	60	60	23

TABLE 4.4 Parameters used in modeling mildly hypertensive adults using Vissim.

Watts	F_{mb}	F_{ms}	VO_{2mcb}	$Vo_{2mc(wr)}$	Q_b	Q_s	V_m	V_t	τ_m	τ_q	τ_f	CaO_2
30-60	0.31	0.43	0.2	0.5	7.04	8.48	150	30	65	65	65	23
60-90	0.43	0.54	0.5	0.8	8.48	10.05	150	30	65	65	65	23
90-120	0.54	0.66	0.8	1.1	10.05	11.94	150	30	65	65	65	23
120-150	0.66	0.77	1.1	1.4	11.94	13.54	150	30	65	65	65	23
150-180	0.77	0.88	1.4	1.7	13.54	15.12	150	30	65	65	65	23
180-210	0.88	1.00	1.7	2.0	15.12	17.06	150	30	65	65	65	23

Dr. Gutkin determined cardiac output by using the following correlation, where VO_2 is measured in ml/kg/min.

$$CO = 66 + (52 \times VO_2) \quad (4.1)$$

The time delays were slightly increased to model the hypertensive patients in order to compensate for their higher blood pressure. The rate of intensity of work has been shown to also change the slope of VO_2, (in both normals and hypertensives) (17). Since there is not enough information to determine the difference in the experimental conditions between Dr. Gutkin's group and the data used by Kyuichi, Takahashi, and Miyamoto, the same time delays and volumes were used for the normals as in the recreation of the model discussed in Chapter 3.

The volume of oxygen in the muscle cells was assumed to be a linear function of the work rate. Using the parameters for baseline and the rate of change for VO_{2mc} from the model, the linear regression becomes:

$$VO_{2mc} = 0.01(\text{watts}) - 0.1 \quad (4.2)$$

Based on the redistribution ratio proposed in the model (Equation 3.1), VO_{2max} is at 200 watts. This is the point in which F_m has a value of 1. It is after this point, that the muscle cells require more oxygen than can be provided by the blood (refer to Figure B.7). For the Vissim models VO_{2max} was adjusted for both the normals and the hypertensives, ~ 240 and ~ 210 watts respectively. As a result, K_f

now becomes 0.0033 for the normals and 0.0038 for the hypertensives. Graphs of the Normals vs. Time from 30 to 240 watts and the Hypertensives vs. Time from 30 to 210 watts are shown in Figures 4.1 and 4.2, respectively.

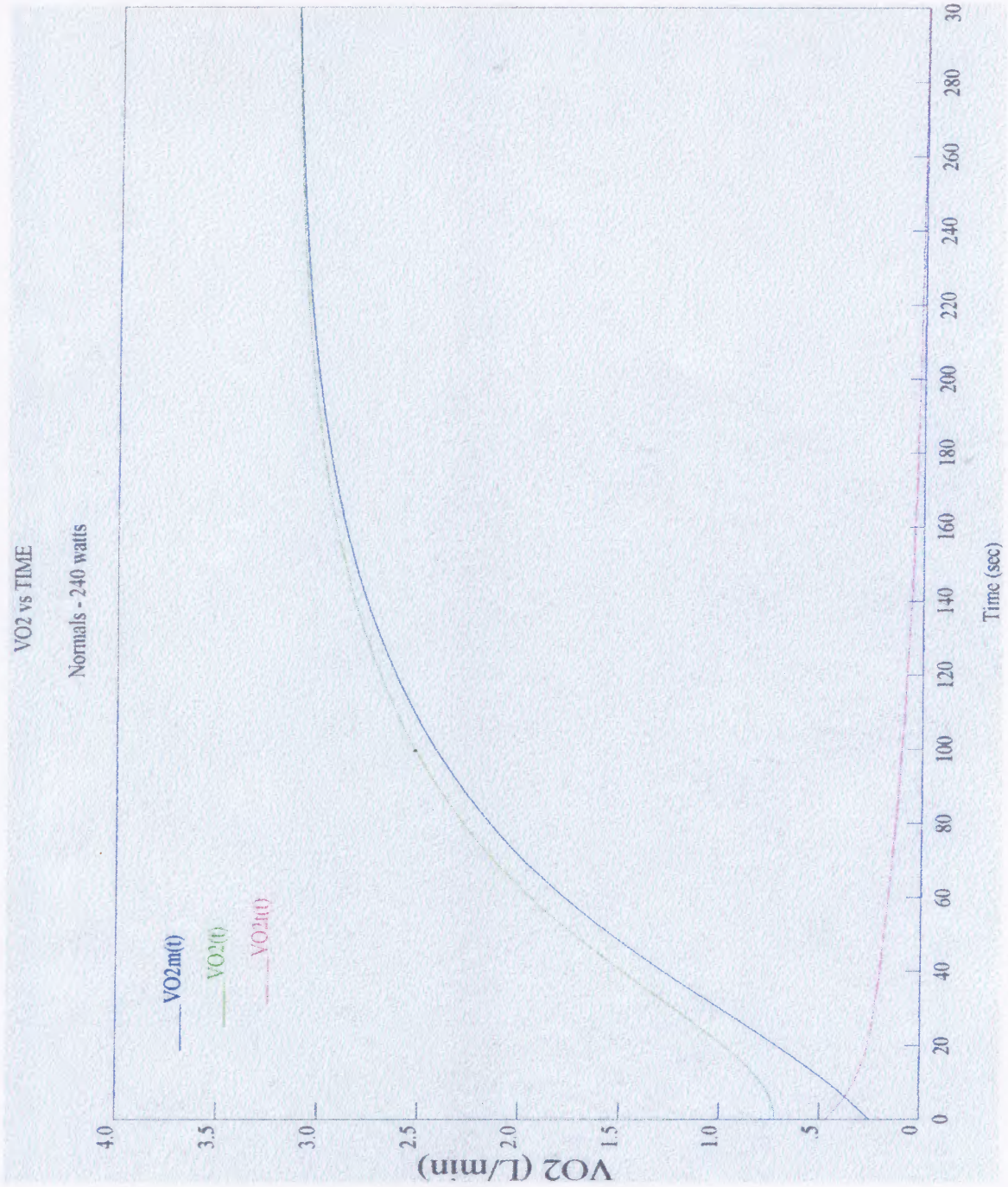

Figure 4.1 Graph of oxygen consumption vs. time in normal adults using Vissim as exercise is increased from 30 – 240 Watts. This graph shows amount of oxygen diffusing out of the active muscles, inactive tissues, and the sum of these two compartments as a function of time using the parameters in Table 4.3.

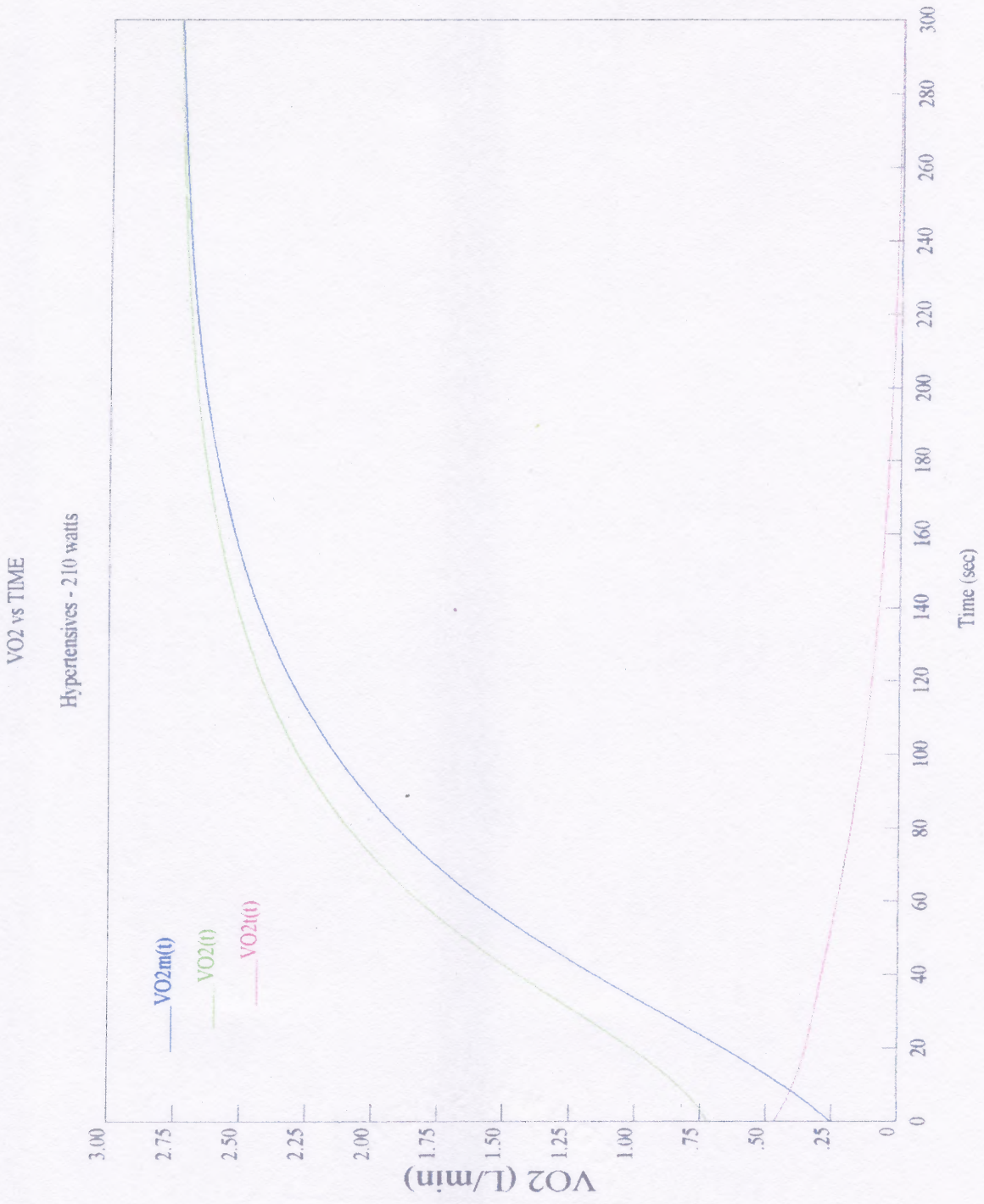

Figure 4.2 Graph of oxygen consumption vs. time in mildly hypertensive patients using Vissim as exercise is increased from 30 – 210 Watts. This graph shows amount of oxygen diffusing out of the active muscles, inactive tissues, and the sum of these two compartments as a function of time using the parameters in Table 4.4.

The 33 normals and 49 hypertensives were modeled individually and compared to the data Dr. Gutkin Obtained. The means of the groups were graphed in Figures 4.3 and 4.4. The Graphs of Oxygen uptake vs. work rate in both normals and hypertensives show linear relationships. The flattening off at 210 watts in the hypertensive model is typical behavior of an individual reaching VO_{2max}. The observed values still exhibit an increase linearly at 210 watts, suggesting they have not reached VO_{2max}.

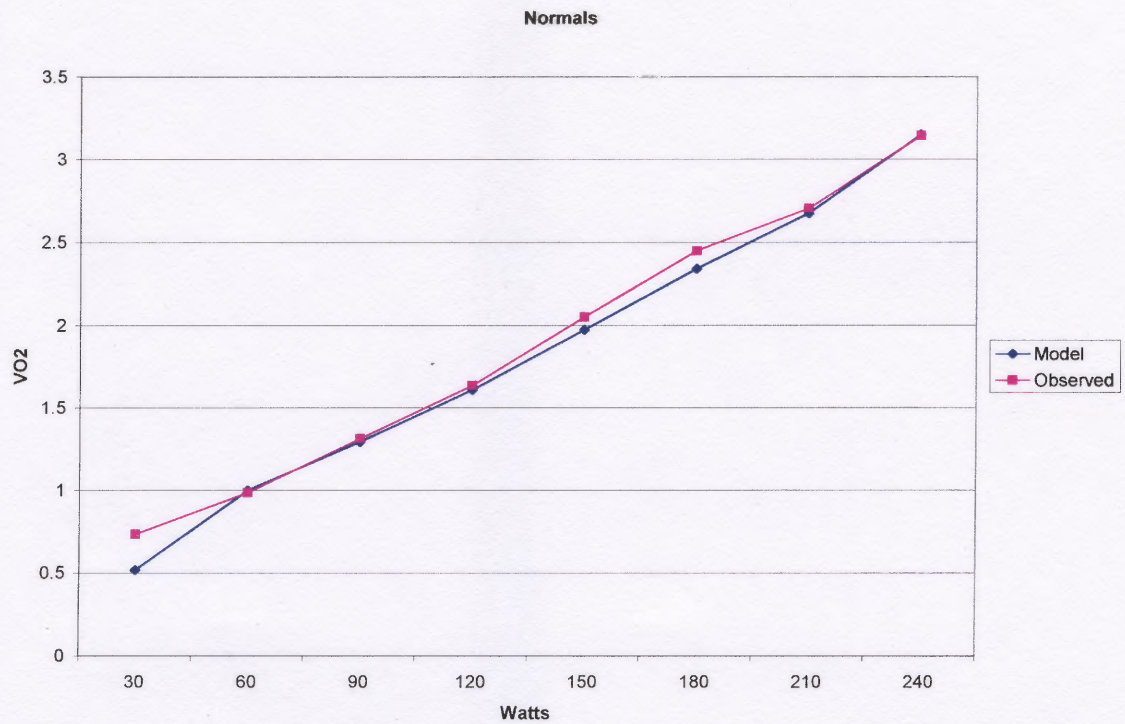

Figure 4.3 Graph of VO_2 values observed by Dr. Gutkin from his group of normotensives and the VO_2 values predicted using Vissim. These values and relative statistics are listed in Table 4.1

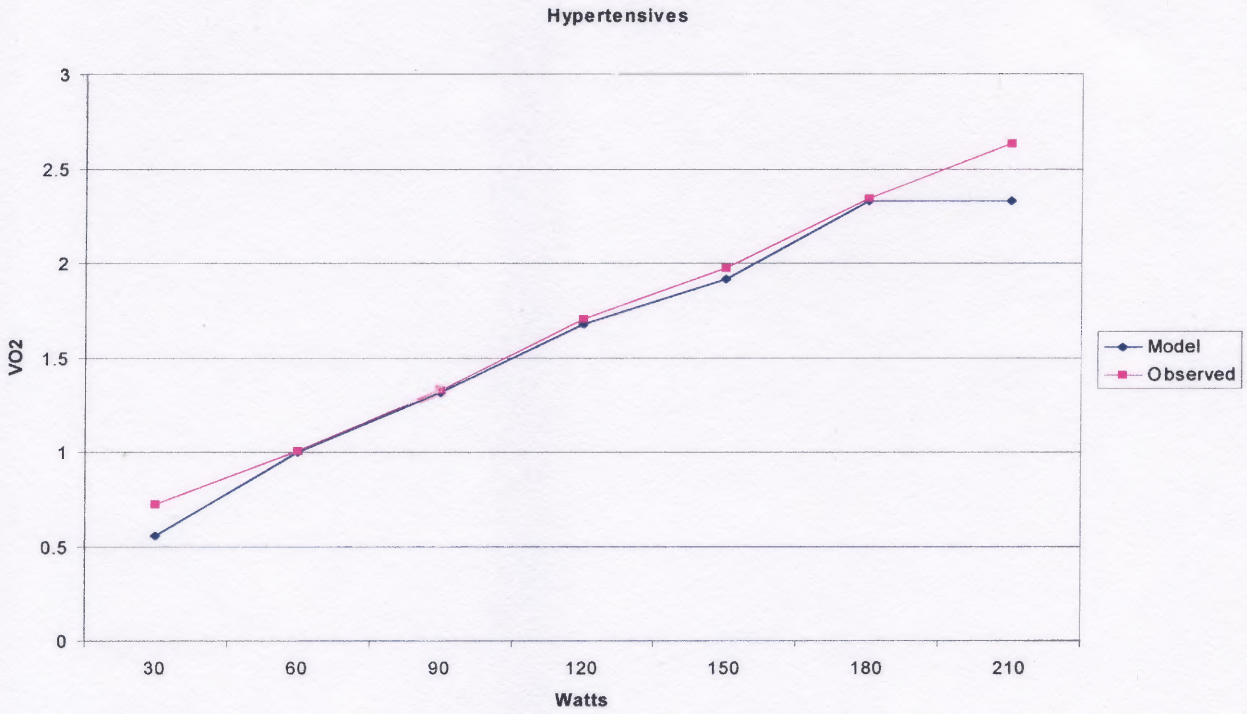

Figure 4.4 Graph of VO_2 values observed by Dr. Gutkin from his group of hypertensives and the VO_2 values predicted using Vissim. These values and relative statistics are listed in Table 4.2

Using Excel's descriptive statistics, the experimental and actual data was compared, refer to Table 4.1 and 4.2. The Range of values and standard deviation obtained from the model for both the hypertensives and normals were much less than the actual data. The values derived by the model at 30 watts differs significantly to the data obtained from Dr. Gutkin. This difference is attributed to using parameters from Kyuichi Niizeki, Tatsuhisa Takahashi, and Yoshimi Miyamoto. The averages that they obtained for baseline (30 watts) and steady state (100 watts) were approximately 0.55 and 1.25 L/min, respectively. At higher work rates the model is able to predict VO_2 values more in line with the

observed values. There is less than a 2 % difference between the mean values obtained at 60, 90 and 120 watts in comparing the experimental data to the actual data for both the hypertensives and normals, refer to Table 4.5.

Table 4.5 Comparison of the means between experimental and data recorded by Dr. Gutkin.

Watts	Normals	Hypertensives
30	42.1	30.0
60	1.2	0.7
90	1.6	1.1
120	1.7	1.4
150	3.9	3.0
180	4.6	0.5
210	1.0	13.0
240	0.2	

CHAPTER 5

CONCLUSIONS AND SUGGESTIONS

The computer model has accomplished two objectives. The model can replicate the response of an exercising subject with respect to time after the onset of exercise and the model has shown that given assumptions and parameters the balance between oxygen transport and oxygen requirement is very delicate.

Dr. Gutkin's data was fitted with the model proposed by Kyuichi Niizeki, Tatsuhisa Takahashi, and Yoshimi Miyamoto. The predicted VO_2 results varied significantly at baseline and at 210 watts for the hypertensives. Graphs of the observed data vs. work rate show a linear relation in both the hypertensives and the normals, suggesting the model is incorrect at those two points. The difference at baseline was contributed to the parameters suggested by the author's of the model. Their data was much lower than the data Dr. Gutkin obtained at 30 watts. The predicted values obtained at 210 watts for the hypertensives were off by 13%. This seems to have resulted from the value set for the distribution ratio.

In analyzing the modeling equations, oxygen uptake depends on cardiac output and the arterio-venous oxygen content. The model shows that there does not seem to be any great reserve of oxygen available at the working muscles. As a result, anaerobisis for ATP production is needed after VO_{2max} is reached.

The values for Q and VO_2 collected during Dr. Gutkin's study do not vary significantly. The assumption for his study was that cardiac output for those suffering from hypertension would decrease, failing to match the potential of a

healthy person. Data from Dr. Gutkin's group indicates that in mild hypertensives the body can compensate for those factors contributing to high blood pressure during exercise.

As modeling tools become available, it will be easier to investigate this model further. The version of Vissim that was used has many limitations. There were many instances in simulating this model, where the number of blocks were exceeded. Even if they weren't exceeded, the file would move blocks when it was opened, due to the size of the file. A program without these limitations should be able to replicate the model proposed by Kyuichi Niizeki, Tatsuhisa Takahashi, and Yoshimi Miyamoto more proficiently.

One suggestion for further study is to use a larger group of subjects in order to collect more data at VO_{2max}. Only about half of Dr. Gutkin's patients made it to 150 watts, and this number dropped dramatically at increasing work rates. This data could then be used to expand the current model to predict the rise in VO_{2m} as VO_2 levels off as in Figure B.7.

APPENDIX A

WORKING EQUATIONS IN VISSIM FORMAT

This appendix provides the working equations in Vissim format. These equations were used in recreating the model proposed by Niizeki, Takahashi, and Miyamoto. After this model was working successfully, the same equations were used (changing key parameters) to fit the data supplied by Dr. Gutkin and Cynthia Procaccio.

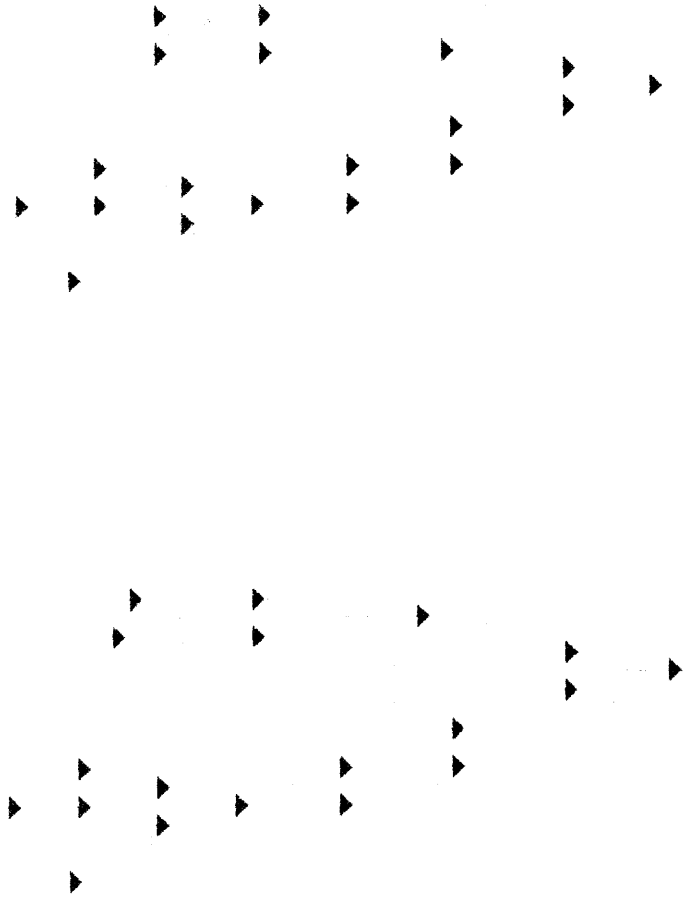

Figure A.2 Vissim equations used in determining the distribution ratio with respect to time, ($F_m(t)$), and the volume of oxygen in the muscle compartment with respect to time, ($VO_{2mc}(t)$). These equations use baseline and steady state values as well as a time constants in determining $F_m(t)$ and $VO_{2mc}(t)$.

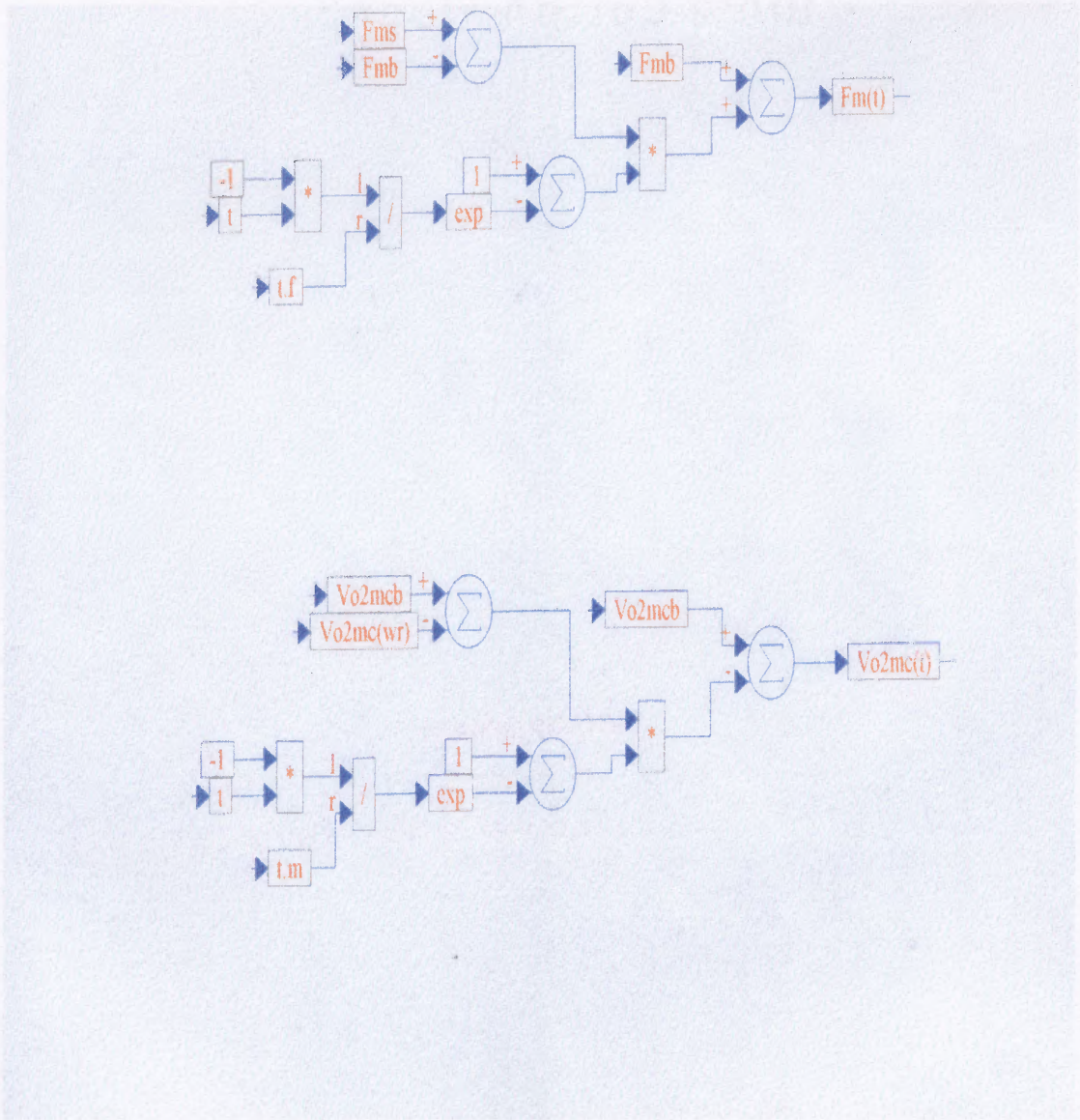

Figure A.2 Vissim equations used in determining the distribution ratio with respect to time, ($F_m(t)$), and the volume of oxygen in the muscle compartment with respect to time, ($VO_{2mc}(t)$). These equations use baseline and steady state values as well as a time constants in determining $F_m(t)$ and $VO_{2mc}(t)$.

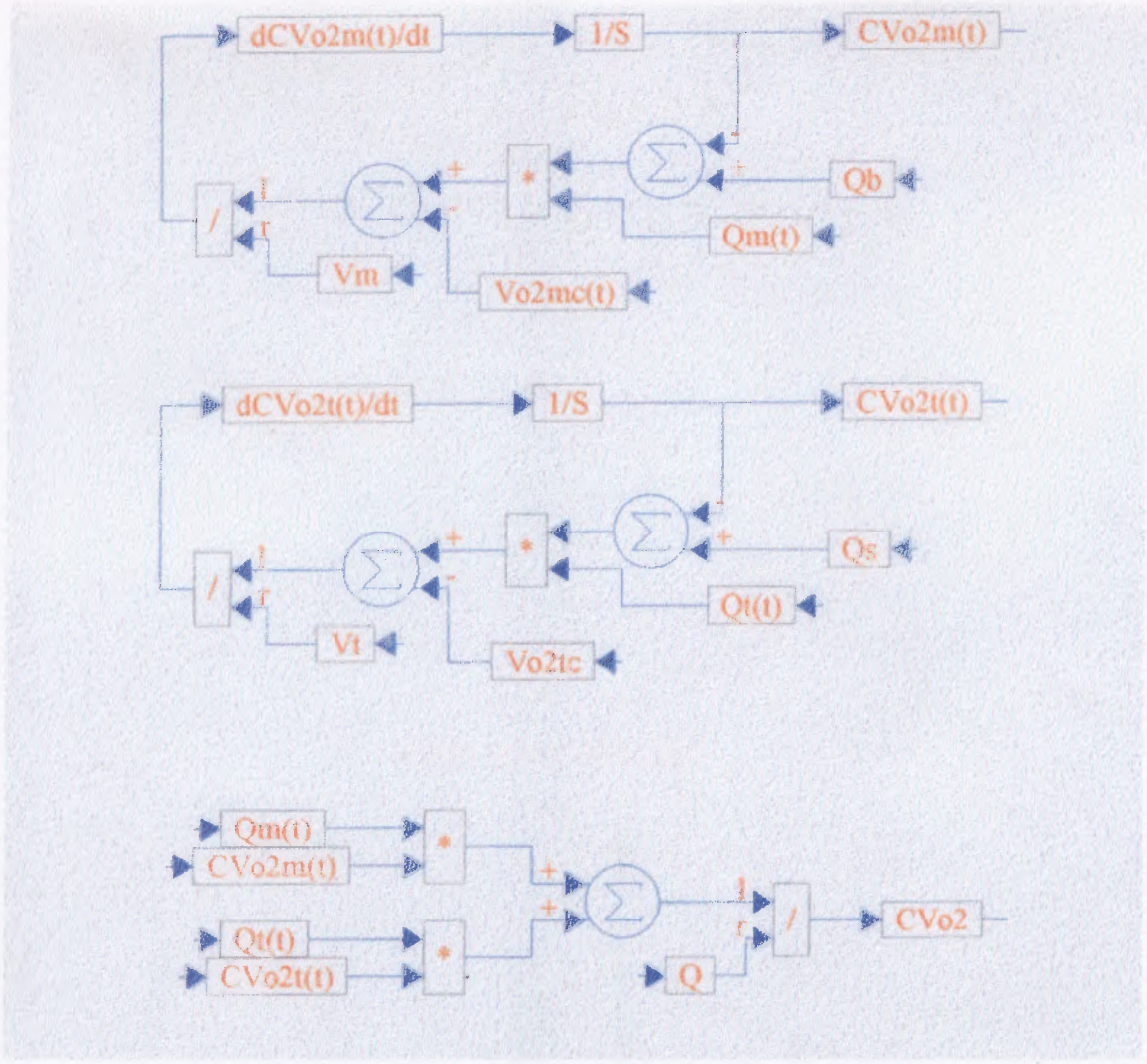

Figure A.3 Vissim equations used to determine the concentration of venous oxygen in the active muscles, $[CvO_{2m}(t)]$, inactive tissues, $[CvO_{2t}(t)]$, and the total concentration, $[CvO_2(t)]$, of venous oxygen at any point in time. The determining factors in these equations are the volumes of the compartments, volume of oxygen and blood flow in these compartments.

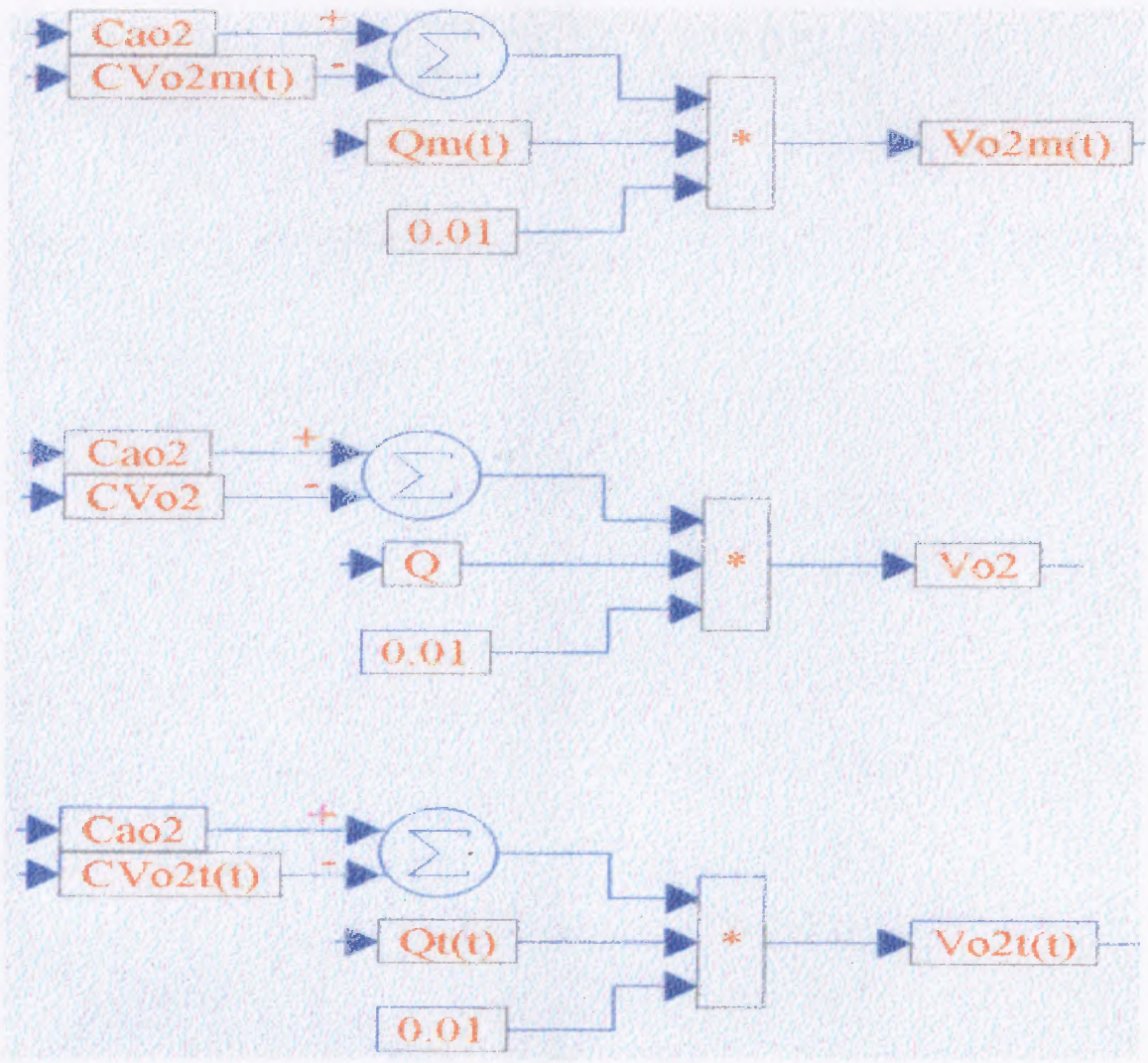

Figure A.4 Vissim equations used in determining oxygen consumption in the active, ($VO_{2m}(t)$), inactive compartments, ($VO_{2t}(t)$), and total oxygen consumption, (VO_2). These equations are based on the difference of venous oxygen and arterial oxygen and blood flow.

APPENDIX B

GRAPHS OF WORKING EQUATIONS IN VISSIM

This appendix provides graphs of the working equations in Vissim format. Figures B.1 – B.5 simulate the model created by Niizeki, Takahashi, and Miyamoto. Figure B.6 demonstrates how changing the time constant affects blood flow. Figure B.7 shows where oxygen is exhausted and anaerobic respiration takes over to accommodate the muscles' need for oxygen.

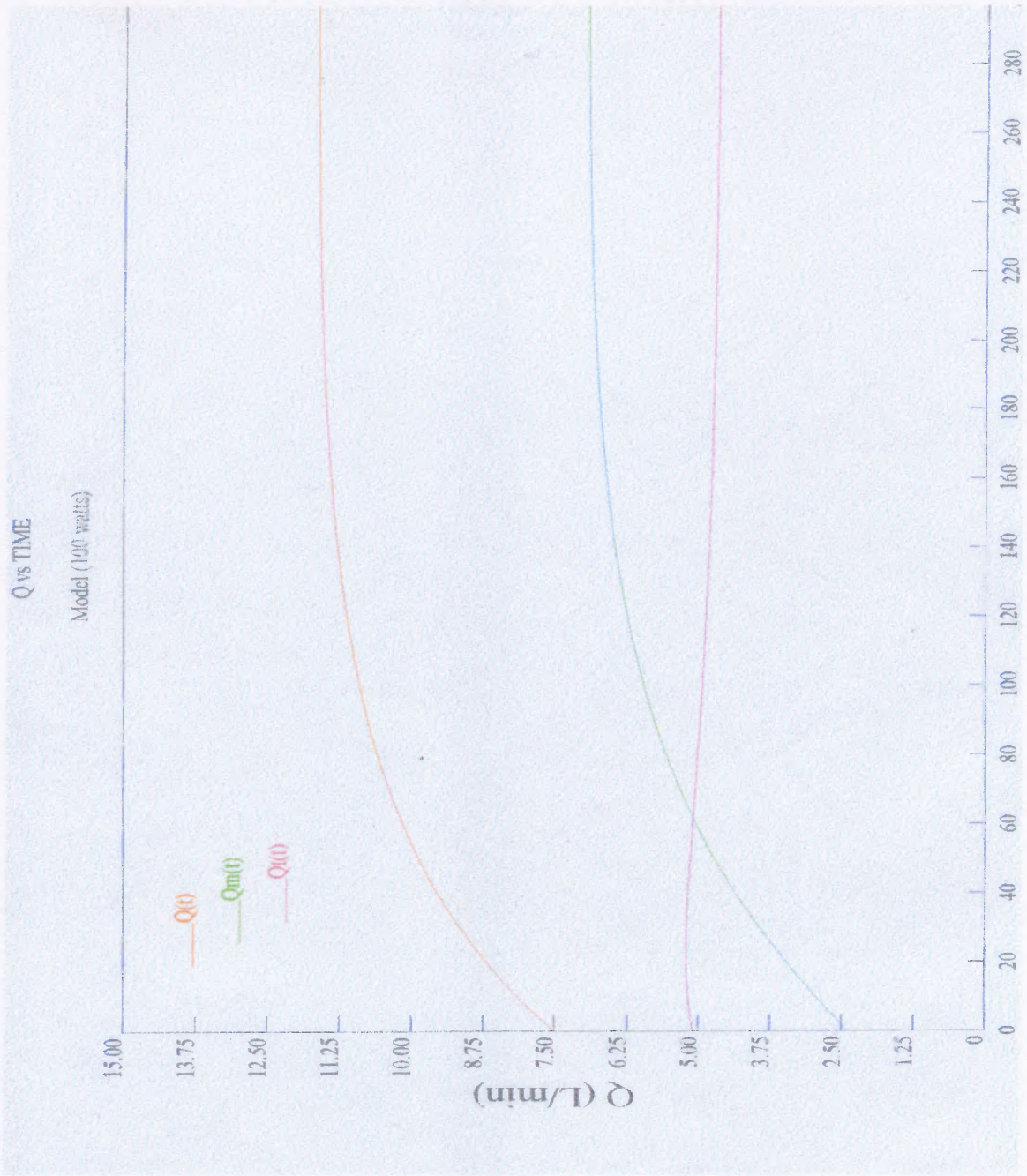

Figure B.1 Graph of blood flow, blood flow in the muscle compartment, and blood flow in the inactive tissue as a function of time, (measured in seconds). This was achieved by using the equations and parameters supplied by Niizeki, Takahashi, and Miyamoto to predict blood flow as exercise was increased from 30 to 100 Watts. Q(t) is the sum of $Q_m(t)$ and $Q_t(t)$.

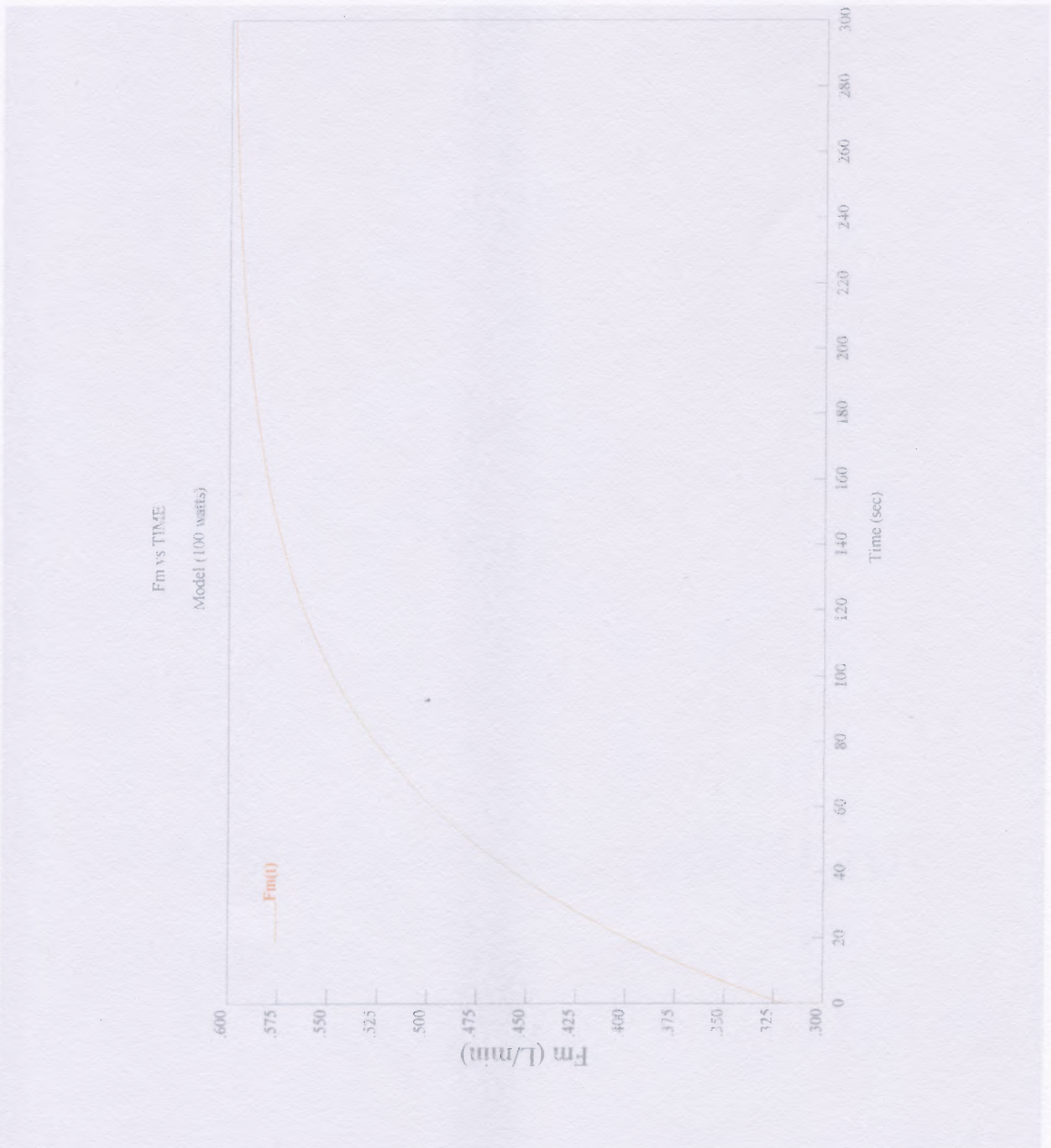

Figure B.2 Graph of the distribution ratio, (F_m), vs. time. This was achieved by using the equations and parameters supplied by Niizeki, Takahashi, and Miyamoto to predict the distribution of blood in the active muscles as exercise was increased from 30 to 100 Watts.

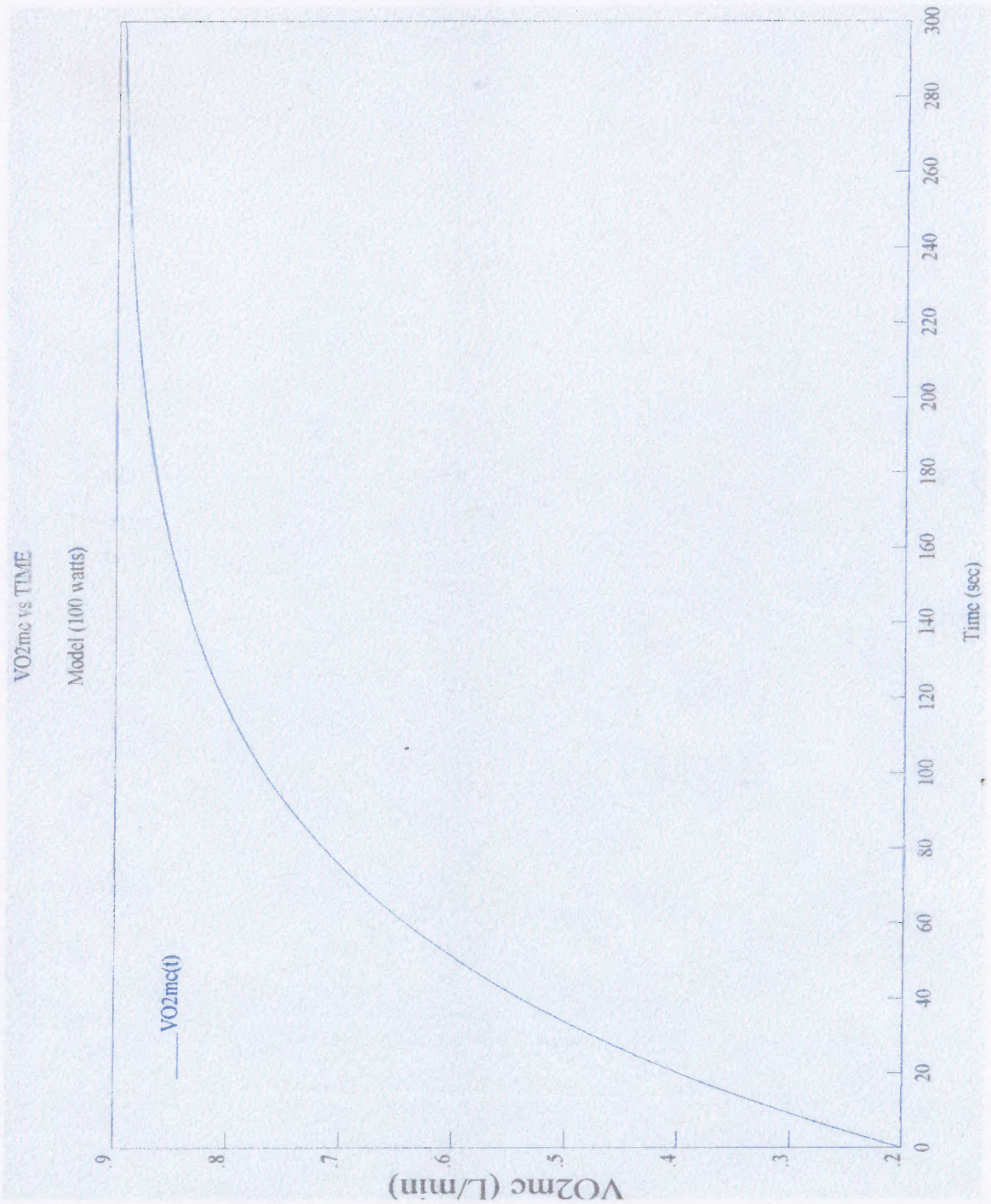

Figure B.3 Graph of the volume of oxygen in the muscle compartment, (VO_{2mc}), vs. time. This was achieved by using the equations and parameters supplied by Niizeki, Takahashi, and Miyamoto to predict volume of oxygen in the muscle compartment as exercise was increased from 30 to 100 Watts.

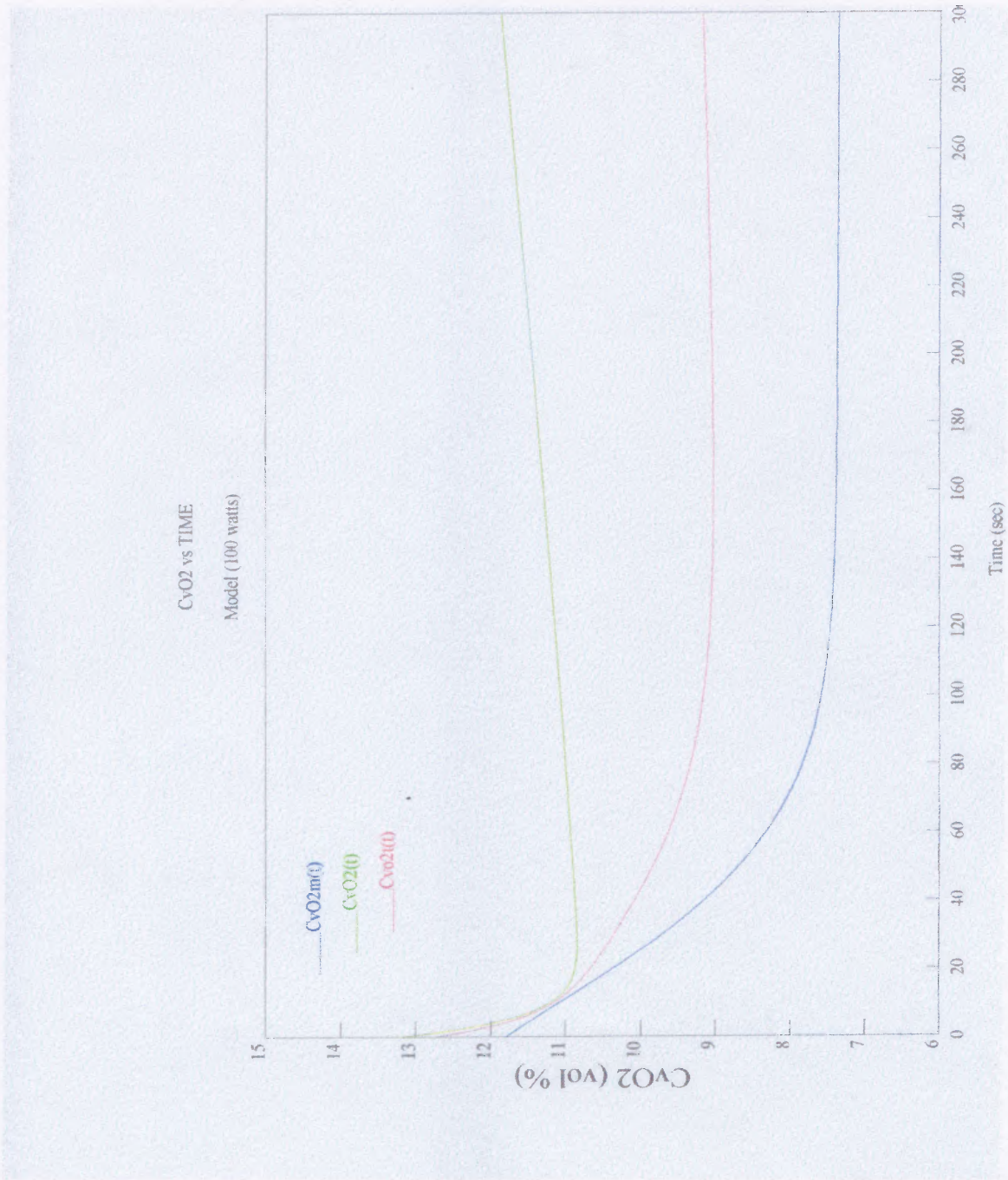

Figure B.4 Graph of the concentrations of total venous oxygen, venous oxygen in the active tissues, and venous oxygen in the inactive tissue compartments as functions of time. This was achieved by using the equations and parameters supplied by Niizeki, Takahashi, and Miyamoto to predict concentrations of venous oxygen when exercise was increased from 30 to 100 Watts.

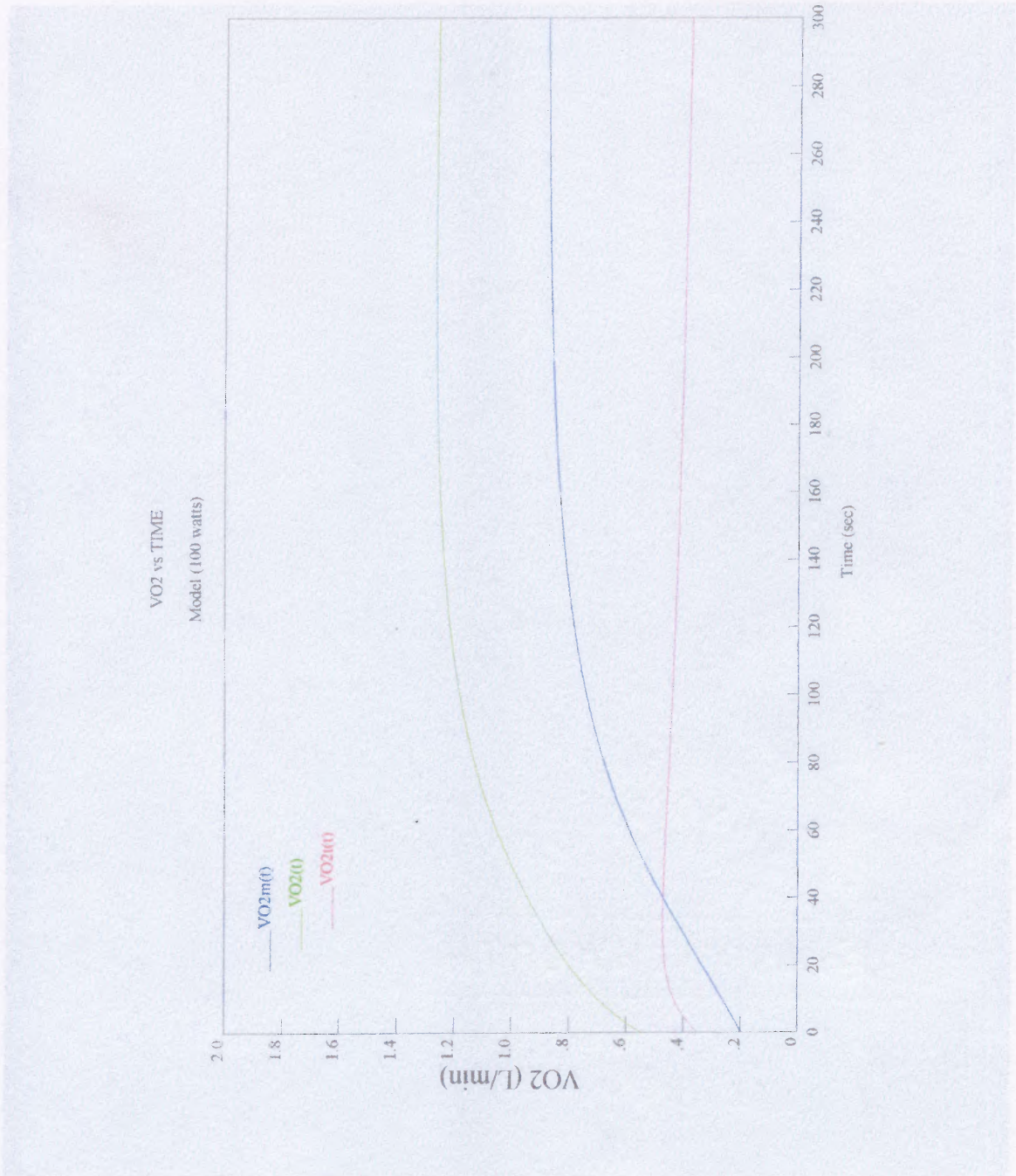

Figure B.5 Graph of total oxygen consumption, oxygen consumption in the inactive tissues and oxygen consumption in the active tissue compartments as functions of time. This was achieved by using the equations and parameters supplied by Niizeki, Takahashi, and Miyamoto to predict oxygen consumption when exercise was increased from 30 to 100 Watts.

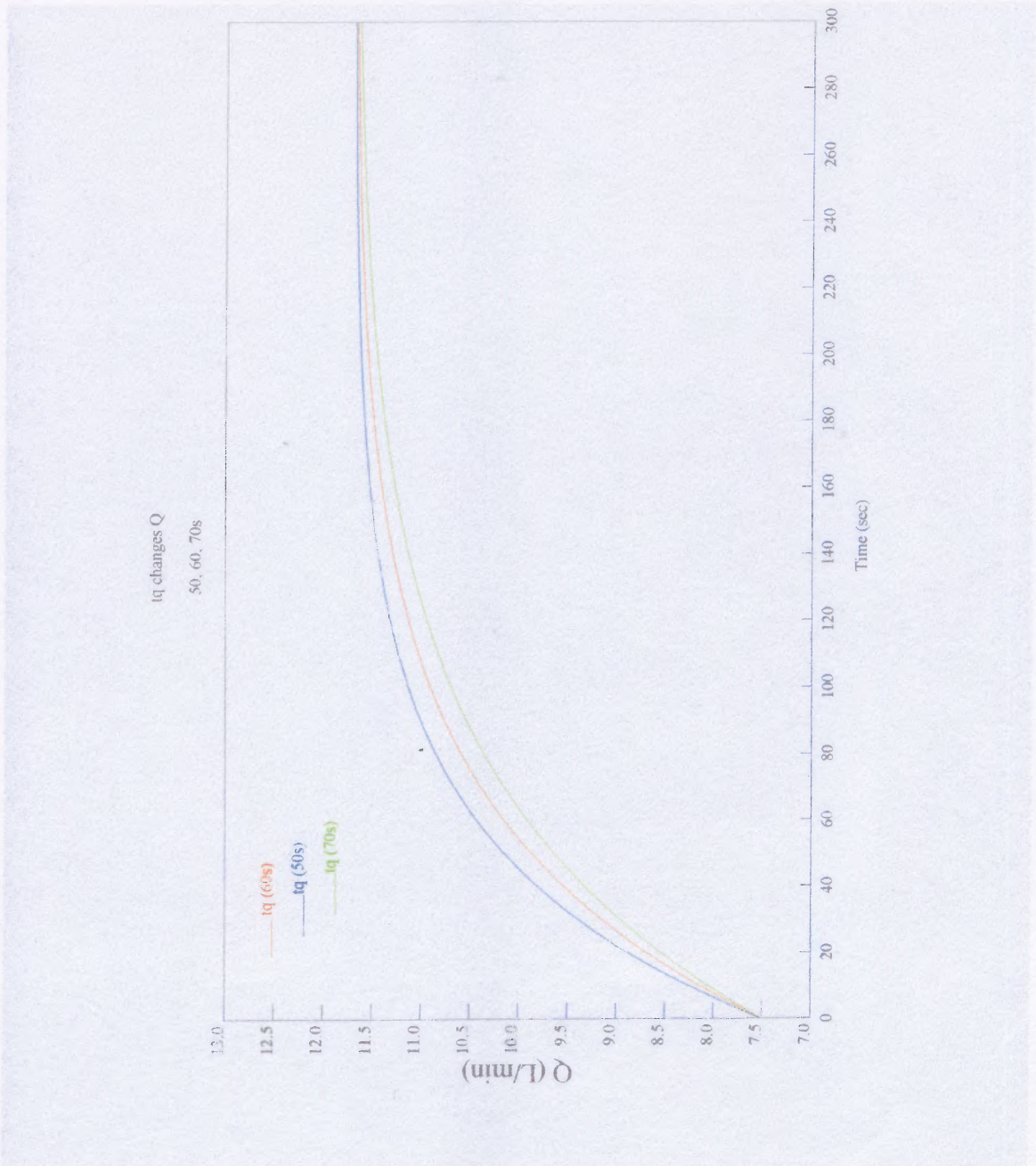

Figure B.6 Graph of blood flow, (Q), vs. time using three different time constants, (τ_q). This graph illustrates the effects on Q by changing τ_q.

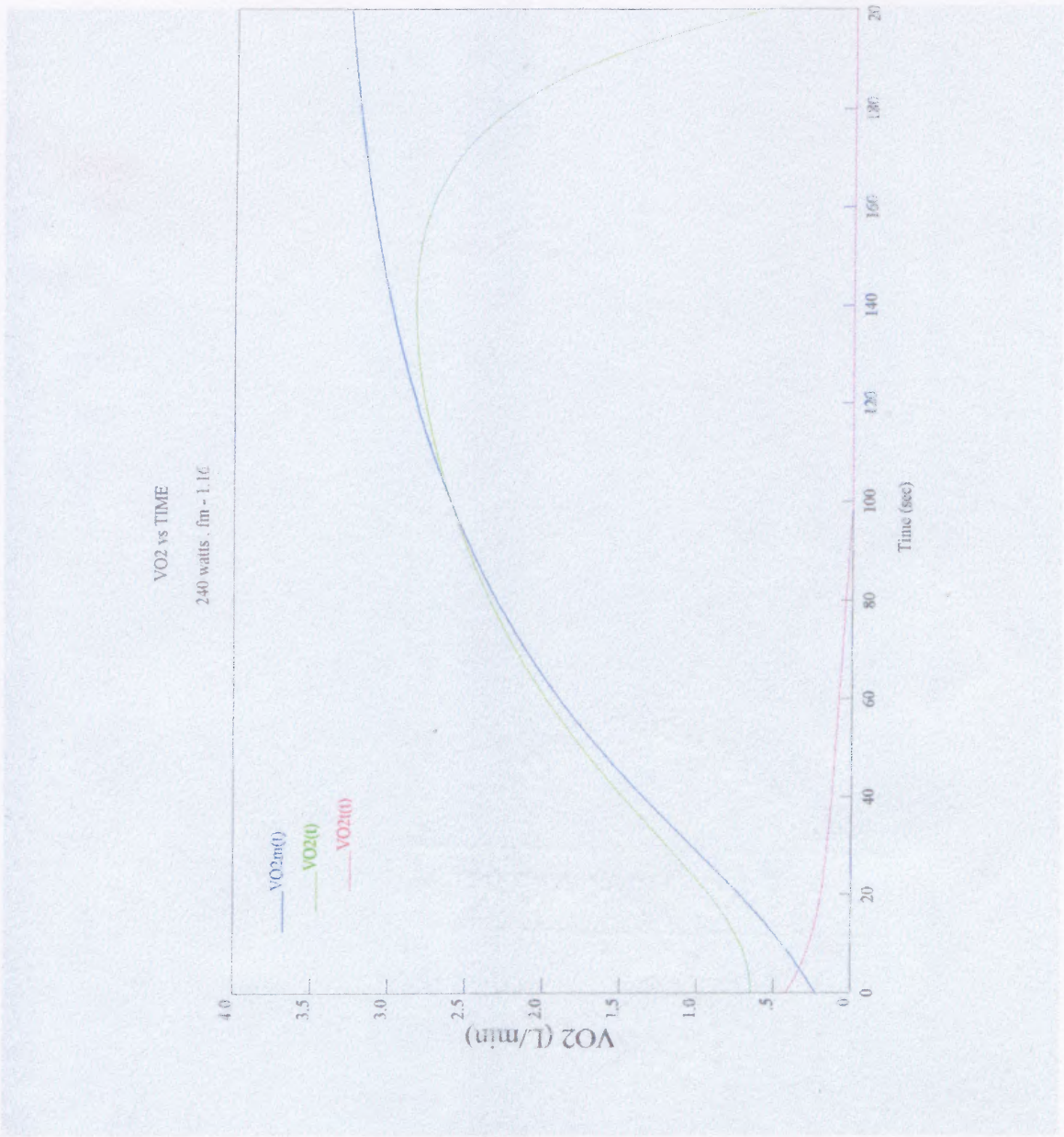

Figure B.7 Graph of oxygen consumption vs. time from a baseline work rate of 30 watts to a work rate of 240 watts and exceeding the distribution ratio (F_m = 1.16) to find VO_{2max}. Data from Dr. Gutkin's group of normals was used to construct this graph.

WORKS CITED

1. Aguilaniu, B., Flore, P., Maitre, J., Ochier, J., Lacour, J., and Perrault, H. "Early Onset of Pulmonary Gas Exchange Disturbance During Progressive Exercise in Healthy Active Men" Journal of Applied Physiology (2002): 1879-84.

2. Barstow, T., Buschtal, S., Zanconato, S and Cooper, D. "Muscle Energetics and Pulmonary Oxygen Uptake Kinetics During Moderate Exercise" Journal of Applied Physiology (1994): 1742-9.

3. Barstow, T., Lamarra, N., and Whipp, B., "Modulation of Muscle and Pulmonary O_2 Uptakes by Circulatory Dynamics During Exercise" Journal of Applied Physiology (1990): 979-89.

4. Barstow, T., and Mole, P. "Simulation of Pulmonary O_2 Uptake During Exercise Transients in Humans" Journal of Applied Physiology (1987): 2253-61.

5. Bishop, D., Bonetti, D., and Dawson, B. "The Influence of Pacing Strategy on VO_2 and Supramaximal Kayak Performance" Medicine, Science, Sports and Exercise (2002): 1041-7.

6. Carbrera, M., and Chizeck, H.,"On the Existence of a Lactate Threshold During Incremental Exercise: A Systems Analysis" The American Physiological Society (1996): 1819-28.

7. Cochrane, J., and Hughson, R. "Computer Simulation of O_2 Transport and Utilization Mechanisms at the Onset of Exercise" Journal of Applied Physiology (1992): 2382-8.

8. Demarie, S., Quaresima, V., Ferrari, M., Sardella, F., Billat, V., and Faina, M. "VO_2 Slow Component Correlates with Vastus Lateralis De-Oxygenation and Blood Lactate Accumulation During Running" The Journal of Sports Medicine and Physical Fitness (2001): 448-55.

9. Hill, D., Poole, D., and Smith, J. "The Relationship Between Power and the Time to Achieve VO_{2max}" Medicine and Science in Sports and Medicine (2002): 709-14.

10. Hoff, J., Wisloff, U., Engen, L., Kemi, O., and Helgerud, J. "Soccer Specific Aerobic Endurance Training" British Journal of Sports Medicine (2002): 218-21.

11. Hughson, R., and Tschakovsky, M., "Cardiovascular Dynamics at the Onset of Exercise." Medicine and Science in Sports and Exercise (1999): 1005-1010.

12. Lyabakh, K. "Mathematical Modeling of Oxygen Transport to Skeletal Muscle During Exercise. Hypoxia and VO_{2max}." Advances in Experimental Medicine and Biology (1999): 585-93.

13. Mandigout, S., Melin, A., Lecoq, A., Courteix, D., Obert, P. "Effect of Two Aerobic Training Regimens on the Cardiorespiratory Response of Prepubertal Boys and Girls" Acta Paediatrician (2002): 403-8.

14. Mitchell, J., and Blomqvist, G. "Maximal Oxygen Uptake." The New England Journal of Medicine (1971): 1018-1022.

15. Mitchell, J., Sproule, B., and Chapman, C. "The Physiological Meaning of the Maximal Oxygen Intake Test." University of Texas Southwestern Medical School, Dallas Texas (1957): 538-547.

16. Miyamoto, Y., and Niizeki, K., "Dynamics of Ventilation, Circulation, and Gas Exchange to Incremental and Decremental Ramp Exercise" The American Physiological Society (1992): 2244-2254.

17. Modesti, P., Olivo, G., Pestelli, F., Guarnaccia, V., Gensini, G., Malfanti, P., and Serneri, G. "Anaerobic Metabolism in Hypertensive Patients During Exercise Stress Test." American Journal of Hypertension (1994): 469-473.

18. Niizeki, K., Takahashi, T., and Miyamoto, Y. "A Model Analysis of Asymmetrical Response of Pulmonary VO_2 During Incremental and Decremental Ramp Exercise." Modeling in Physiology (1995): 1816-1827.

19. Pedersen, P., Sorensen, J., Jensen, K., Johansen, L., and Levin, K. "Muscle Fiber Type Distributing and Nonlinear VO_2 - Power Output Relationship in Cycling" Medicine, and Science in Sports and Exercise (2002): 655-61.

20. Perrey, S., Candau, R., Millet, G., Borrani, F., and Rouillon, J. "Decrease in Oxygen Uptake at the End of a High-Intensity Submaximal Running in Humans." International Journal of Sports Medicine (2002): 298-304.

21. Proctor, D., Shen, P., Dietz, N., Eickhoff, T., Lawler, L., Ebersold, E., Loeffler, D., and Joyner, M. "Reduced Leg Blood Flow During Dynamic Exercise in Older Endurance - Trained Men" The American Physiological Society (1998): 68-75.

22. Rossiter, H., Ward, S., Kowalchuk, J., Howe, F., Griffiths, J., and Whipp, B. "Dynamic Asymmetry of Phosphocreatine Concentration and O_2 Uptake Between the On - and Off - Transients of Moderate - and High - Intensity Exercise in Humans" Journal of Physiology (2002): 991-1002.

23. Severinghaus, J. "Exercise O_2 Transport Model Assuming Zero Cytochrome pO_2 at VO_{2max}" The American Physiological Society (1994): 671-678.

24. Teh, K., and Aziz, A. "Heart Rate, Oxygen Uptake, and Energy Cost of Ascending and Descending the Stairs" Medicine and Science in Sports and Exercise (2002): 695-9.

25. Vinet, A., Nottin, S., Lecoq, A., and Obert, P. "Cardiovascular Responses to Progressive Cycle Exercise in Healthy Children and Adults" International Journal of Sports Medicine (2002): 242-6.

26. Weber, C., Schneider, D. "Increases in Maximal Accumulated Oxygen Deficient After High – Intensity Interval Training Are Not Gender Dependent" Journal of Applied Physiology (2002): 1795-801.

27. Whipp, B., Lamarra, N., and Ward, S. "Obligatory Anaerobiosis Resulting From Oxygen Uptake – to - Blood Flow Ratio Dispersion in Skeletal Muscle: a Model" European Journal of Applied Physiological Occupational Physiology (1995): 147-52.

28. Whipp, B., Rossiter, H., and Ward, S. "Exertional Oxygen Uptake Kinetics: A Stamen of Stamina?" Biochemical Society Transactions (2002): 237-47.

29. Yano, T., Yunoki, T., and Ogata, H. "Relationship Between the Slow Component of Oxygen Uptake and the Potential Reduction in Maximal Power Output During Constant - Load Exercise" Journal of Sports Medicine and Physical Fitness (2001): 165-9.