MAXIMAL OXYGEN CONSUMPTION RATES IN ONE-LEG AND TWO-LEG EXERCISE: A THEORETICAL MODEL

by

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Abstract

The goal of this project was to create a theoretical model to predict maximal oxygen consumption rates in one-leg and two-leg exercise. A MATLAB code was developed to simulate both capillary-level oxygen transport (in the legs) and systemic oxygen transport. Predicted values for oxygen consumption closely matched experimental data. The model was used to explain the trend of a lower maximal oxygen consumption rate in two-leg exercise compared to one-leg exercise. As activity increases from rest to one-leg exercise to two-leg exercise, the oxygen demand of the active components, the cardiac output, and the blood flow rate also increase. However, the fraction of cardiac output to the active leg(s) decreases when the second leg is activated. At the capillary level, the oxygen extraction is increased at the arteriolar end of each capillary, resulting in regions of hypoxic tissue towards the venous end. Venous oxygen saturation is decreased, leading to lower venous P_{O_2} returning to the lungs. The increased cardiac output decreases the time that the deoxygenated blood has in contact with the alveoli. As a result, arterial P_{O_2} for blood exiting the lungs is lower. This decreases the pressure gradient between the tissue and the capillary and limits diffusive transport. In summary, the reduction of oxygen consumption rate per unit muscle mass in two-leg exercise relative to one-leg exercise is accounted for quantitatively by the model and shown to result from the combined effects of reduced flow and reduced oxygen saturation of blood to each leg in two-leg exercise.

Chapter 1: Introduction

The high metabolic rate of animals and humans is achieved through oxidative metabolism. With oxygen, the amount of energy that can be generated from a given amount of fuel (e.g. glucose) is greatly increased. At high levels of exercise, the ability to supply enough oxygen is a critical factor limiting the rate at which muscles can work. Therefore, the oxygen transport mechanisms need to be considered.

Oxygen is transported by convection over large distances in the blood vessels. From the blood, it diffuses over a short distance into muscle fibers. In the cells, aerobic oxidation is the primary pathway by which adenosine diphosphate (ADP) is converted to adenosine triphosphate (ATP). ATP acts as the primary energy source for many essential yet "energetically unfavorable processes" [17]. As such, cellular dependence on oxygen is paramount.

While this conversion takes place at a cellular level, its importance at a macroscopic and physiological level is also critical. Specific to this study, the ability of humans to move, exercise, or even maintain resting metabolic conditions, is brought about through this whole body requirement for oxygen.

Oxygen transport occurs through both convective and diffusive methods. Convection carries blood throughout the body based on the pressure gradient created by cardiac contraction. The left ventricle pumps blood out of the aorta and provides the force to keep blood flowing. At the capillary level, the gradient of the partial pressure of oxygen between oxygen-rich hemoglobin and oxygen-demanding active tissue results in

diffusive transport. For the purposes of this paper, the partial pressure of oxygen, denoted P_{O_2}, is referred to as the oxygen content of blood.

Transport of oxygen to tissues, and thereby cells, is primarily dependent on blood flow. Blood is composed of red blood cells (erythrocytes), white blood cells (leukocytes), and plasma. While small amounts of oxygen may dissolve in the plasma component of blood, oxygen is predominantly linked to erythrocytes. Each erythrocyte contains a concentrated solution of hemoglobin. One hemoglobin molecule is composed of a central heme (iron) core. Each heme unit is capable of binding four molecules of oxygen. As one molecule of oxygen binds to a binding site, a conformational change is elicited and the affinity for the remaining empty sites to bind more oxygen is increased [17]. This association and dissociation of hemoglobin can be explained visually through the oxy-hemoglobin dissociation curve seen below in Figure 1.

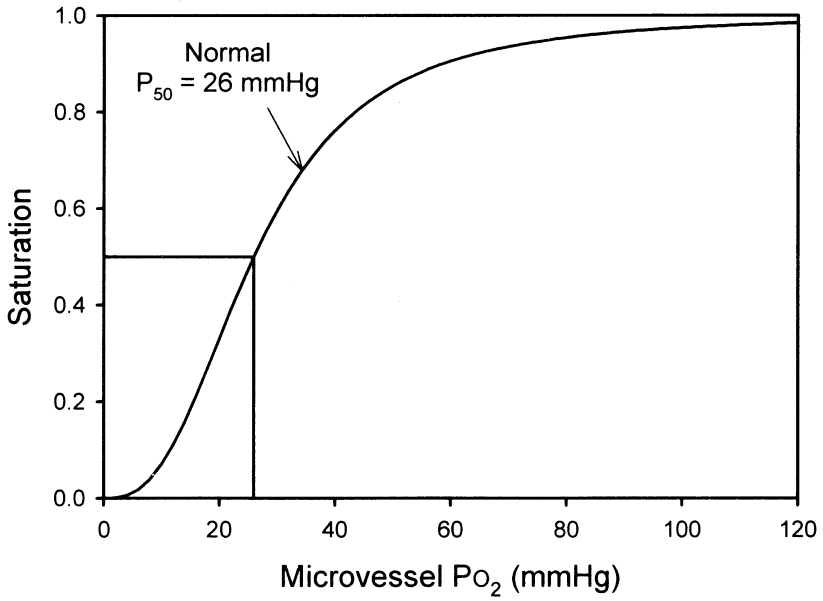

Figure 1: Hemoglobin Dissociation Curve

The curve presented in Figure 1 is approximated by the Hill equation. The curve shows the relationship between the vessel P_{O_2} and hemoglobin saturation. A greater oxygen concentration in the vessel corresponds to greater hemoglobin saturation. More oxygen is present; hence, more oxygen can be bound. Until all oxygen binding sites on a hemoglobin molecule have been occupied, increases in P_{O_2} will result in increased hemoglobin saturation. The curve is non-linear. This can be explained by the conformational change in hemoglobin explained above. Oxygen dissociation from hemoglobin works in the reverse method. During the middle phase of the curve, small drops in the vessel P_{O_2} will result in significant dissociation of oxygen molecules from hemoglobin. This type of dissociation occurs at the tissue level.

At a high P_{O_2}, the high oxygen content in the blood allows for saturation of hemoglobin molecules. Oxygenation of hemoglobin occurs in the lungs due to the high concentration of oxygen from respiration. Oxygen diffuses through the alveoli and into the blood, binding to the hemoglobin vehicles. As blood flows through the lungs, it becomes saturated with oxygen and passes through the remaining portions of the circulatory system, finally being pumped through the systemic circulation to deliver the oxygen to tissues. Many generations of branching of blood vessels leads to the capillary level, at which point tissues are directly supplied with oxygenated blood. At the tissue level, there is a lower P_{O_2} because oxygen is continuously consumed and converted by cells. As a result of the pressure gradient, oxygen molecules dissociate from the heme subunits and enter the cellular components of tissue where they can be used to carry out the conversion of ADP into ATP, amongst other functions. The de-oxygenated

hemoglobin molecules pass through the remaining circulation of the body and return to the cardiac and pulmonary circulations, wherein they can bind to and deliver oxygen in a reoccurring fashion.

The importance of oxygen supply at the cellular level motivates studies to better understand capillary level transport, both experimentally and theoretically. In 1919, August Krogh developed the Krogh cylinder model [15]. Krogh recognized a capillary arrangement that was regular and parallel in skeletal muscle and developed this further. In 1986, Groom et al performed a study in which a cast corrosion model of rat skeletal muscle was created, the result of which is shown in Figure 2 [7]. Groom's results supported Krogh's depiction of muscle capillary as a parallel orientation of independent capillaries. The parallel arrangement of capillaries is characteristic to skeletal muscle. The regularity of the capillaries reduces the difficulty of creating a model.

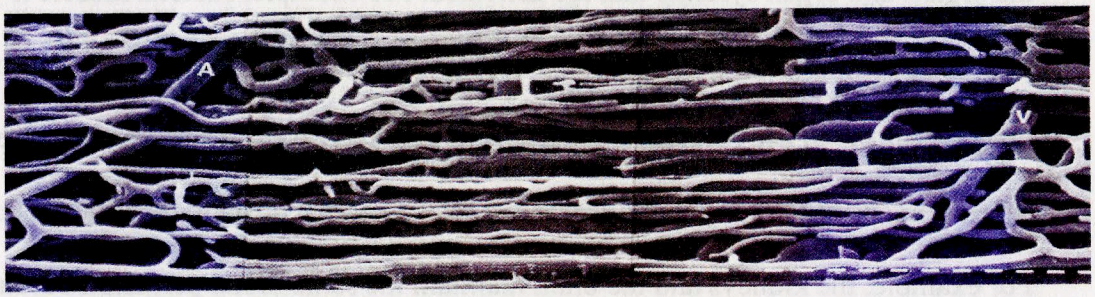

Figure 2: Rat Skeletal Muscle Microvessels

The Krogh model depicts a cylindrical capillary of radius r_c surrounded by a cylindrical ring of tissue of radius r_t, as seen in Figure 3 [22]. Blood passing through the capillary is capable of diffusing oxygen to the tissue cylinder, as far as the radius r_t but not less than r_c. (Figure 5 [21] depicts the parameters discussed above.)

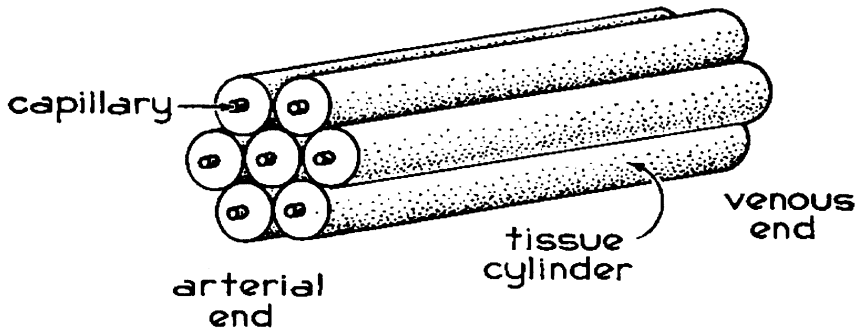

Figure 3: Krogh Cylinder Model

Krogh's equation began with a modification of Fick's Second Law of Diffusion. A full derivation is given in "Chapter 2: Methods" of this paper. Combining Fick's Second Law of Diffusion with Krogh's arrangement allows for a model of blood flow and oxygen transport from capillaries to tissue in skeletal muscle.

A variety of regulatory mechanisms distribute blood flow to meet the demands of the organs and organ systems that are activated. For example, skeletal muscle is primarily involved in movement; hence during exercise or motion, blood flow (and therefore oxygen supply) to active skeletal muscle is largely increased. However, there are also several organs to which the blood supply remains nearly constant, regardless of activity. For example, the kidneys and the brain maintain the same blood perfusion because of the necessity of their function. Table 1 indicates variations in blood flow in many organs comparing a resting state to leg exercise [16].

Table 1: Division of Cardiac Output

Organ	Rest		Leg Exercise	
	Flow (l/min)	Cardiac Output (%)	Flow (l/min)	Cardiac Output (%)
Leg muscle	0.5	9	3.9	36
Heart	0.25	4	0.35	3
Skin	0.5	9	1.5	14
Brain	0.75	13	0.75	7
Splanchnic	1.4	24	1.1	10
Kidneys	1.1	19	0.9	8
Inactive muscle	0.7	12	0.6	6
Lungs	5.8		10.8	

The maximal rate of oxygen consumption is denoted as $\dot{V}_{O_{2max}}$. Many studies have shown that $\dot{V}_{O_{2max}}$ during exercise is lower in cases of hypoxia. For example, Richardson et al [24] examined the effect of hypoxic and normoxic conditions on $\dot{V}_{O_{2max}}$ in single leg knee extensor exercise at a variety of work rates. Their data show that in hypoxic conditions (18% oxygen), the maximal rate of oxygen consumption reached a plateau at higher work rates but was consistently lower than the $\dot{V}_{O_{2max}}$ in normoxic conditions (21% oxygen). This implies that lower oxygen content was the limiting factor in reaching $\dot{V}_{O_{2max}}$. Richardson et al also noticed a trend towards similar leg blood flow and oxygen diffusivity in normoxic and hypoxic conditions. These results lead to the conclusion that because both leg blood flow and diffusivity of oxygen to tissue were not distinctly different in normoxic and hypoxic condition, the oxygen content and oxygen diffusing capacity to adapt to changing demands are factors limiting maximal oxygen consumption in hypoxic conditions.

Wagner et al demonstrated that the significant venous concentration of oxygen (15-30%) suggests a limitation to diffusive oxygen transport because not all of the oxygen is extracted [27]. This shows that even under normoxic conditions, there is a limit to oxygen transport.

McGuire and Secomb [19] explored the relationship between oxygen demand and oxygen consumption. As demand increases, delivery falls short of demand, first at the venous end and then farther upstream towards the arteriolar end of the capillary. More oxygen consumption earlier in the capillary leads to less oxygen availability to the remaining length of the capillary and, as a result, more hypoxic (oxygen deficient) tissue. This limits $\dot{V}_{O_{2max}}$ because less tissue is able to consume oxygen. $\dot{V}_{O_{2max}}$ is diminished in these cases by both convective and diffusive transport limitations.

Figure 4 shows the relationship between demand and consumption [21]. Ideally, there would be a linear relationship between the two: for every unit increase in demand, there would be a unit increase in consumption, depicted by the linear plot. However, this is not the case. The curved plots indicate that as oxygen demand increases, consumption also increases but only to a certain extent. The result of the plateau is insufficient oxygenation of tissue, and hence, the formation of hypoxic tissue. The alternating values represent capillary density. These can be disregarded for purposes of this study. The standard case is a capillary density of 468 capillaries per square millimeter.

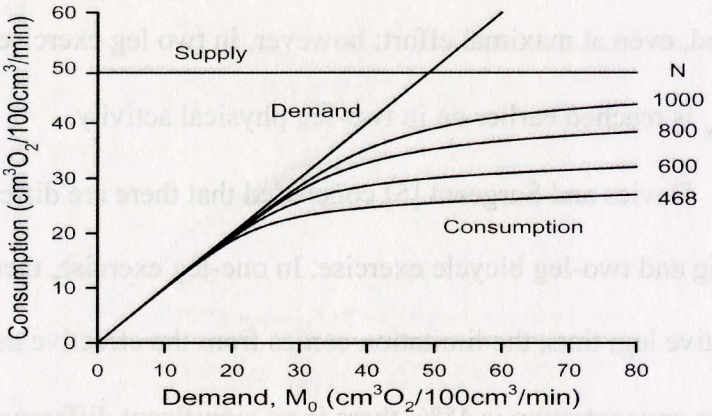

Figure 4: Consumption and Demand

Figure 5 shows the formation of hypoxic regions of the tissue cylinder in relation to the direction of blood flow. The shaded regions towards the right end of the cylinder represent hypoxic tissue. It can be seen that hypoxic regions form first at the venous end of the capillary.

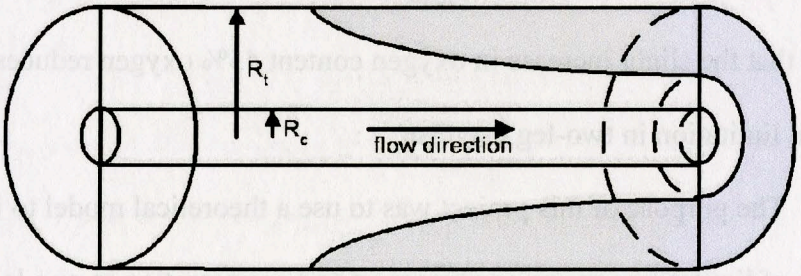

Figure 5: Krogh Cylinder with Hypoxia

Davies and Sargeant [5] evaluated physiological responses to differences in the oxygen concentration of inspired air in one-leg and two-leg exercise. Five subjects performed one-leg and two-leg exercise on a bicycle at two different inspired oxygen concentrations: ~21% oxygen (air) and 45% oxygen. was determined by observing a plateau in measurements. For one-leg exercise, this plateau was not

reached, even at maximal effort; however, in two leg exercise, it was. This indicates that $\dot{V}_{O_{2max}}$ is reached earlier on in two-leg physical activity.

Davies and Sargeant [5] concluded that there are different limitations to activity in one-leg and two-leg bicycle exercise. In one-leg exercise, there is a greater blood flow to the active leg; thus, the limitation comes from the effective muscle. When the inspired oxygen concentration is 45%, there is no significant difference in $\dot{V}_{O_{2max}}$. The implication here is that $\dot{V}_{O_{2max}}$ in one-leg exercise is not limited by oxygen content. Even under hyperoxic conditions (45% oxygen), only a certain amount can be bound to hemoglobin, and the oxygen content of blood is only slightly increased. In two-leg exercise under normoxic conditions, the oxygen supply is insufficient to meet the oxygen demands of active tissue. At 45% oxygen, $\dot{V}_{O_{2max}}$ is similar in one-leg and two-leg exercise. This shows that the slight increase in oxygen content 45% oxygen reduces the effects of oxygen limitation in two-leg exercise.

The purpose of this project was to use a theoretical model to investigate the effects of limitations on oxygen transport and consumption in one-leg and two-leg exercise. The approach used is a theoretical model that combines both capillary-level oxygen transport and systemic circulation components. The experimental data for one-leg and two-leg exercise provided by Davies and Sargeant [5] was used to validate the model created. The values for cardiac output that were input into the model were taen directly from the experimental values measured by Davies and Sargeant. The paper presented oxygen consumption rates for one-leg and two-leg exercise at maximal effort. These values were computed by the model and compared with experimental data.

By graphing various saturations and consumptions for the components involved, the hypothesis is that the lower $\dot{V}_{O_{2max}}$ in two-leg exercise compared to one-leg exercise can be explained in two ways. First, limitations on systemic oxygen delivery will become apparent from determining arterial oxygen saturation. Second, limitations of capillary-level oxygen transport will be observed in calculating the venous saturation.

The novel aspect of this approach is that it combines a compartmental/systemic analysis with capillary level oxygen transport. Modeling exists for each oxygen transport (convective and diffusive) independently; however, this model incorporates both.

Chapter 2: Methods

Using MATLAB, a program was written to account for blood flow through the systemic circulation. This included modeling capillary level oxygen transport in the legs and using known values for the oxygen demand, blood flow, oxygen consumption, and oxygen extraction of a few other key organs. Key parameters are defined in Table 2 and Table 3.

Table 2: General Parameter Definitions

Parameter	Definition	Value	Units	Source
Poi	Partial pressure of oxygen of inspired air	100	mmHg	21
r_c	Capillary radius	2.5×10^{-4}	cm	21
r_t	Tissue cylinder radius	20×10^{-4}	cm	21
deltaz	Capillary slice thickness	0.001	cm	
Co	Oxygen carrying capacity of blood	0.2	cm^3O_2/cm^3blood	21
P_{50}	Arterial P_{O_2} at which hemoglobin is 50% saturated	26	mmHg	21
n	Hill equation exponent	2.4		21
Sh	Sherwood number	2.5		21
Palv	Alveolar pressure	100	mmHg	28
length	Capillary length	0.05	cm	21
Ncap	Capillaries in one leg	$5000/(\pi r_t^2 length)$	$capillaries/cm^2$	20
Ktissue	Krogh diffusion constant in tissue	9.4×10^{-10}	$(cm^2/s)(cm^3O_2/cm^3/mmHg)$	21
Kpl	Krogh diffusion constant in plasma	8.3×10^{-10}	$(cm^2/s)(cm^3O_2/cm^3/mmHg)$	21
k	Lung oxygen transport coefficient	0.6		12, 28

Table 3: Blood Flow and Demand Parameters

Parameter	Definition	Value	Units	Source
Qco	Cardiac output	Rest: 6.3 One-leg: 17.4 Two-leg: 21.75	L/min	5
Qleg1	Blood flow to leg 1	Rest: 0.5 One-leg: 0.5 Two-leg: 8.225	L/min	25
Qleg2	Blood flow to leg 2	Rest: 0.5 One-leg: 11.6 Two-leg: 8.225	L/min	25, 10
g1	Oxygen demand of passive leg	Rest: 0.46/6000 One-leg: 0.46/6000 Two-leg: 60/6000	$cm^3O_2/cm^3blood/s$	10
g2	Oxygen demand of active leg	Rest: 0.46/6000 One-leg: 60/6000 Two-leg: 60/6000	$cm^3O_2/cm^3blood/s$	10
Qbrain	Blood flow to the brain	0.75	L/min	16, 23
Qkidney	Blood flow to the kidney	1	L/min	16, 14, 3
Qother	Blood flow to the "other" components	3.55	L/min	16

The model represents systemic blood flow as a circuit including selected organ systems. Figure 6 below depicts Leg 1, Leg 2, the brain, the kidneys, and 'other' components in a parallel organization. This grouping is placed in series with the lungs. At rest, both Leg1 and Leg 2 are inactive. During one-leg exercise, Leg 1 is inactive and Leg 2 is active. Leg 1 and Leg 2 are both active during two-leg exercise. The "other" component of the circuit is composed primarily of the gastrointestinal tract. The "other," brain, and kidney boxes are systems where oxygen demand, oxygen extraction, and blood flow remain constant, regardless of activity.

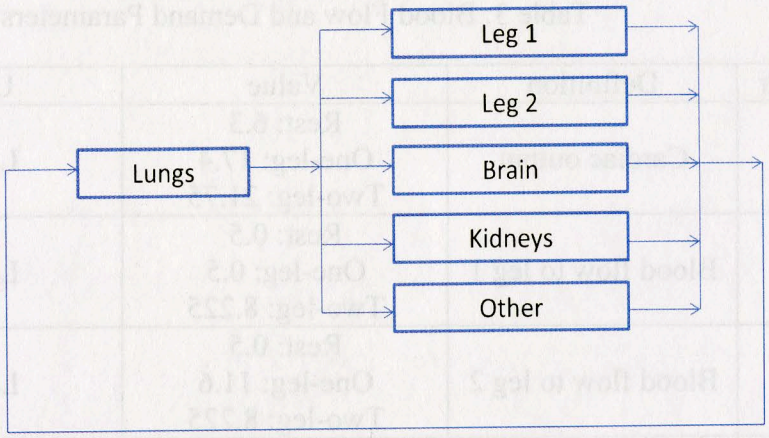

Figure 6: Blood Flow Schematic

Values for oxygen demand, oxygen extraction, resting blood flow, and active blood flow of each subsystem were obtained from literature and are based on data from experimental studies. The model for each subsystem is derived first. The interaction between subsystems is then considered to combine values and to predict overall levels of oxygen consumption.

2.1 Lungs

In 2002, Kavanagh et al [12] modeled the effects of tumor oxygenation and hemoglobin affinity. As part of this study, they developed a simplified model for oxygen transport in the lungs, which is used here. The model calculates arterial saturation based on a given venous saturation. They defined the following equations:

——— (1)

— (2)

(3)

——— (4)

$$Q\,C'(P)\frac{dP}{dt} = Q \times C_O \frac{P_{50}^n}{(P_{50}^n \times P^n)^2} \times n \times P^{n-1} \quad (5)$$

$$\frac{dP}{dt} = \frac{k_t}{Qco \times Co}(P_{atm} - P)\left(\frac{(P_{50}^n + P^n)^2}{P_{50}^n \times n \times P^{n-1}}\right) \quad (6)$$

Equation (1) represents the conversation of mass. Equations (2), (3), (4), and (5) derive the oxygen content of blood as a function of P_{O_2}. (Equation (4) represents blood oxygen saturation.) Rearrangement, combination, and substitution of these equations result in the differential equation, Equation (6). In these equations, 't' represents the passage through the alveolar capillaries. It is calculated as an arbitrary distance where $0 \leq t \leq 1$.

An initial value of P_{O_2} is provided and a MATLAB command returns solutions in graphical and numerical form. Figure 17, Figure 18, and Figure 19 depict changes in the partial pressure of oxygen as blood travels through the lungs. The numerical solutions provide arterial saturation and P_{O_2} . These values are then used as inputs for the five parallel components of the circuit.

2.2 Legs

Oxygen transport in the legs is modeled at the capillary level using a Krogh-type model. Middleman [22] presents the basic derivation of the model, and it is later modified to fit the conditions of this project.

Fick's Second Law of Diffusion is the basis for mathematical modeling of the Krogh cylinder. A single capillary in the leg is evaluated as a series of equal-length slices. Equation (7) describes the time-dependent diffusion of tissue oxygen

concentration. It is presented in cylindrical coordinates to stay congruent with the cylindrical appearance of the blood capillary and surrounding tissue.

$$\frac{\partial c}{\partial t} = D_t\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial z^2}\right) - g(c) \qquad (7)$$

Assuming steady state conditions, the $\frac{\partial c}{\partial t}$ term becomes zero. The concentration of oxygen does not change with time but rather with radius. In addition, the length of a capillary is divided into slices. Transport in the 'z' direction is removed because the oxygen saturation along the slices is calculated independently and summed along each slices. Furthermore, the oxygen demand (g) is, in this case, independent of the concentration of oxygen present. Oxygen demand is prescribed at a constant level for each organ and only varies in the leg if the leg is active or passive. As a result, this equation is simplified to:

$$0 = D_t\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r}\right) - g_o$$

A further modification to this equation is given by the solubility equation: $c = \alpha P$ where α represents the solubility constant and P is the partial pressure of oxygen at the concentration c. As a result of this substitution, a new parameter is introduced: k_{tissue}. This is the Krogh diffusion constant in tissue. Using the relationship $k_{tissue} = D_t \times \alpha$ and rearranging the derivative, the following equation is achieved.

$$0 = k_{tissue}\frac{1}{r}\frac{d}{dr}\left(r\frac{dP}{dr}\right) - g_0$$

Two initial conditions generate a solution to this second order differential equation.

1. At $r = r_c$, $P = P_b$, where $P_b = P_{O_2}$

Condition 1 indicates that the partial pressure of oxygen is equal to the partial pressure of oxygen in the blood at the capillary wall. At the capillary wall, it is assumed that no oxygen transport, consumption, or extraction has taken place; therefore, there is no change in the oxygen content, and the partial pressure of oxygen at r_c is the same as the partial pressure of oxygen in the blood.

2. At $r = r_t$, $\frac{\partial P}{\partial r} = 0$

Condition 2 supplies the information that at the tissue radius, the maximum radial distance that oxygen can travel, the change in oxygen content with radius is negligible. No oxygen can diffuse past a radial distance of r_t. Therefore, the change in oxygen pressure at this point is zero. The boundary condition at $r = r_t$ is known as the "no flux" boundary. No oxygen crosses this boundary. Applying these initial conditions and integrating twice results in Equation (8) for capillary P_{O_2}.

$$P(r) = P_b + \frac{g_0}{4k_{tissue}}\left[(r^2 - r_c^2) - 2\left(ln\frac{r}{r_c}\right)r_t^2\right] \qquad (8)$$

From the above equation, there are three factors that affect the tissue oxygen level. Blood P_{O_2} is the oxygen content of blood (P_b). A higher P_b value indicates greater oxygen content. This means that there is more oxygen to deliver to the tissue. As a result, tissue will be well-oxygenation. The radius of the tissue cylinder also affects tissue oxygen level. At larger values of r_t, the tissue cylinder has a greater volume and thus a larger amount of tissue to which oxygen needs to be supplied. In cases of large r_t, tissue will not be as well-oxygenated as compared to cases of lower r_t. Finally, the oxygen

demand, g, also influences tissue oxygen levels. As the demand for oxygen increases, more oxygen is consumed. The oxygen supply is insufficient to meet the demand, and tissue is not as well-oxygenated.

Figure 7 shows the decline in oxygen content with increasing radius. Increasing demand (g) will lead to a steeper decline between r_c and r_t. Increasing the tissue cylinder radius (r_t) will lead to a very low at r_t. However, increasing P_b will lead to a higher at r_c and hence a larger higher at r_t than the typical case presented below.

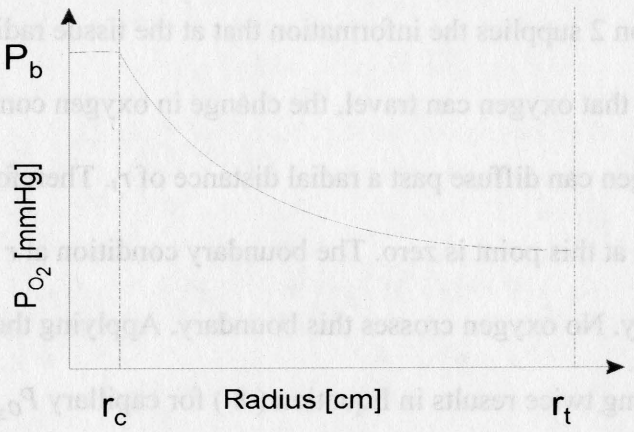

Figure 7: Variations in Between r_c and r_t

Radial diffusive transport of oxygen experiences impedance within the blood known as intravascular resistance [19]. As a result, the at the capillary wall may differ from the average blood , and a new term is introduced to represent the difference between the average blood and the at r_c. McGuire and Secomb [21] adapted the equation presented by Hellums [9] to represent the oxygen diffusion from the capillary per unit length per unit time. The diffusive flux of oxygen from the capillary can also be represented as the second equation.

(9)

$$q = -2\pi r_c D\alpha \frac{dP}{dr}|_{r_c} \quad (10)$$

Equating the equations above and using the relationships $M_t = \pi K_{pl} Sh = \frac{1}{K}$, allows for the a solution to $[P_b - P(r_c)]$ to represent the intravascular resistance (11). This term is then combined with the Equation (8) to determine the final form of capillary P_{O_2} shown as Equation (12).

$$[\boldsymbol{P_b - P(r_c)}] = \frac{-g_0 (r_c^2 - r_t^2)}{K_{pl} Sh} \quad (11)$$

$$\boldsymbol{P(r) = P_b + \frac{g_0}{4k_{tissue}}\left[(r^2 - r_c^2) - 2\left(ln\frac{r}{r_c}\right)r_t^2\right] - \frac{g_0 (r_c^2 - r_t^2)}{K_{pl} Sh}} \quad (12)$$

As previously stated, a single capillary is divided into slices, as shown in Figure 8. The calculations described below are performed for each slice.

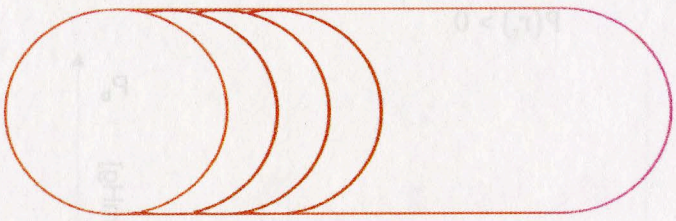

Figure 8: Capillary Slices

For the first slice, *P(r)* is calculated. If $P(r_t)$ is less than or equal to zero, the program solves for the radius at which *P(r)* equals 0, indicated by r_d. This is the maximum radial distance that oxygen has diffused. If $P(r_t)$ is greater than 0, it is assumed that oxygen has diffused to the entire tissue cylinder $r = r_t$.

For each slice, the oxygen consumption, change in saturation (ΔS), saturation (S), and new P_{O_2} are calculated based on the formulas below.

$$if\ P(r_t) > 0: consumption = g\pi\Delta z(r_t^2 - r_c^2) \quad (13)$$

:

(14)

The above calculations are carried out for each slice. At each slice, $P(r_t)$ can denote exactly where, radially, tissue becomes hypoxic. The two conditions of $P(r_t)$ can be shown visually in Figure 9.

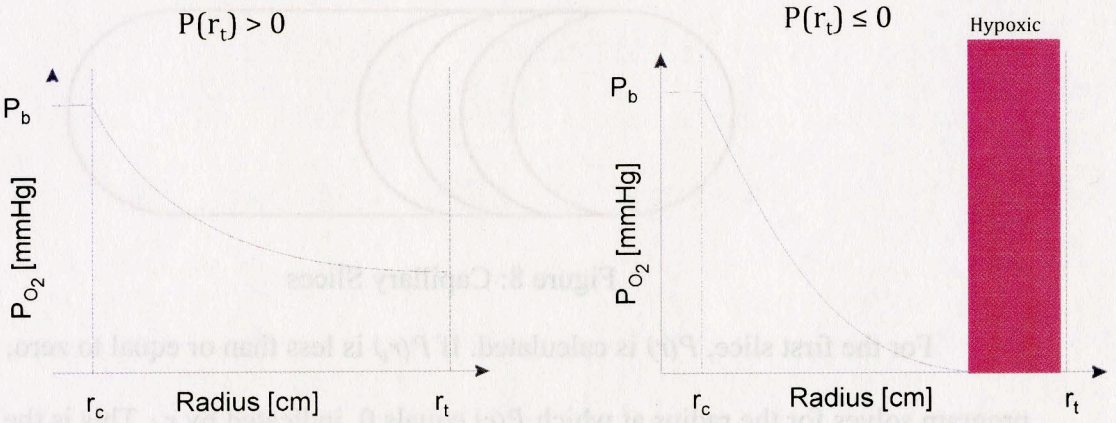

Figure 9: Conditions of $P(r_t)$

At each slice, the following characteristics are calculated: partial pressure of oxygen, oxygen consumption, change in blood oxygen saturation, and new saturation. In summing the values calculated in each slice, the total oxygen consumption, average oxygen consumption, and venous saturation can be calculated for each leg in active or

passive states, whichever condition is determined by user input. These values are then used to contribute to the whole body oxygen consumption, discussed later.

This portion of the program is called twice, one time for each leg. If the simulation represents an individual at rest or performing two-leg exercise, the values for each leg will be equal.

2.3 Brain

As previously discussed, there are several organs that receive the same blood flow regardless of activity. In human physiology, cerebral blood flow is consistently held at 750/60 cm^3/sec [16]. The brain is also effective at extracting 37% of the oxygen from the blood supplied to this vital organ [23]. Based on these values, the venous oxygen saturation after passing through the brain is given by Equation (14).

$$Svbrain = Sart - 0.37 \quad (15)$$

2.4 Kidney

The kidney is another vital organ where blood flow is held constant. In the renal circulation, the blood flow is maintained at 1 L/min or 1000/60 cm^3/sec. Effective extraction of oxygen is roughly 7.3% [14, 3]. While this value is quite small, the extensive vasculature allows for a significant amount of oxygen to be readily available.

$$Svkidney = Sart - 0.073 \quad (16)$$

2.5 Other

The model created assumes that the most significant proportion of cardiac output (outside of the previously discussed major organs) is distributed to the splanchnic circulation, as referenced in Table 1. The "other" component of this model receives a

constant blood flow of 3.55 L/min. Extraction is estimated to be roughly 38.6%. While there are many other significant organ systems that are affected by exercise, they are not included in this model for the sake of simplicity.

2.6 Whole Body

The main program uses published values for parameters and user input for the number of active legs in order to designate flow rates, oxygen demand to each leg, and total cardiac output. Obviously, as the activity increases (from rest to one to two-legs), so does the cardiac output and oxygen demand of the active leg(s). Defining these values based on user input provides the necessary values to activate each of the subroutines.

The total body venous saturation at the end of the circuit is calculated by the formula below:

$$Sv = \frac{(Qleg1 \times Svleg1) + (Qleg2 \times Svleg2) + (Qbrain \times Svbrain) + (Qkidney \times Svkidney) + (Qother \times Svother)}{Qleg1 + Qleg2 + Qbrain + Qkidney + Qother} \quad (17)$$

This venous saturation feeds back into the subroutine for the lungs and becomes the new initial value to solve the differential equation. Once the difference between venous saturation output from the whole body circuit and the previous venous saturation input into the lungs is less than 0.001, it is assumed a steady state has been reached, and the code ceases and outputs final values. At this point, the total body oxygen consumption can be calculated by Equation (17).

$$Total\ body\ oxygen\ consumption = Qco \times Co \times (Sart - Sv) \quad (18)$$

2.7 Parameter definitions:

Cardiac output is the volume of blood pumped out of the heart in a given amount of time. Cardiac output increases with more activity to meet the demands of the body. For

this project, Davies and Sargeant [5] experimentally measured cardiac output at rest and during one and two-leg exercise. These values are used to define cardiac output for the same situations in the code and can be seen in Figure 10.

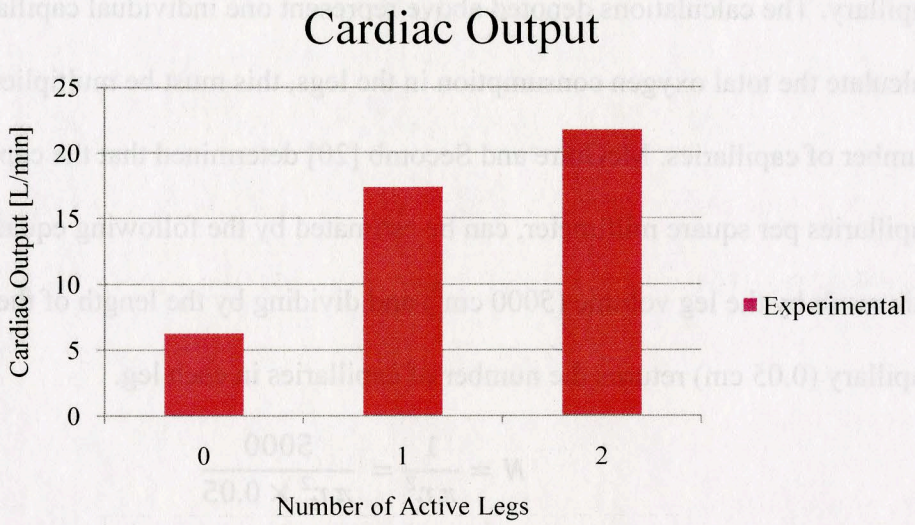

Figure 10: Cardiac Output and Active Legs

Cardiac output is presented above for resting, one-leg, and two-leg states. It is obvious that going from the resting state to one-leg exercise creates a large increase in the cardiac output; however, the increase from one-leg to two-leg exercise is much smaller.

Cardiac output is further divided into the volume of blood per unit time that is directed to each organ. As previously stated, the blood supply to the brain, kidney, and "other" components does not vary with activity. However, the blood flow to each leg differs based on activation. Saltin et al [25] experimentally measured the blood flow to the femoral artery to be 6-10 L/min during knee extensor exercise and 0.3 L/min at rest. In this model, the active leg during one leg exercise receives 11.6 L/min and the passive

leg receives 0.5 L/min. During two-leg exercise, each leg receives a blood flow of approximately 8.7 L/min.

The division of cardiac output to the legs is further divided into the blood flow per capillary. The calculations denoted above represent one individual capillary. In order to calculate the total oxygen consumption in the legs, this must be multiplied by the total number of capillaries. McGuire and Secomb [20] determined that the capillary density, in capillaries per square millimeter, can be estimated by the following equation. Multiplying this result by the leg volume (5000 cm^3) and dividing by the length of the average capillary (0.05 cm) returns the number of capillaries in each leg.

$$N = \frac{1}{\pi r_t^2} = \frac{5000}{\pi r_t^2 \times 0.05}$$

Equation 1: Capillary Density

Oxygen demand is defined as the volume of oxygen per unit of blood per second that a component requires. This model only defines this parameter for the legs and varies depending on the activity (or lack of activity) of the leg. This is used in Equation (12) and Equation (13) to calculate the actual oxygen consumption.

Chapter 3: Results

Figure 11, Figure 12, and Figure 13 depict the blood oxygen saturations exiting each organ at rest, one-leg exercise, and two-leg exercise. The shaded leg boxes represent active legs.

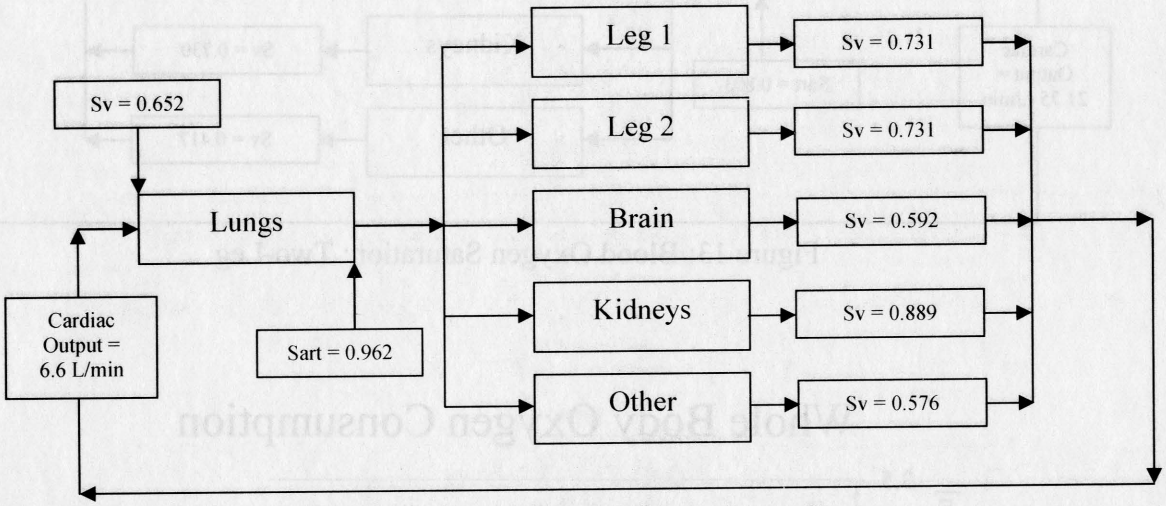

Figure 11: Blood Oxygen Saturation at Rest

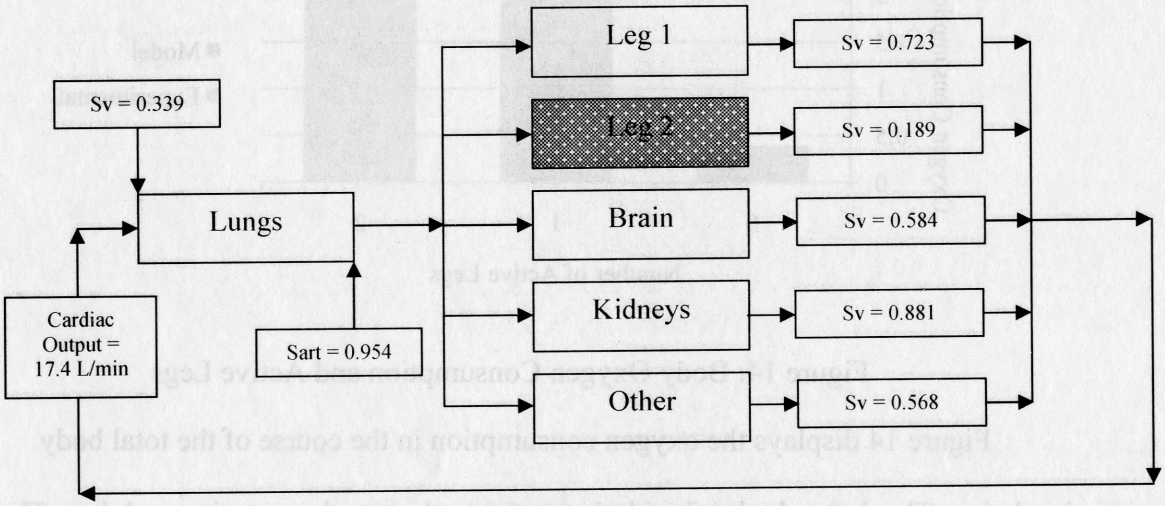

Figure 12: Blood Oxygen Saturation: One-Leg

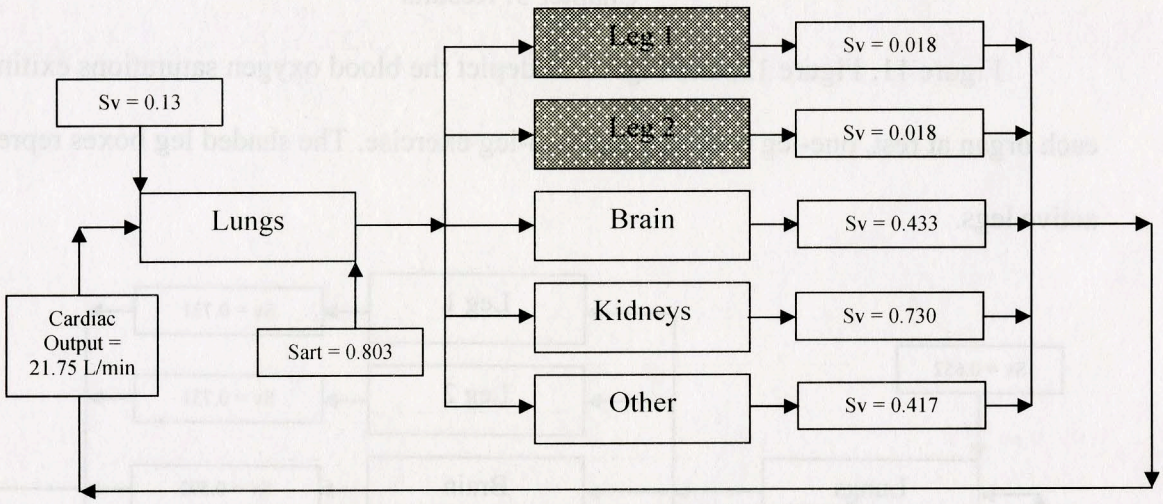

Figure 13: Blood Oxygen Saturation: Two-Leg

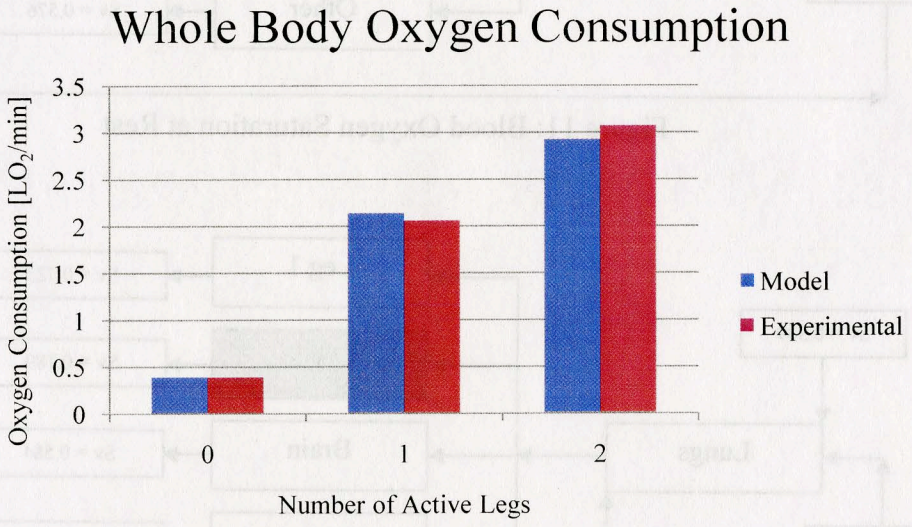

Figure 14: Body Oxygen Consumption and Active Legs

Figure 14 displays the oxygen consumption in the course of the total body circulation. The data calculated with the model is close to the experimental data. The corresponding percent error is presented in Table 4.

Table 4: Percent Error

Conditions	Percent Error (%)
Rest	0.0120
One-leg	4.0224
Two-leg	4.6145

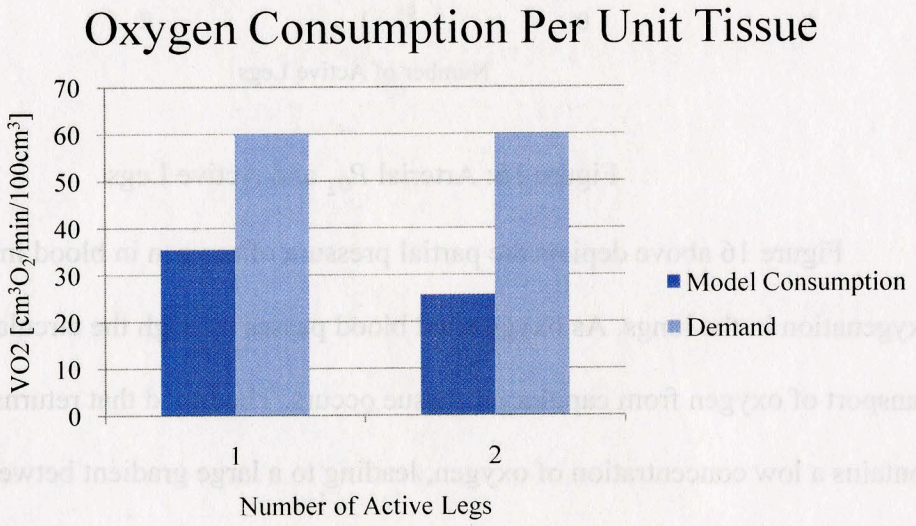

Figure 15: Oxygen Demand and Consumption Per Unit Tissue

At rest, the oxygen demand and consumption are equal. The low demand is easily met by the oxygen content of blood. When one-leg exercise is performed, the demand is elevated, but the model predicts a consumption that does not meet the demand. This indicates that regions of the tissue cylinder are becoming hypoxic. There is an even greater expression of hypoxia when two legs are active. The model consumption per unit is lower for two-leg activity than for one-leg.

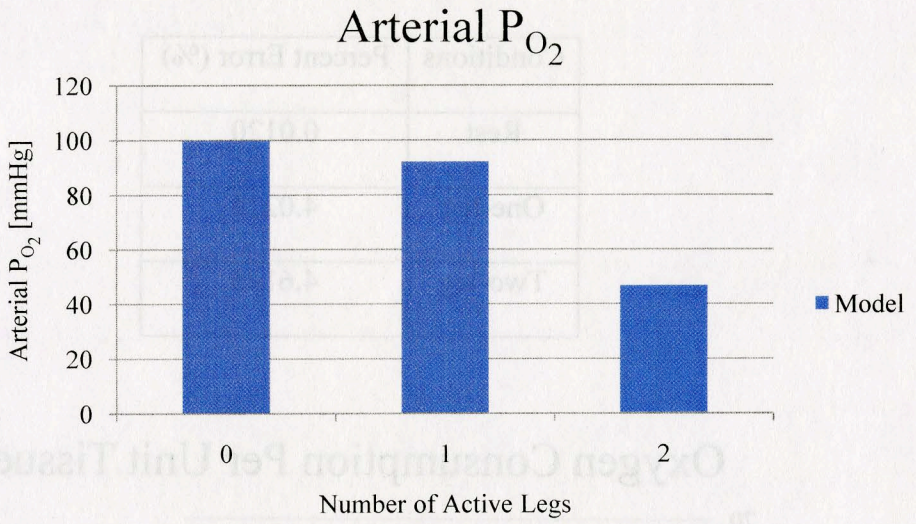

Figure 16: Arterial P_{O_2} and Active Legs

Figure 16 above depicts the partial pressure of oxygen in blood immediately after oxygenation in the lungs. As oxygenated blood passes through the circulation, diffusive transport of oxygen from capillary to tissue occurs. The blood that returns to the lungs contains a low concentration of oxygen, leading to a large gradient between the venous P_{O_2} and the alveolar P_{O_2}. This allows for rapid diffusion of oxygen across the alveoli and into the blood. Hence, the arterial P_{O_2} is greater than the venous P_{O_2} [28]. However, as activity increases, blood flow rate through the alveoli is expedited. The time during which oxygen can diffuse to the blood is significantly reduced. This accounts for the decrease in arterial blood P_{O_2} with increasing activity.

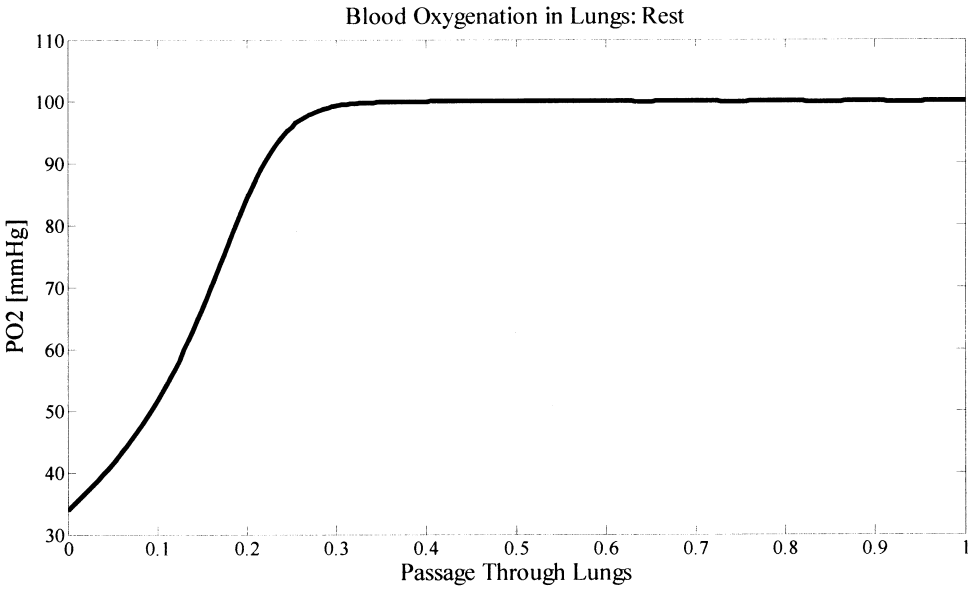

Figure 17: Arterial P_{O_2} at Rest

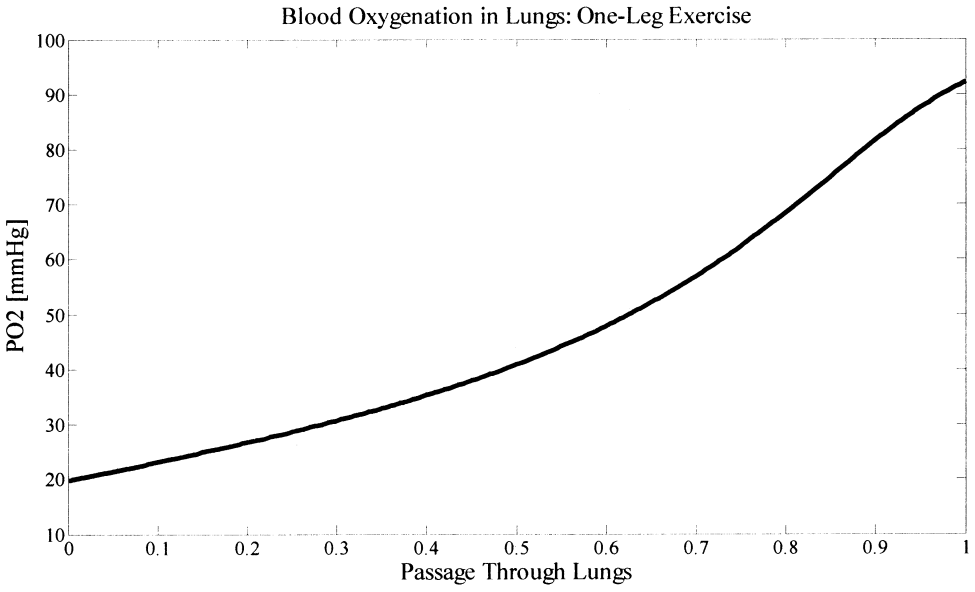

Figure 18: Arterial P_{O_2} in One-Leg Exercise

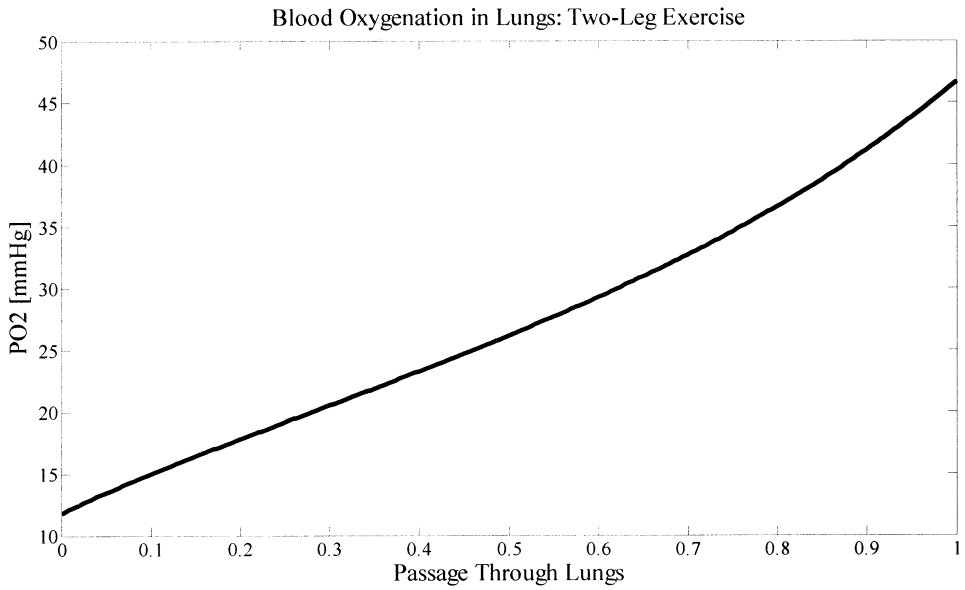

Figure 19: Arterial P_{O_2} in Two-Leg Exercise

Figure 17, Figure 18, and Figure 19 were generated in MATLAB and show the oxygen saturation for rest, one-leg, and two-leg activity. The plots depict the solution to the differential equation in Equation (6). The x-axis represents distance through the lungs while the y-axis shows the arterial P_{O_2} of blood. It becomes visible that as activity increases, there is a lower arterial blood P_{O_2}.

Several variables were charted in the course of this model. The effect of each level of exercise on each is summarized in Table 5. It is important to note that double arrows do not indicate a factor of two increase for the variable. They represent a relative increase to the resting value and single-leg value.

Table 5 : Summary of Variable Outcomes

Variable	Rest	One-Leg	Two-Leg
Cardiac Output	↔	↑	↑↑
Blood Flow Rate	↔	↑	↑↑
Arterial Saturation	↔	↓	↓↓
Arterial P_{O2}	↔	↓	↓↓
Leg 1 Venous Saturation	↔	↔	↓
Leg 2 Venous Saturation	↔	↓	↓↓
Kidney/Brain/Other Venous	↔	↓	↓↓
Whole Body Venous Saturation	↔	↓	↓↓
Venous P_{O2}	↔	↓	↓↓

Chapter 4: Discussion

4.1 Cardiac Output

Cardiac output is the product of heart rate and stroke. These factors determine the flow rate of blood and, consequently, are the limiting factors in determining the amount of contact any organ has with blood. Heart rate, and therefore cardiac output, increases as a compensatory mechanism to allow increased perfusion of the body to meet the increased demand of necessary materials. As the flow rate increases, there is less time for exchange of materials between blood and tissue. At rest, heart rate and cardiac output are relatively low because basal oxygen demands are easily met. As activity increases to one-leg exercise, the activated leg demands a greater oxygenated blood supply. The heart contracts even more frequently to increase the cardiac output further when two legs are activated.

As heart rate reaches its limit, so does cardiac output. In this case, the low oxygen content of blood and divided blood flow to active components may be insufficient to meet the oxygen demands of the active tissue.

4.2 Venous and Arterial Saturation and P_{O_2}

As blood oxygen diffuses from the capillaries into surrounding tissue, the oxygen content of blood, measured as P_{O_2}, and venous saturation, decrease. The blood returning to the lungs is then re-oxygenated and circulates again. As the oxygen demand increases, the venous P_{O_2} and venous saturation will both decline. This is seen as the S_v value of Figure 11, Figure 12, and Figure 13 lower in value as the more legs are activated. While the oxygen consumption is shown to increase (because there is less oxygen returning to

the respiratory circulation), tissue can, and will, become hypoxic because the demand during activity has also increased.

The lower venous P_{O_2} with increased activity creates a larger gradient between the alveolar and venous P_{O_2}. Returning to Equation (5), this pressure difference should result in a greater change in pressure with time, thereby facilitating the diffusion process more rapidly and maintaining the arterial P_{O_2}. However, with the rapid transit time of the blood through the lungs associated with elevated flow rate, the arterial saturation is actually lowered. Figure 11, Figure 12, and Figure 13 depict this decreasing arterial saturation (*Sart*) with leg activation.

An increased oxygen demand results in greater oxygen consumption and a lower venous P_{O_2}; however, diffusive limitations of oxygen from alveoli to blood imposed by the rapid flow rate through the lungs result in a falling arterial oxygen saturation.

4.3 Whole Body Oxygen Consumption

Davies and Sargeant [5] provided experimental data for the rate of oxygen intake. The model was developed with the goal of replicating this data. In producing values agreeing with experimental data, the model is given validity in the other values that are taken from it i.e. saturations and oxygen consumptions.

4.4 Leg Venous Saturation

Applying the Krogh configuration to capillary level oxygen transport in the legs allows for the calculation of the oxygen consumption per unit of tissue. This is seen in Figure 15: Oxygen Demand and Consumption Per Unit Tissue. When resting conditions are considered, the venous saturation for each leg is roughly 73% (Figure 11). As a leg

becomes active, the oxygen demand increases and the venous saturation decreases due to the increase in oxygen consumption. Figure 15 shows that the per unit tissue oxygen consumption decreases from one-leg to two-leg activity. The consumption does not meet the demand in either case. The lack of oxygen consumption can be attributed to several factors. As previously discussed, the oxygen demand of the active legs increases; however, the arterial saturation also decreases. This means that there is lower oxygen content to meet the higher demand. Furthermore, while the cardiac output rises to meet the demands, the blood flow rate also increases. As a result, there is less contact time between the capillary blood and tissue. As the tissue does not receive sufficient oxygen supply, it becomes hypoxic.

4.5 Brain, Kidney, and Other Venous Saturation

The brain, kidney, and other components of the model receive consistent blood flows and maintain the same demand regardless of activity. However, the arterial saturation entering these organs and organ systems is dependent on the total body circulation. As stated earlier, both the arterial and venous oxygen saturations decrease with increased activity. As a result the P_{O_2} entering these constant components is lower and the venous saturation of each organ is also lowered.

4.6 Limitations of Model

The model created is a simplified representation of a complex system. It treats each organ as a homogenous unit and does not account for any variability. For example, a lobe of the lung is divided into three zones [28]; however, this model neglects to differentiate between the three zones and defines a universal alveolar pressure. In

addition, capillaries in the legs are not identical and their length, flow, and spacing are variable and not uniform, as they are treated here.

A second limitation to this model is the parameter values used. Many of the parameters presented in Table 2 and Table 3 are known to be within reasonable accuracy (i.e. cardiac output, diffusion parameters, flow rates, and oxygen consumption). However, oxygen demand (g) is not known. This model assumes a maximal demand of $g = 60/6000$ $cm^3O_2/cm^3blood/s$; however, the model is not terribly sensitive to this value. Figure 4: Consumption and Demand shows that small increases in the demand do not elicit a proportional increase in consumption, especially in the plateau phase. Another example is the value of k_L, the lung oxygen transport coefficient. This value (0.6) was chosen in order to give appropriate saturations under various conditions. The model could be refined to compare model results with experimental results for arterial saturation under various conditions.

The intent of creating this model was to explore factors limiting oxygen consumption in two-leg exercise at both the capillary and whole body levels. At the systemic level, increased cardiac output means an increased flow rate of blood through the lungs, limiting the time blood has in contact with alveoli and reducing the arterial P_{O_2} and arterial oxygen saturation. At the capillary level, the reduced oxygen content of blood means there is less oxygen available to meet the increased demand of tissue. In two-leg exercise, the cardiac output is divided between two legs, further reducing oxygen content. This results in more hypoxic tissue in the legs. The oxygen returning to the lungs has a

low venous saturation. This cycle continues, reducing oxygen availability to the systemic circulation.

Appendix A: MATLAB Code

```
%%%%% main routine
clear all
clc
global Ktissue rc rt deltaz Co P50 n Pb Kpl Sh Palv k Qco length \
%%1 = passive
%%2 = active
Poi = 100;
    %%mmHg
g1 = 0.46/6000;
    %%cm^3/cm^3/s
    %%Oxygen demand of passive leg
g2 = 60/6000;
    %%cm^3/cm^3/s
    %%Oxygen demand of active leg
Ktissue = 9.4*10^(-10); %%bently et al
rc = 2.5*10^-4; %%cm
rt = 20*10^-4; %%cm
deltaz = 0.001; %%cm
Co = 0.2;
    %%cm^3O2/cm^3blood
    %%O2 carrying cap
u = 0.1;
    %%cm/sec
P50 = 26;
    %%mmHg
n = 2.4;
    %%in humans
Pb = 100;
    %%mmHg (1 Torr ~ 1 mmHg)
Kpl = 8.3*10^-10;
    %%Krogh diffusion constant in plasma (cm^2/sec)(cm^3 of
    %%O2*cm^-3*Torr^-1)
Sh = 2.5;
% % rdest = 0.005;
Palv = 100;
% %     mmHg
k = 0.67;
   %%rate const
length = 0.05; %%cm length of Krogh cylinder
Ncap = 5000/(pi*(rt^2)*length); % % number of capillaries in one leg
Qbrain = 750/60; %%cm^3/sec
Qkidney = 1000/60; %%cm^3/sec
Qother = 3550/60;

%%Ask for user input, 1 leg or 2.
numlegs = input('No legs [0], one leg [1], or two legs [2]? ');
if numlegs == 2
    Qco = 21750/60;
        %%cm^3/sec
        %%21.75 L/min
    Qleg2 = (Qco-Qbrain-Qkidney-Qother)/2; %%cm^3/sec
    Qleg1 = Qleg2;
```

```
    g1 = g2;
    expected = 3.07;
elseif numlegs == 1
    Qco = 17400/60;
        %%cm^3/sec
        %%17.4 L/min
    Qleg1 = 500/60; %%cm^3/sec %%Saltin, Radegrabn, Koskolou, Roach
      1998
    Qleg2 = Qco-Qbrain-Qkidney-Qleg1-Qother; %%cm^3/sec
    expected = 2.06;
elseif numlegs == 0
    Qco = 6300/60;
        %%cm^3/sec
        %%6.3 L/min
    Qleg1 = 500/60; %%cm^3/sec
    Qleg2 = Qleg1;
    g2 = g1;
    expected =  0.3903;
end

Qcap1 = Qleg1/Ncap; %%cm^3/sec - blood flow per capillary
Qcap2 = Qleg2/Ncap; %%cm^3/sec
%%Qcap=Qart/Ncap;
Pvin = 20;
counter = 0;

E = 1;
while(E > 0.001) && (counter < 10)
    [Part, Sart] = lungs(Pvin);

    [Svleg1, Pvleg1, consumptionIR1] = leg(g1, Qcap1, Part);
    [Svleg2, Pvleg2, consumptionIR2] = leg(g2, Qcap2, Part);

    Svbrain = Sart - 0.37; %end saturation after brain
    Svkidney = Sart - 0.073; %end saturation after kidney
    Svother = Sart - 0.386; %%end saturation after other

    Sv = (Qleg1*Svleg1 + Qleg2*Svleg2 + Qbrain*Svbrain +
Qkidney*Svkidney + Qother*Svother)/(Qleg1 + Qleg2 + Qbrain + Qkidney +
Qother);
    Pv = P50*(Sv/(1-Sv))^(1/n);

    E = abs (Pvin-Pv);
    counter = counter + 1;
    if E < 10^-3
        break
    end
    Pvin = Pv;
end
```

```
counter;
    Sv
    Pv;
    consumptionIR1
    consumptionIR2
    Svleg1;
    Svleg2;
    Svbrain;
    Svkidney;
    totalbodyconsumption = Qco*Co * (Sart-Sv); %%cm^3/sec
    mLpermin = totalbodyconsumption*60 %%cm^3/min
    Lpermin = (totalbodyconsumption)*(60/(100^3))*1000;
    percenterror = abs(expected-Lpermin)/(expected)*100

%%%%WRITE TO EXCEL FILES
if numlegs == 2
    a = {numlegs Qco};
    xlswrite('test.xls', a, 1, 'A4')
    b = {numlegs Part Sart Pv Sv};
    xlswrite('test.xls', b, 2, 'A4')
    c = {numlegs consumptionIR2 g1*6000};
    xlswrite('test.xls', c, 3, 'A4')
    d = {numlegs Lpermin};
    xlswrite('test.xls', d, 4, 'A4')
    e = {numlegs Svleg1 Svleg2 Svbrain Svkidney Svother};
    xlswrite('test.xls', e, 5, 'A4')

elseif numlegs == 1
    a = {numlegs Qco};
    xlswrite('test.xls', a, 1, 'A3')
    b = {numlegs Part Sart Pv Sv};
    xlswrite('test.xls', b, 2, 'A3')
    c = {numlegs consumptionIR2 g2*6000};
    xlswrite('test.xls', c, 3, 'A3')
    d = {numlegs Lpermin};
    xlswrite('test.xls', d, 4, 'A3')
    e = {numlegs Svleg1 Svleg2 Svbrain Svkidney Svother};
    xlswrite('test.xls', e, 5, 'A3')

elseif numlegs == 0
    a = {numlegs Qco};
    xlswrite('test.xls', a, 1, 'A2')
    b = {numlegs Part Sart Pv Sv};
    xlswrite('test.xls', b, 2, 'A2')
    c = {numlegs consumptionIR2 g2*6000};
    xlswrite('test.xls', c, 3, 'A2')
    d = {numlegs Lpermin};
    xlswrite('test.xls', d, 4, 'A2')
    e = {numlegs Svleg1 Svleg2 Svbrain Svkidney Svother};
    xlswrite('test.xls', e, 5, 'A2')
end
```

```
%% LEG
function [Svleg, Pvleg, Average_ConsumptionIR] = leg(g, Qcap, Part)
global Ktissue rc rt deltaz Co P50 n Pb Kpl Sh Palv k length %%rdest

consumptionIR = zeros(size(51));

% % With intravascular resistance...
rdest=0.01;
for i = [1:51] %%zero to 0.05 cm with a step size of 0.001 cm
        L(i) = (i-1)*0.0001;
        if i == 1
% %             Po(i) = Poi;
            Po(i) = Part;
            consumption(i) = 0;
        end
        P(i) = Po(i) + ((g/(4*Ktissue))*(rt^2-rc^2)) +
            (((g*rt^2)/(2*Ktissue))*(log(rc/rt))) -
            ((g/(Kpl*Sh))*(rt^2-rc^2));
            %%solves for the Pressure at a certain distance L along the
            %%capillary
        if P(i) <=0
            f = @(rd)(Po(i) + ((g/(4*Ktissue))*(rd^2-rc^2)) +
            (((g*rd^2)/(2*Ktissue))*(log(rc/rd))) -
            ((g/(Kpl*Sh))*(rd^2-rc^2)));
            rd = fzero(f,rdest);
            rdest = rd;
                %%0.0005 is the initial guess
                %%solves for the value of rd (radial distance) where
                  the 'P' equation equals 0
            consumptionIR(i) = g*pi*(rd^2-rc^2)*deltaz;
                %%calcuates how much oxygen is consumed at the distance
                  L along
                %%the capillary at the radial distance calculated
        else
            consumptionIR(i) = g*pi*(rt^2-rc^2)*deltaz;
                %%What is the consumption?
                %%(cm^3O2/cm^3blood/min)*(cm^2)*(cm)
                %% cm^3O2/min
        end
% %         Qcap = pi*(rc)^2*u;
        changeinsat = -consumptionIR(i)/(Qcap*Co);
    % %     S = S + changeinsat
        S = 1-1/(1+(Po(i)/P50)^n) + changeinsat;

        if S < 0
            S = 1e-6;
        end

        if i < 51
            Po(i+1) = P50*(S/(1-S))^(1/n);
            %%excludes O2 dissolved in blood
        end
end;
```

```
%%   plot (1:51, consumptionIR)
    Total_ConsumptionIR = sum(consumptionIR)'; %%cm^3O2/min
    Average_ConsumptionIR =
(Total_ConsumptionIR/(pi*rt^2*length))*6000; %%cm^2/cm^3; %%cm^3O2/min
    Svleg = S;
    Pvleg = Po(51);

%%subroutine - lungs

function [Part Sart] = lungs(Pvin)
global Ktissue rc rt deltaz Co P50 n Pb Kpl Sh Palv k length %%rdest

tspan = [0:0.005:1];
y0 = Pvin;
    %%Pvart
[t,P]=ode45('F',tspan,y0);
plot(t,P)
xlabel ('Passage Through Lungs')
ylabel('PO2 [mmHg]')
Part = P(201);
Sart = 1-1/(1+(P(201)/P50)^n);
%%this does not take 'change in saturation' into account. This assumes
that the blood flows through the lungs once. In the legs, it is
necessary to sum the changes in saturation along each increment of the
capillary.

%%subroutine - ODE solver

function dPdt=F(t,P)

global k Qco Palv Co P50 n

dPdt=(k/Qco*((Palv-P)))*(((P50^n + P^n)^2)/(Co*P50^n*n*P^(n-1)));
```

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Maximal Rate of Oxygen Consumption: One-Leg Exercise versus Two-Leg Exercise

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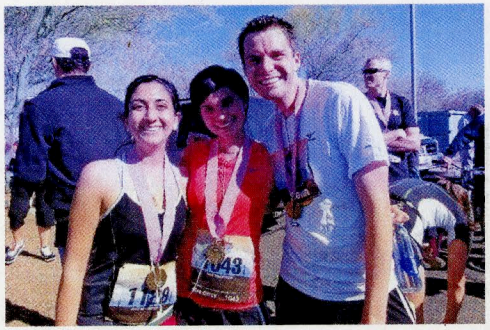
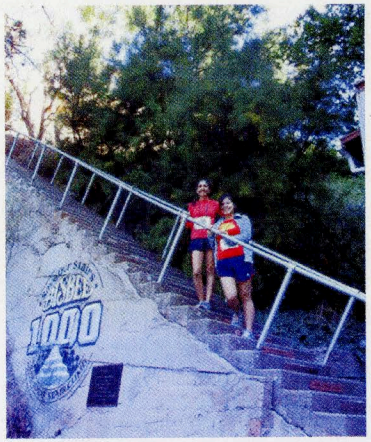
BME GIDP
Accelerated Masters Candidate – May 2011

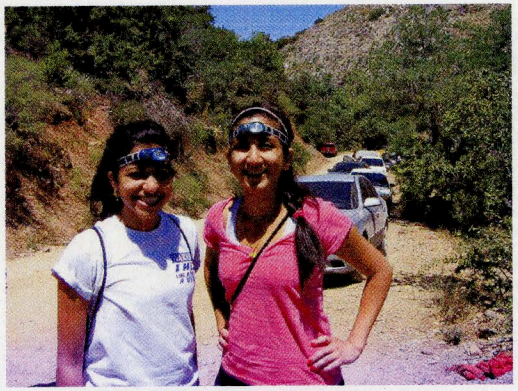
Agenda

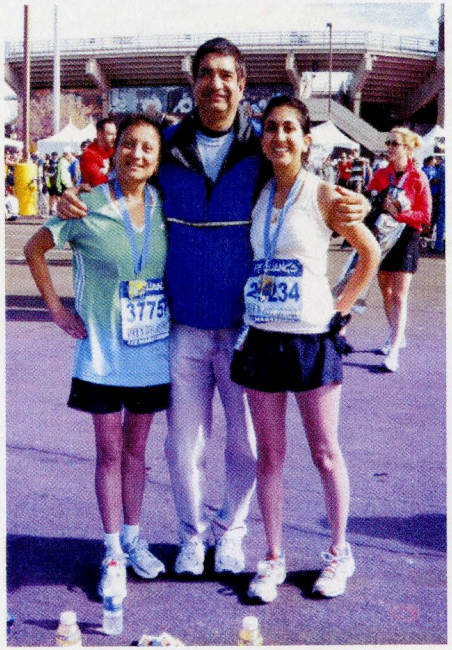
- Personal Interest
- Background
- Problem
- Experimental Studies
- Goal
- Hypothesis
- Methods
- Results
- Conclusion
- Acknowledgements
- Questions

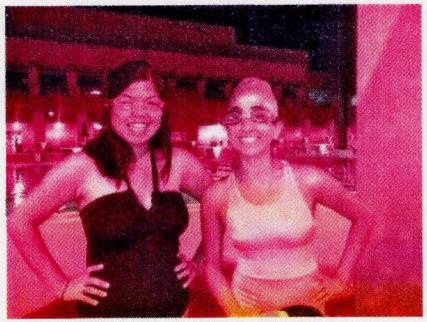
Personal Interest











Background

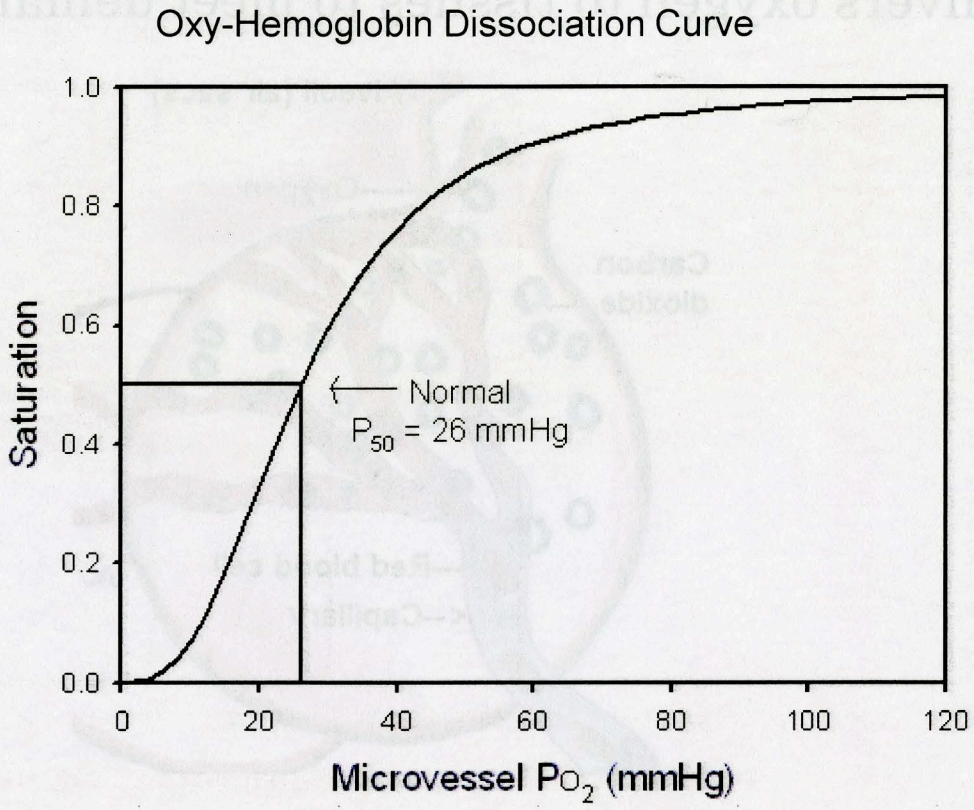
- Cells need energy
  - Mitochondria – powerhouse of cells
    - ADP → ATP (energy source)
    - Need oxygen for this conversion

Background

- Oxygen
  - Carried in blood via hemoglobin

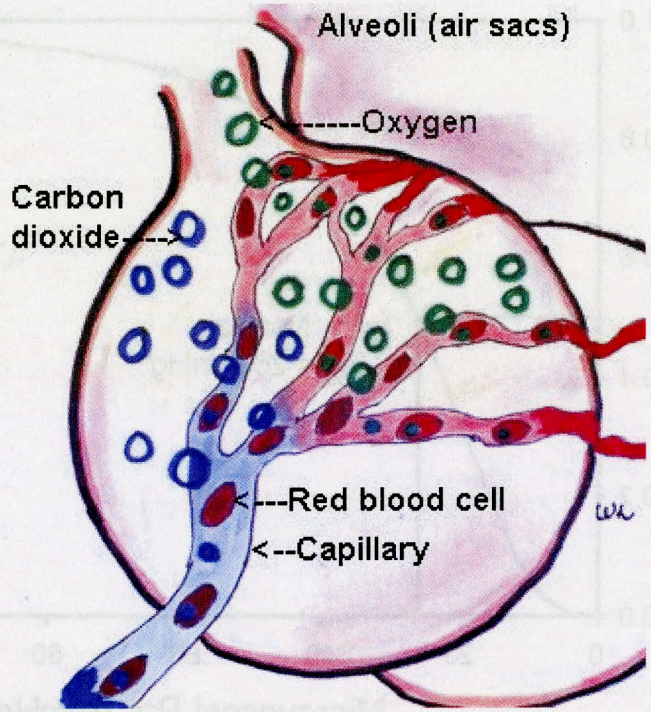
Hill Equation:

$$S = \frac{P^n}{P^n + P_{50}^n}$$



Background

- Blood flow though vessels
  - Oxygenated in the lungs by alveoli
  - Delivers oxygen to tissues to meet demand



http://www.ehow.com/facts_5159074_oxygen-go-lungs.html

Background

- Convection
  - Movement of mass over distances
  - Blood through vasculature
- Diffusion
  - Passive transport
  - Based on a gradient
  - Lungs to blood
  - Blood to tissue

PROBLEM

- One-leg exercise versus two-leg exercise
- During exercise: demand > supply
- Maximal rate of oxygen consumption ($V_{O_{2max}}$)per unit of tissue:
  - Lower in two-leg exercise than one-leg exercise

WHY?

Experimental Studies
Davies and Sargeant

- Physiological responses to one- and two-leg exercise breathing air and 45% oxygen (1974)
- Normoxic: Lower $V_{O_{2max}}$ in two-leg
- Hyperoxic: Similar $V_{O_{2max}}$
- Limitation
  - One-leg: oxygen content
  - Two-leg: blood flow rate

Davies and Sargeant

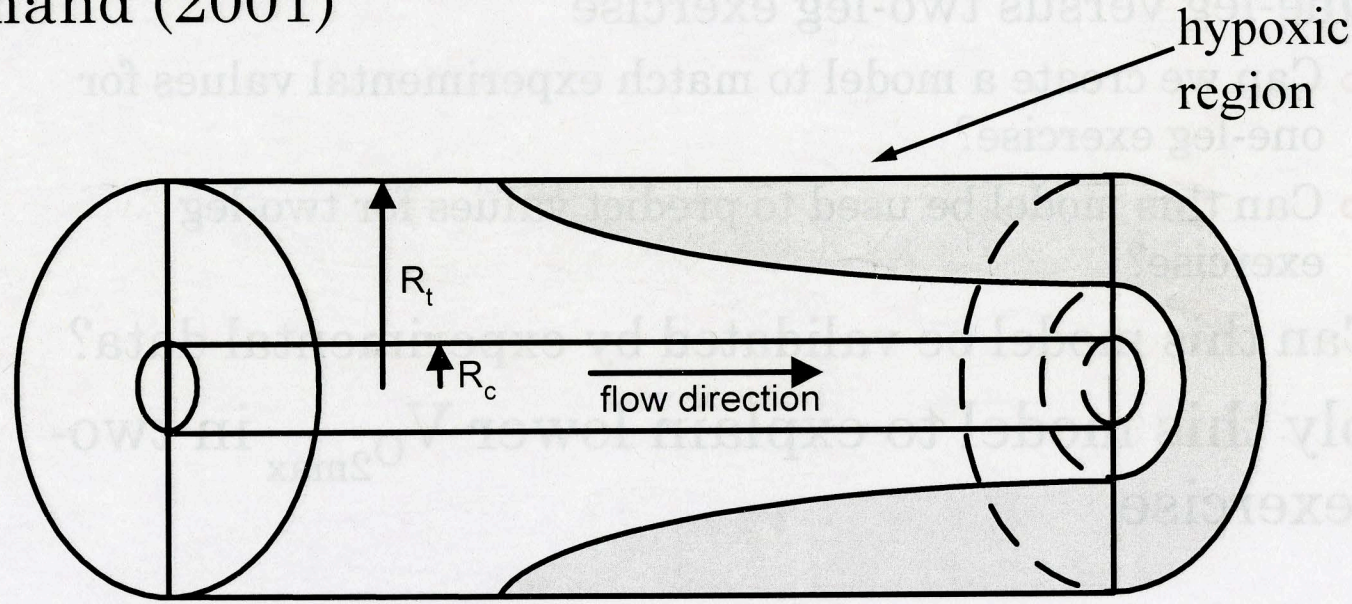
Experimental Studies
Richardson

- Effect of hypoxic and normoxic conditions on single leg knee extensor exercise (1995)
- Higher $V_{O_{2max}}$ in normoxic conditions
- Similar leg blood flow, diffusivity
- Limitation
  - Oxygen content

Richardson

Theoretical Studies McGuire and Secomb

- A theoretical model for oxygen transport in skeletal muscle under conditions of high oxygen demand (2001)



Secomb 2001

Goal

- Create a theoretical model to compare maximal oxygen consumption in:
  - One-leg versus two-leg exercise
    - Can we create a model to match experimental values for one-leg exercise?
    - Can this model be used to predict values for two-leg exercise?
  - Can this model be validated by experimental data?
- Apply this model to explain lower $V_{O_{2max}}$ in two-leg exercise

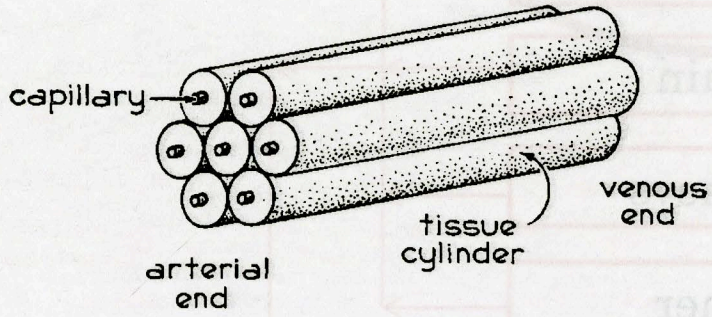
HYPOTHESIS

- Lower $V_{O_{2max}}$ in two-leg exercise can be explained by a model that includes:
  - Limitations on systemic oxygen delivery
  - Limitations of oxygen delivery at the capillary level

METHODS

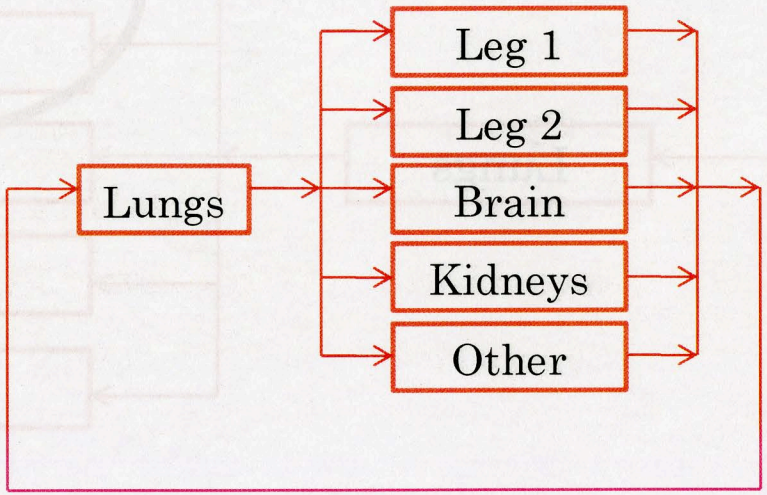
METHODS

- Capillary level
  - Diffusion



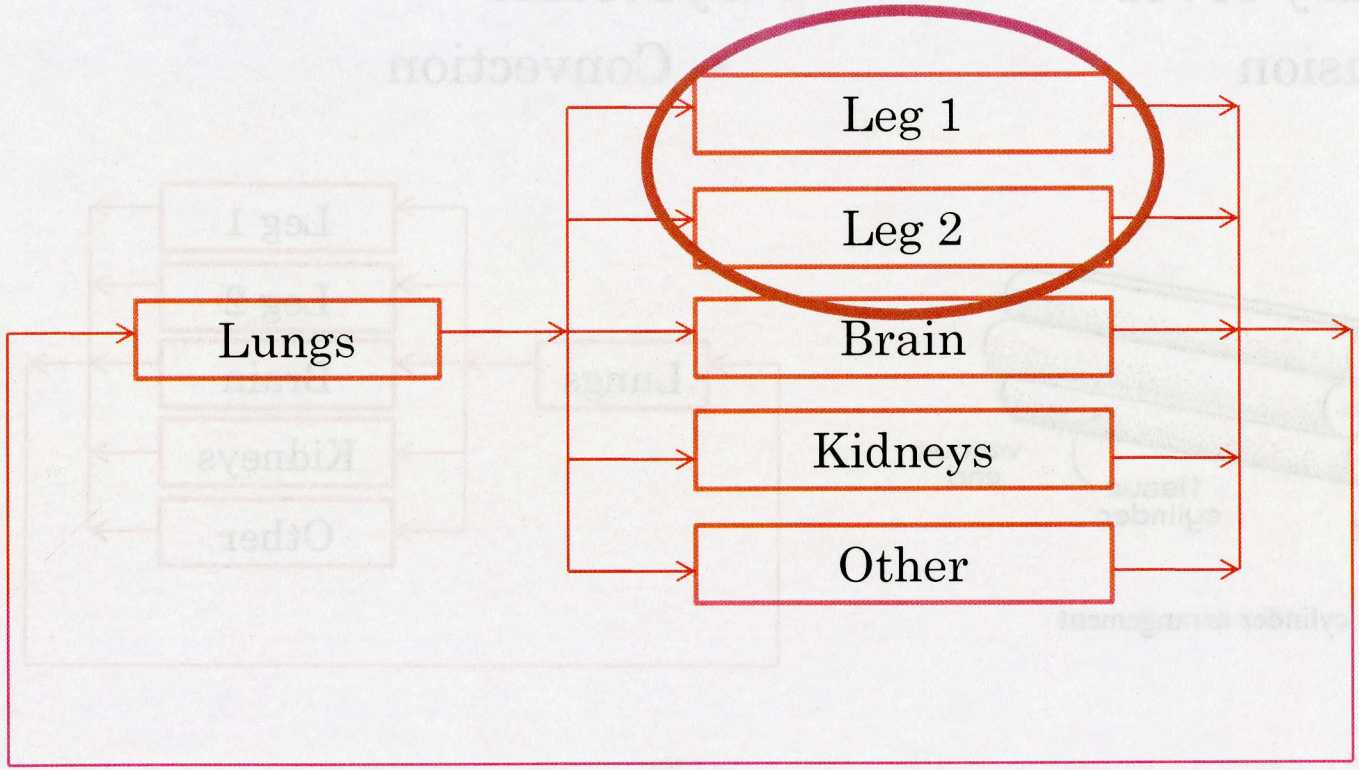
Krogh cylinder arrangement

- Systemic
  - Convection



METHODS

Basic Model



Methods
Capillary level

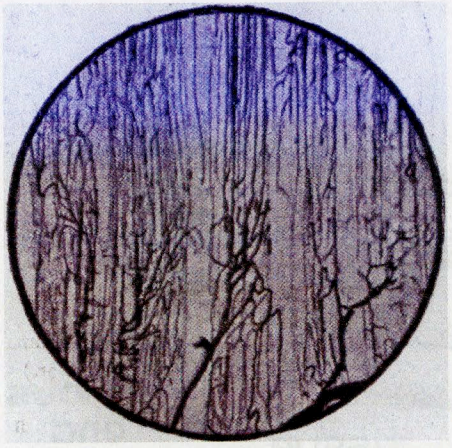


Fig. 1. Longitudinal section of injected M. gastrocnemius of the horse. ×70.

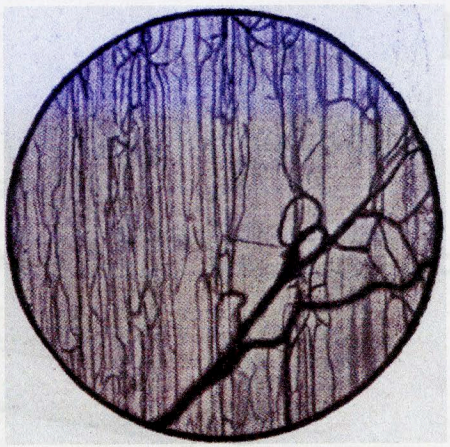
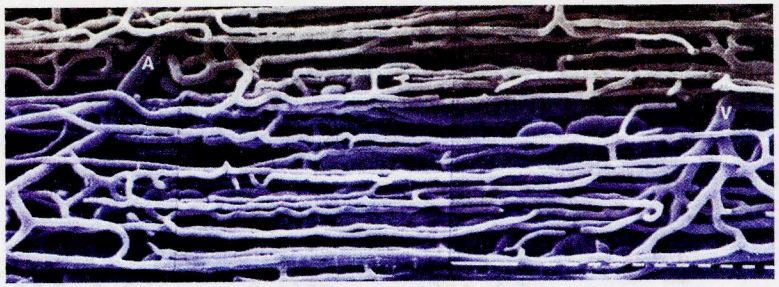


Fig. 2. Injected abdominal muscle wall of the guinea-pig. ×70.

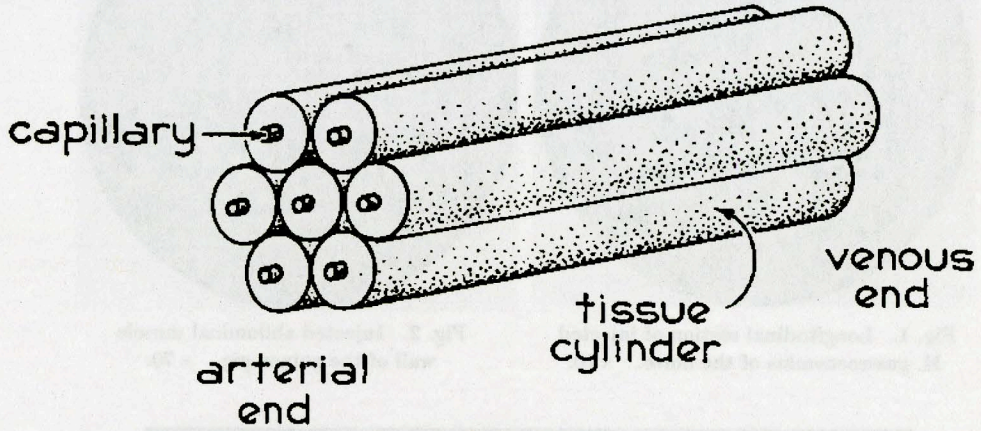


Gastrocnemius muscle

Krogh, Groom

Methods
Capillary level

- Krogh Model



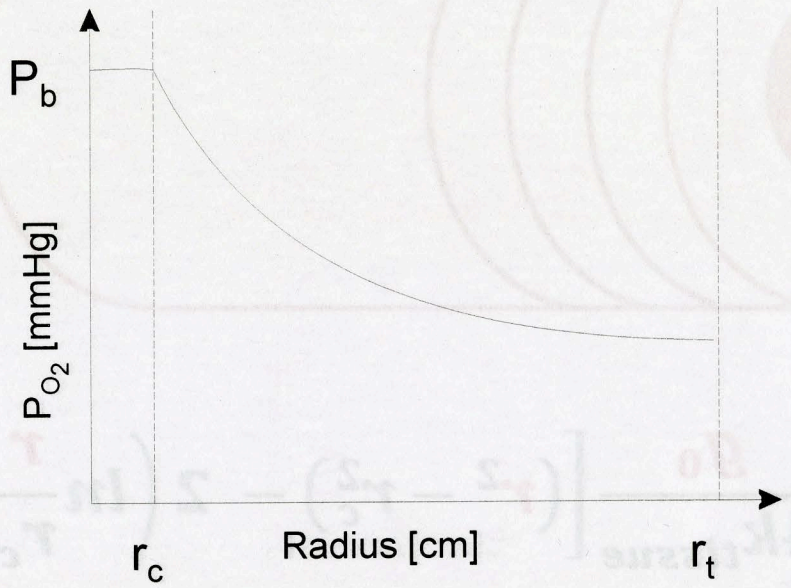
Krogh cylinder arrangement

$$P(r) = P_b + \frac{g_0}{4k_{tissue}}\left[(r^2 - r_c^2) - 2\left(ln\frac{r}{r_c}\right)r_t^2\right]$$

Krogh 1918

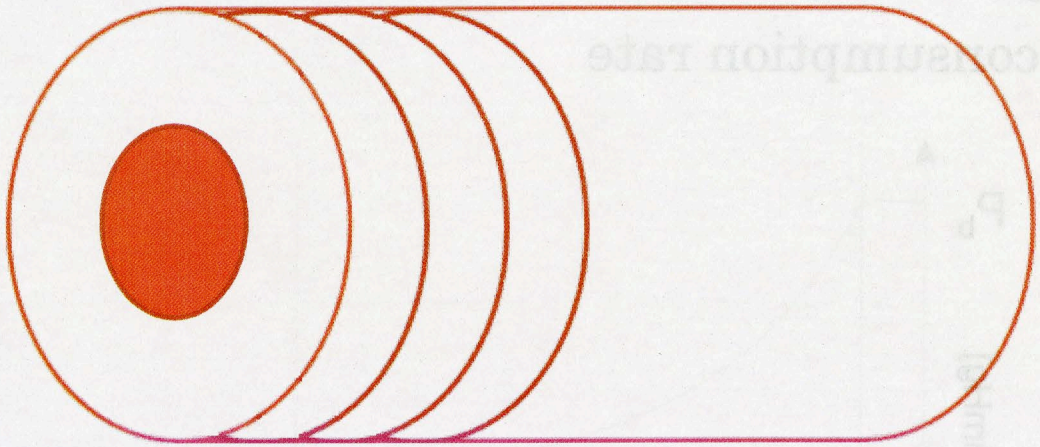
Methods
Capillary level

- Factors influencing tissue oxygen level
  - Blood P_{O_2}
  - Tissue cylinder radius
  - Oxygen consumption rate



$$P(r) = P_b + \frac{g_0}{4k_{tissue}}\left[(r^2 - r_c^2) - 2\left(ln\frac{r}{r_c}\right)r_t^2\right]$$

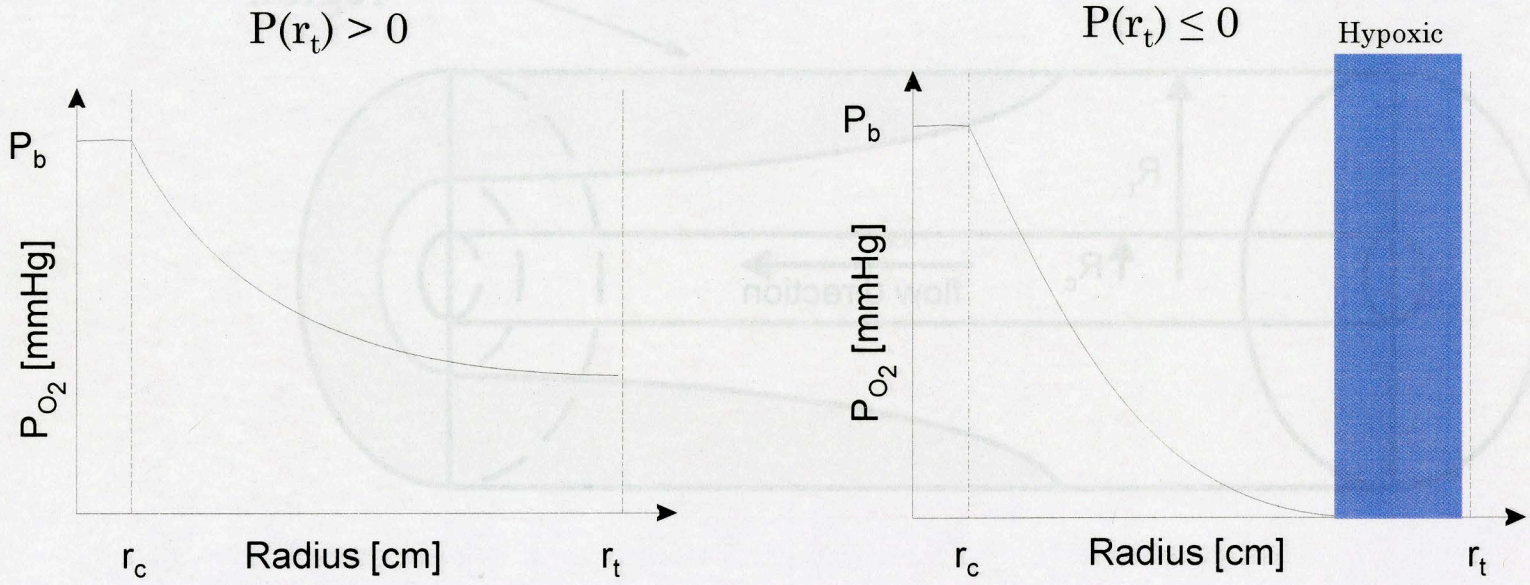
Methods
Capillary level



$$P(r) = P_b + \frac{g_0}{4k_{tissue}}\left[(r^2 - r_c^2) - 2\left(ln\frac{r}{r_c}\right)r_t^2\right]$$

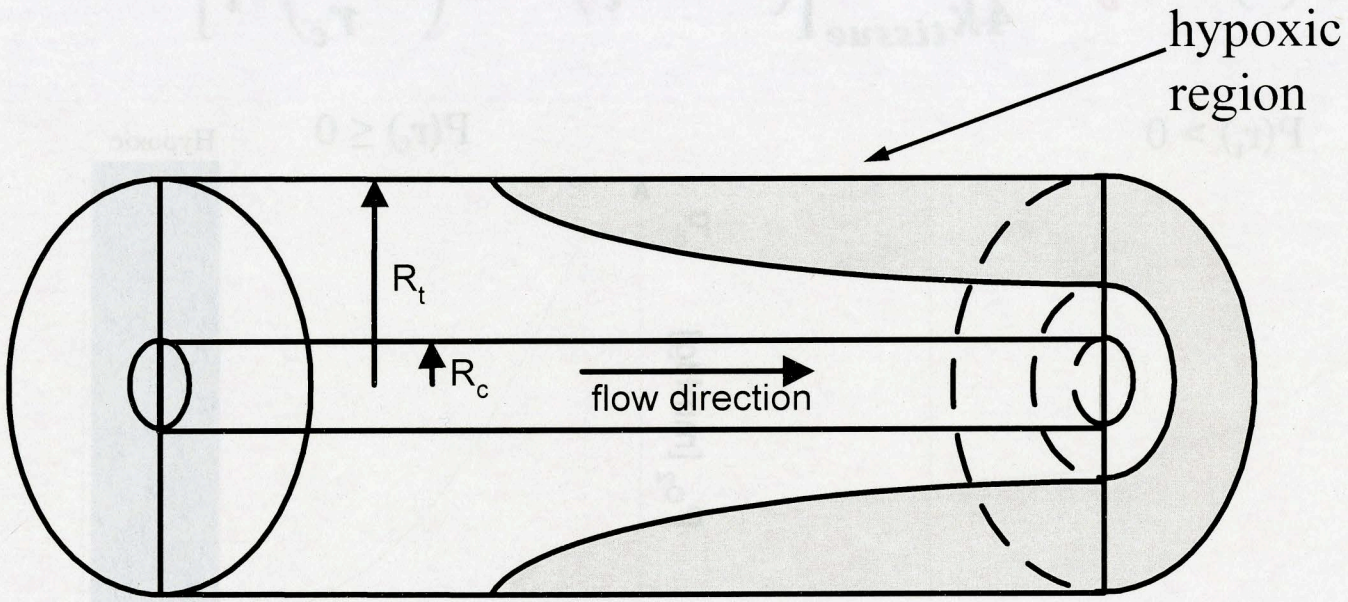
Methods
Capillary level

$$P(r) = P_b + \frac{g_0}{4k_{tissue}}\left[(r^2 - r_c^2) - 2\left(ln\frac{r}{r_c}\right)r_t^2\right]$$



- Can calculate when (radially) tissue becomes hypoxic
  - Here, we assume consumption is 0

Methods
Capillary level

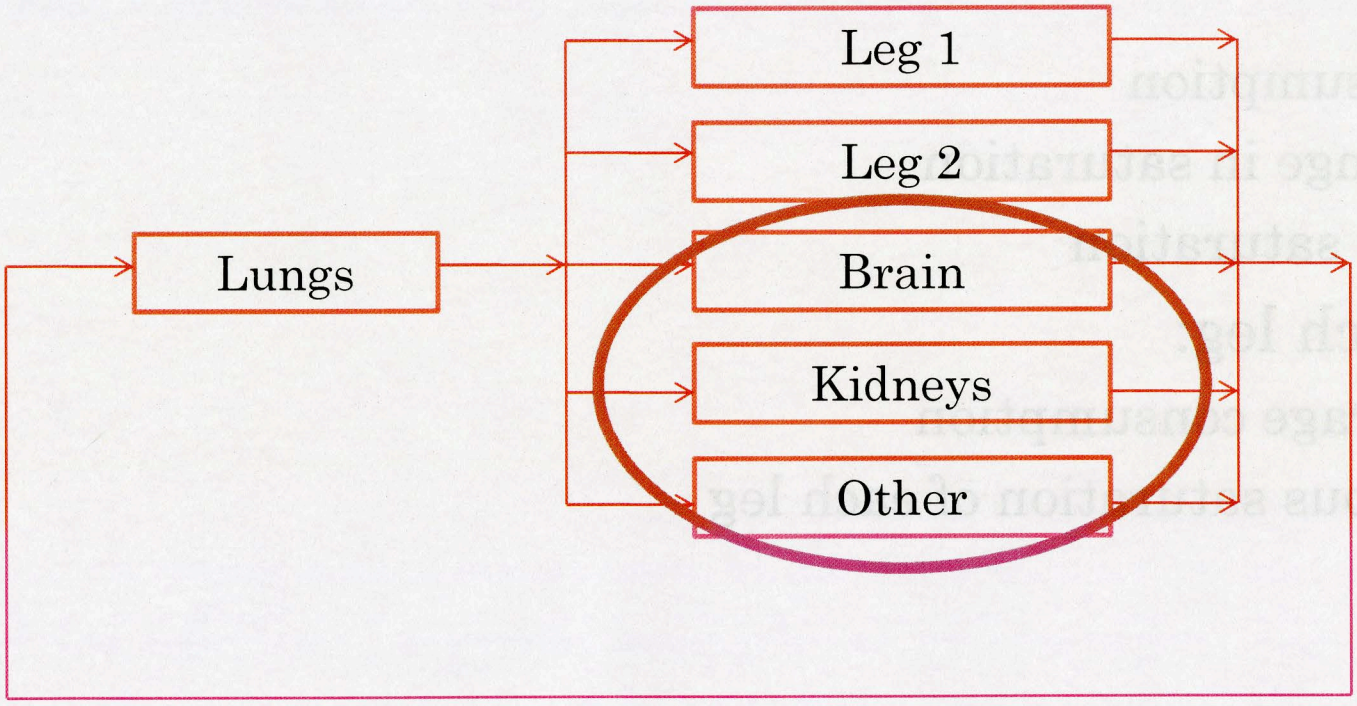


Methods
Capillary level

- For each slice:
  - P_{O_2}
  - Consumption
  - Change in saturation
  - New saturation
- For each leg:
  - Average consumption
  - Venous saturation of each leg

METHODS

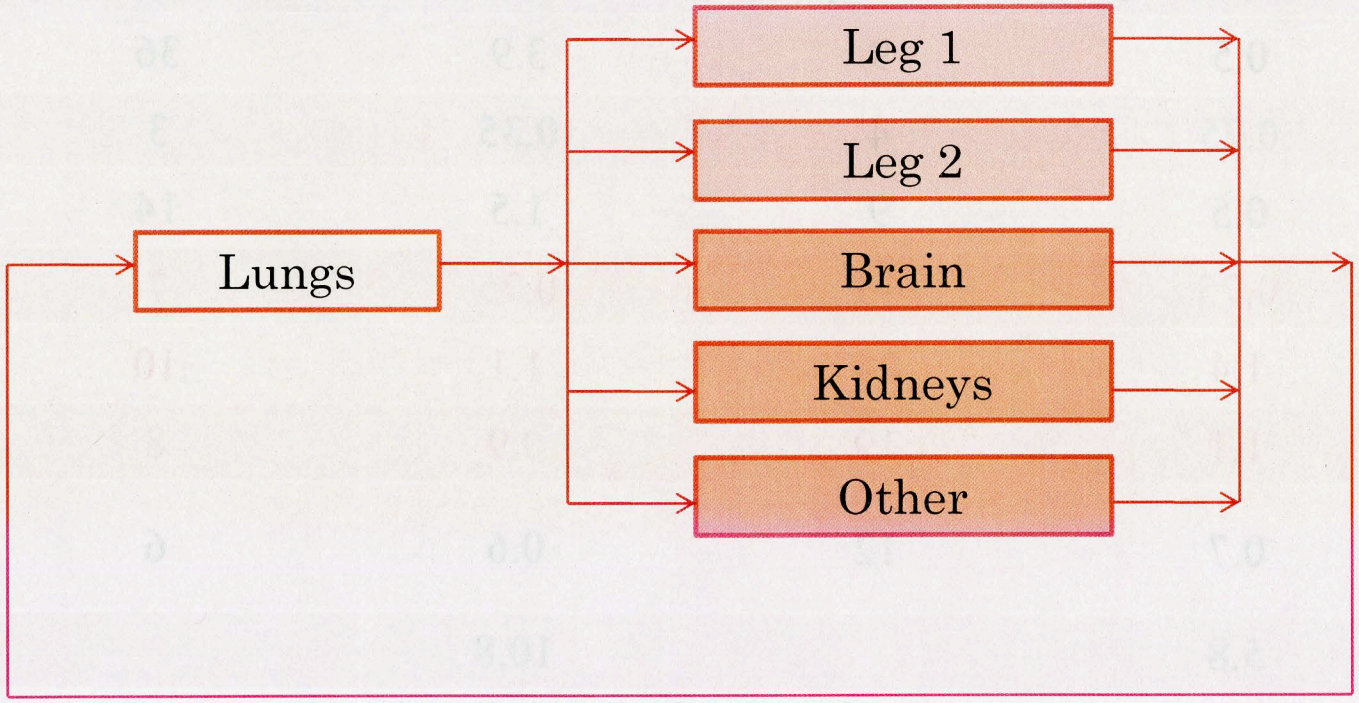
Basic Model



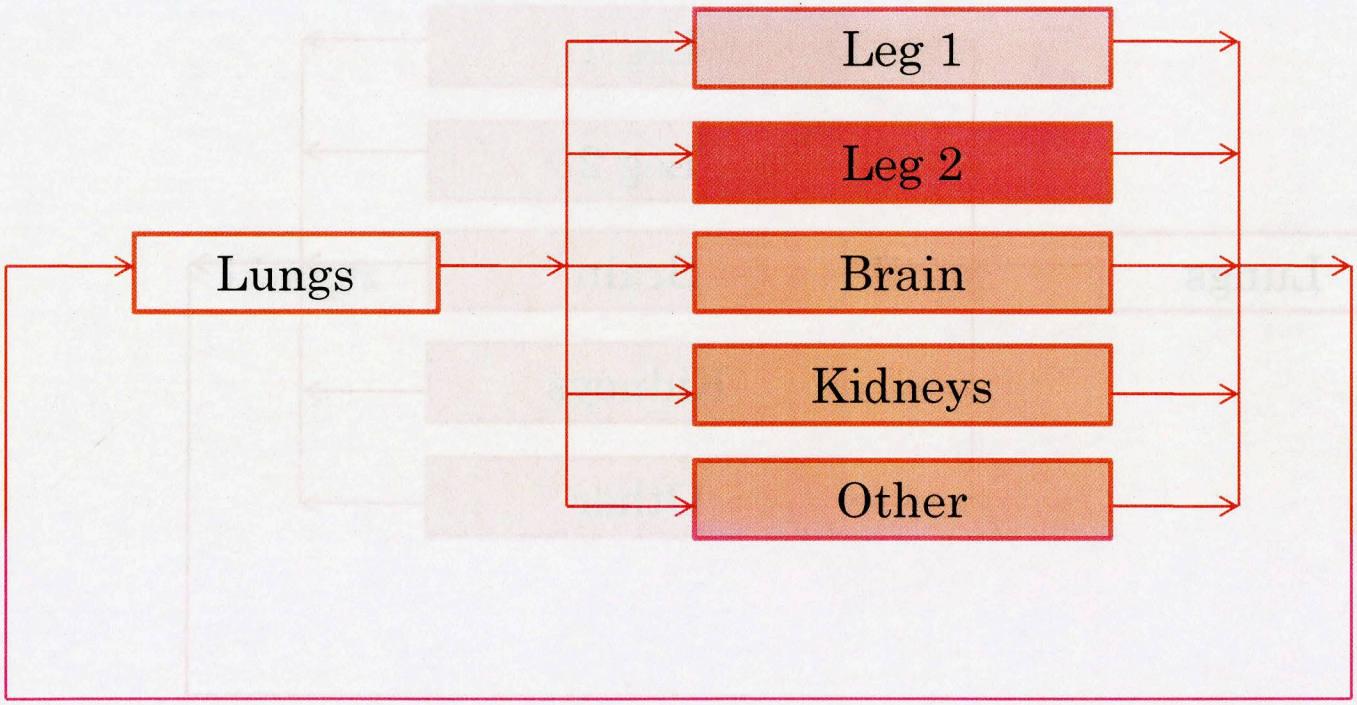
METHODS
SYSTEMIC

Organ	Rest		Leg Exercise	
	Flow (L/min)	Cardiac Output (%)	Flow (L/min)	Cardiac Output (%)
Leg muscle	0.5	9	3.9	36
Heart	0.25	4	0.35	3
Skin	0.5	9	1.5	14
Brain	0.75	13	0.75	7
Splanchnic	1.4	24	1.1	10
Kidneys	1.1	19	0.9	8
Inactive muscle	0.7	12	0.6	6
Lungs	5.8		10.8	

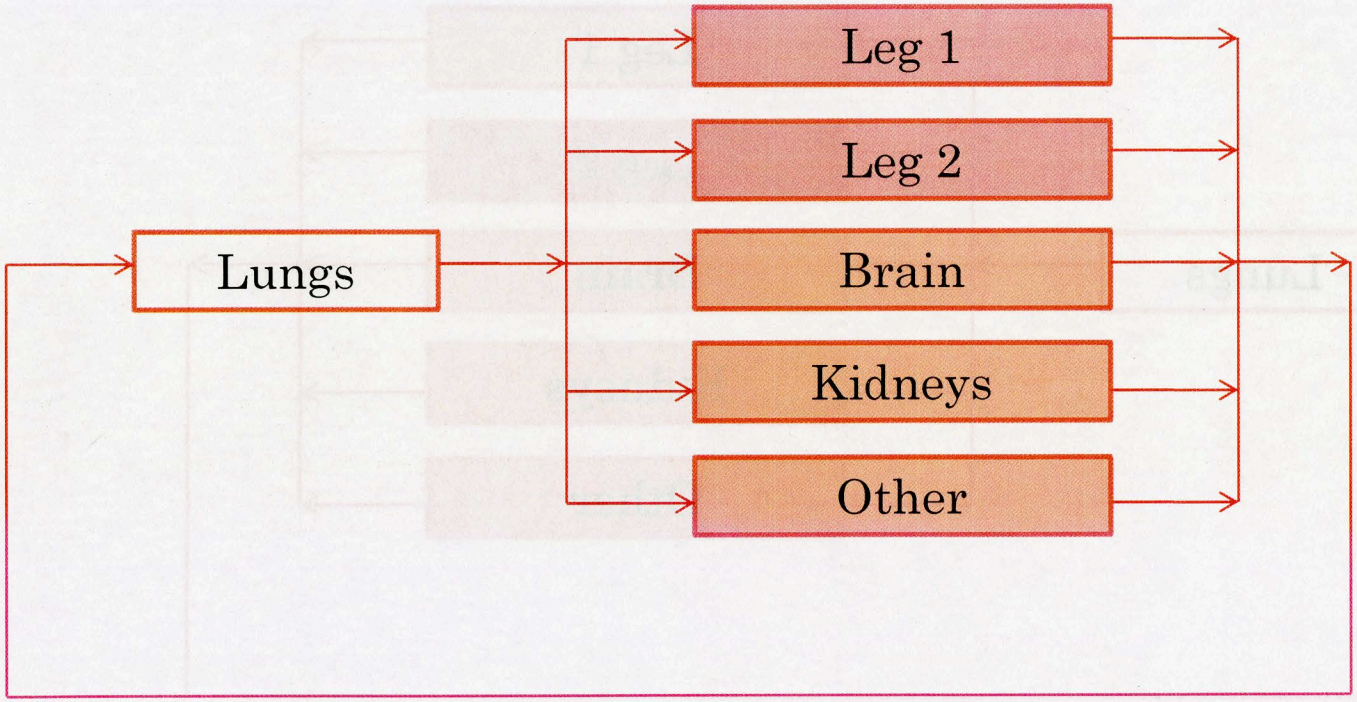
Methods
Rest



Methods
One-Leg



Methods
Two-Leg



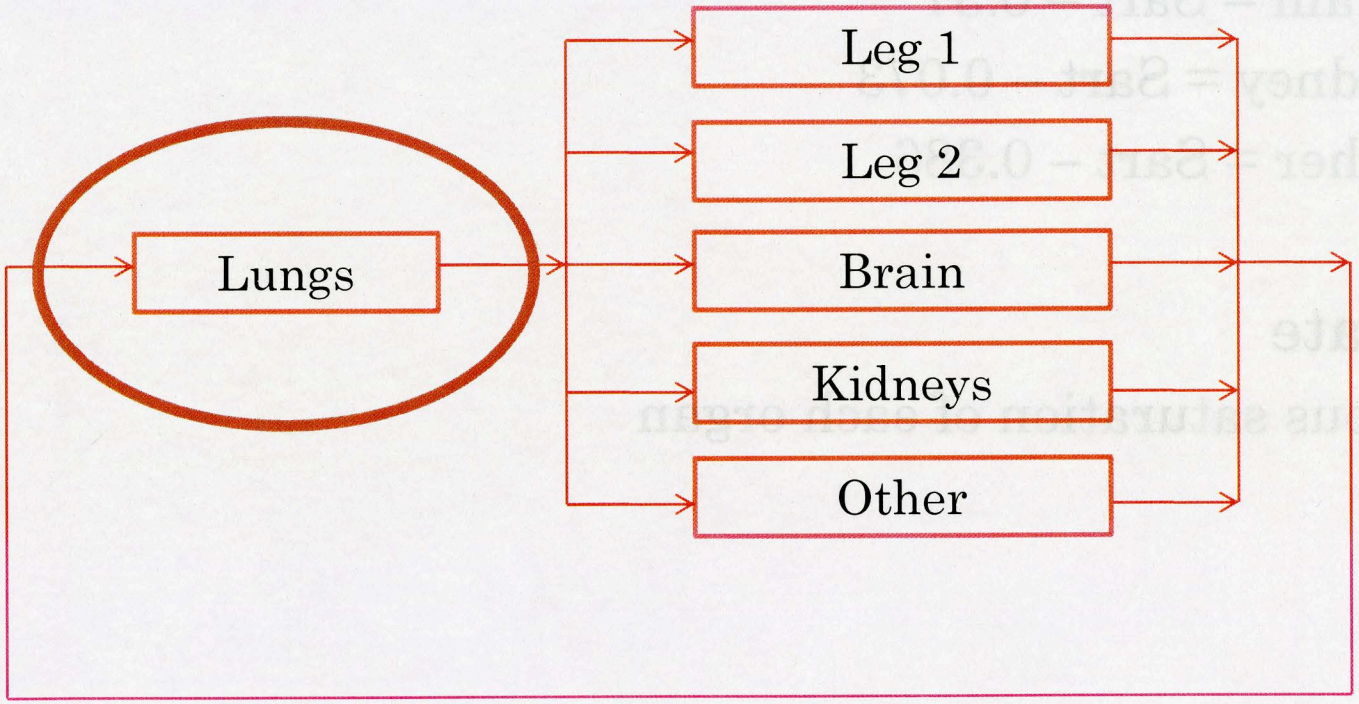
Methods
Systemic

- Sv = Sart – oxygen extraction
  - Svbrain = Sart – 0.37
  - Svkidney = Sart – 0.073
  - Svother = Sart – 0.386

- Calculate
  - Venous saturation of each organ

METHODS

Basic Model

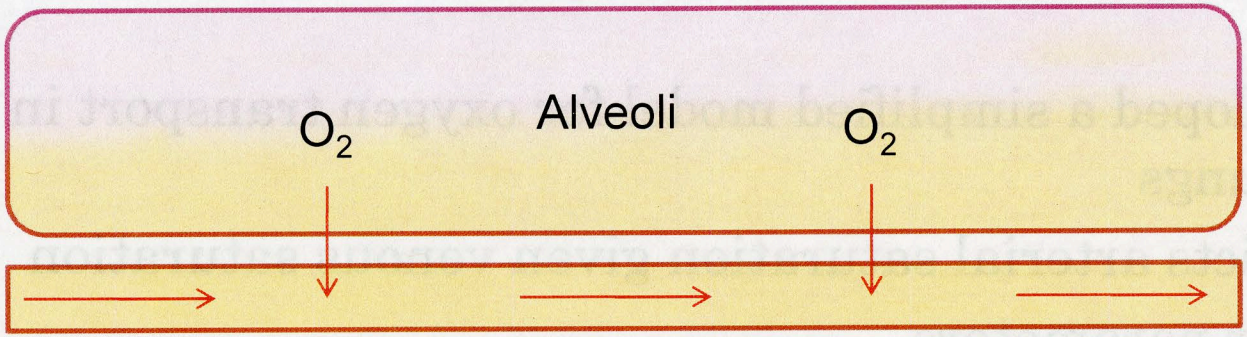


Methods
Systemic

- Lungs
  - Developed a simplified model for oxygen transport in the lungs
  - Predicts arterial saturation given venous saturation
  - Major parameters
    - k – diffusive capacity of lungs
    - Q – flow rate

Kavanagh 2003

Methods
Systemic



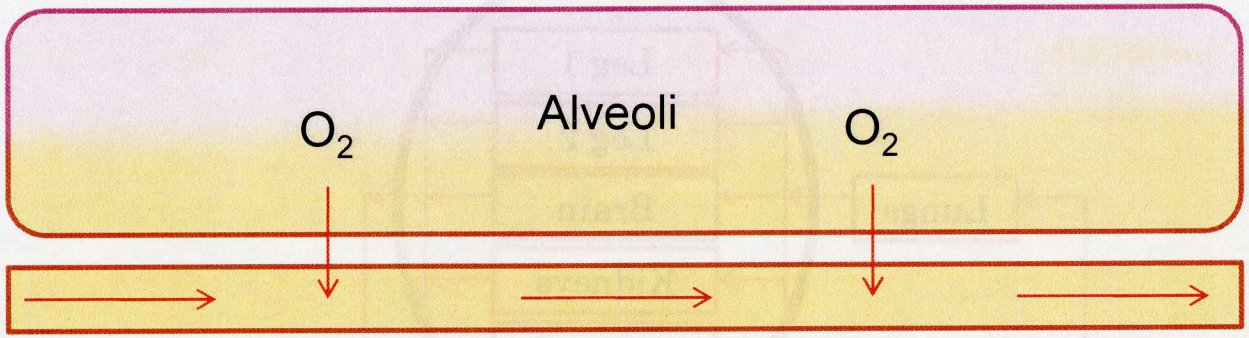
$$Q\,\frac{dC(P)}{dt} = k\,(P_{alv} - P)$$

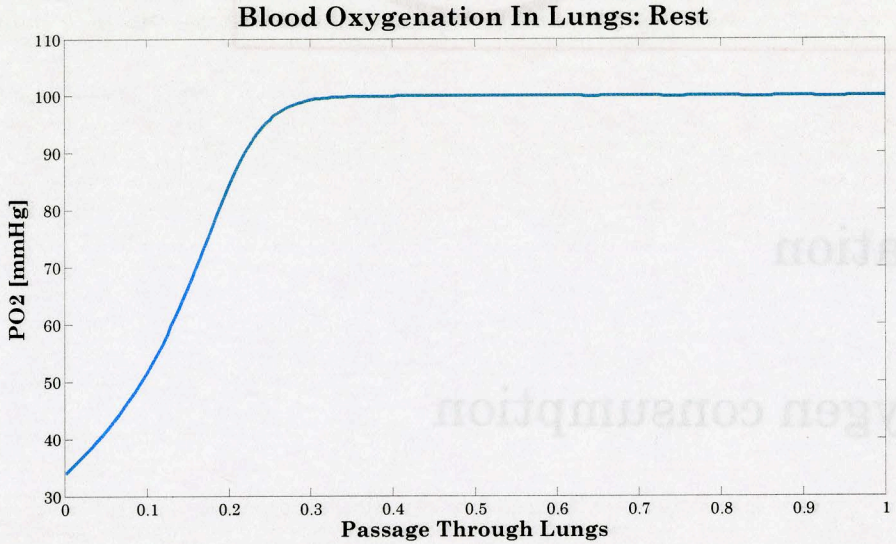
$$\frac{dC(P)}{dt} = \frac{k}{Q}\,(P_{alv} - P)$$

$$C(P) = C_O\,S(P)$$

$$S(P) = \frac{P^n}{P^n + P_{50}^n}$$

Methods
Systemic





Methods
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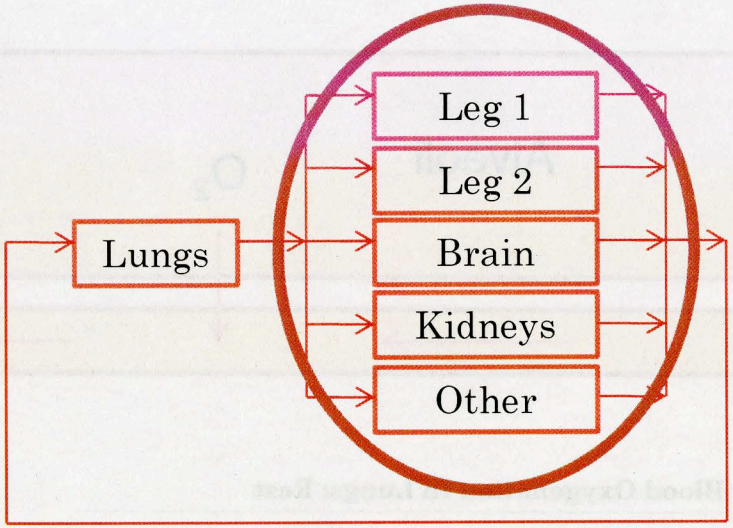


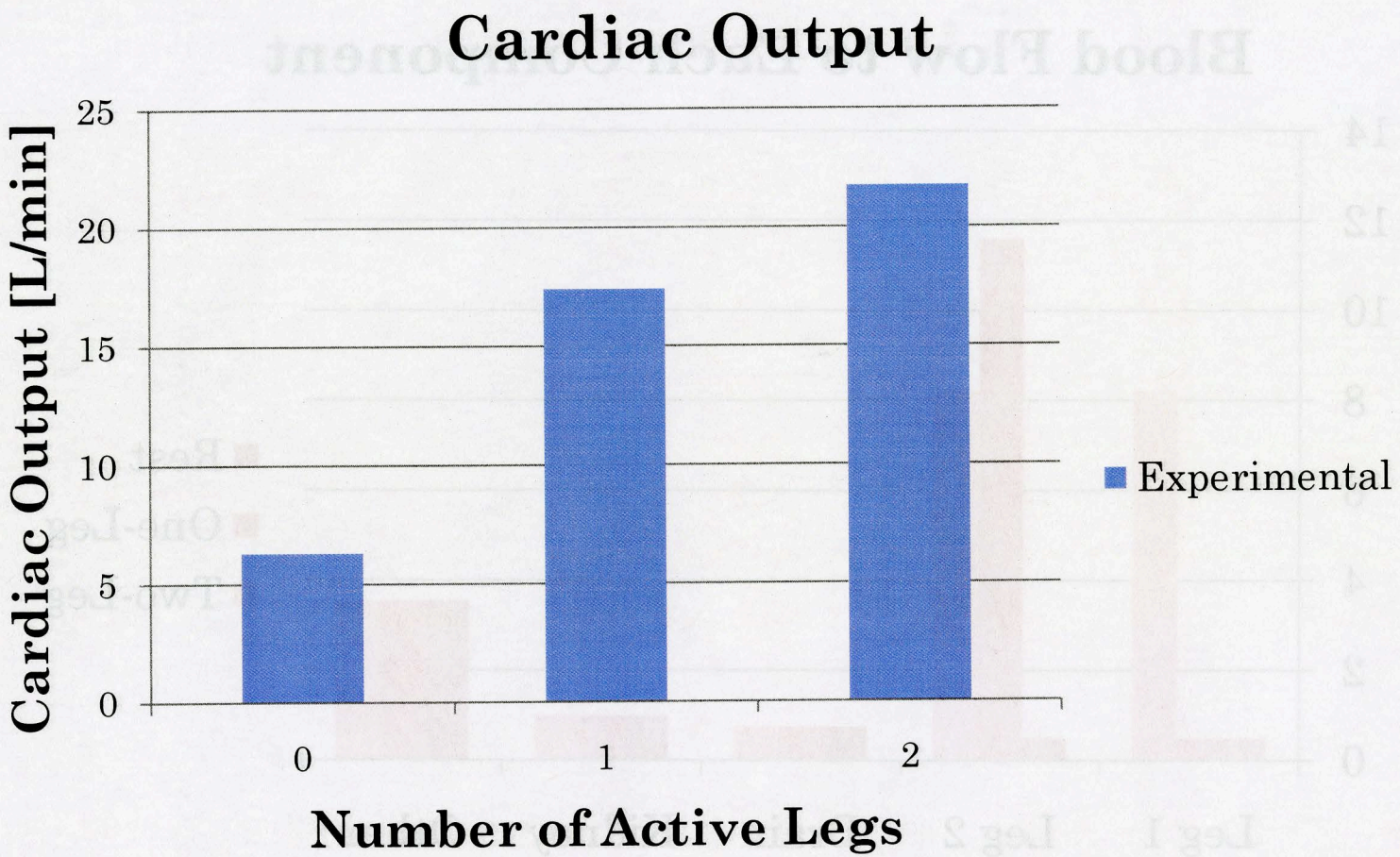
- Calculate
  - Venous saturation
  - Venous P_{O_2}
  - Total body oxygen consumption

Methods
Parameters

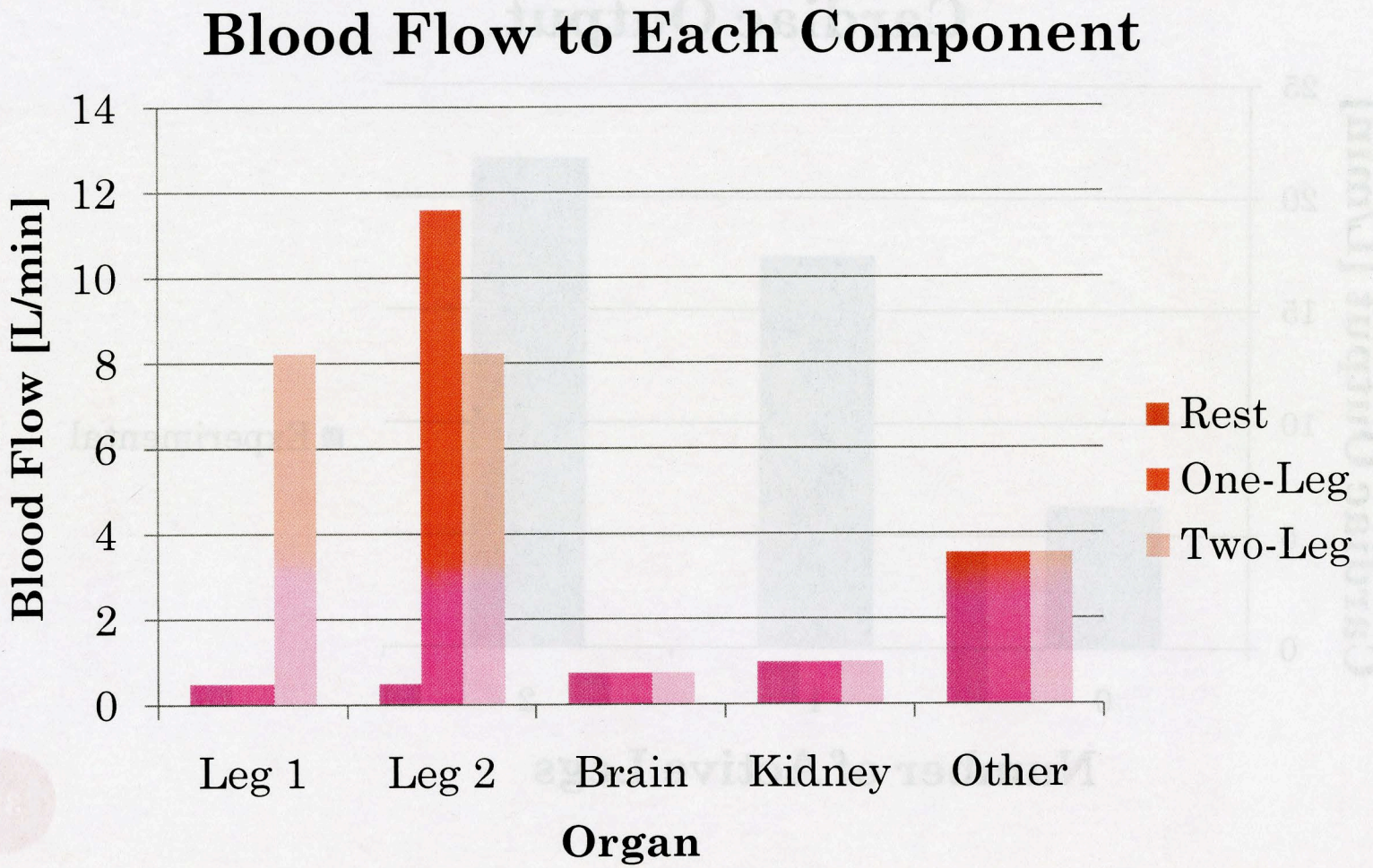
- Demand (g)
- Lung diffusive capacity (k)

RESULTS

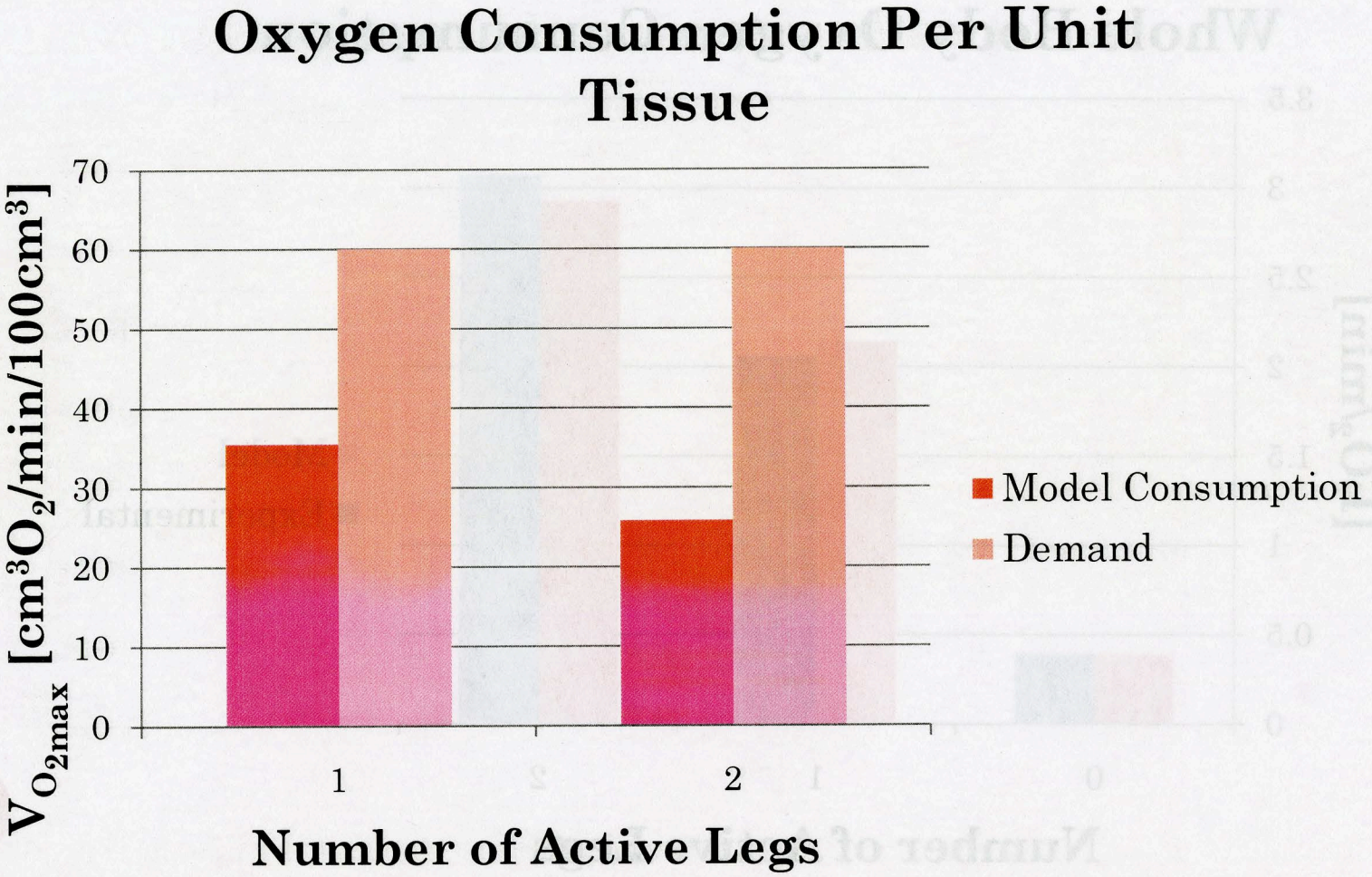
Results
Systemic



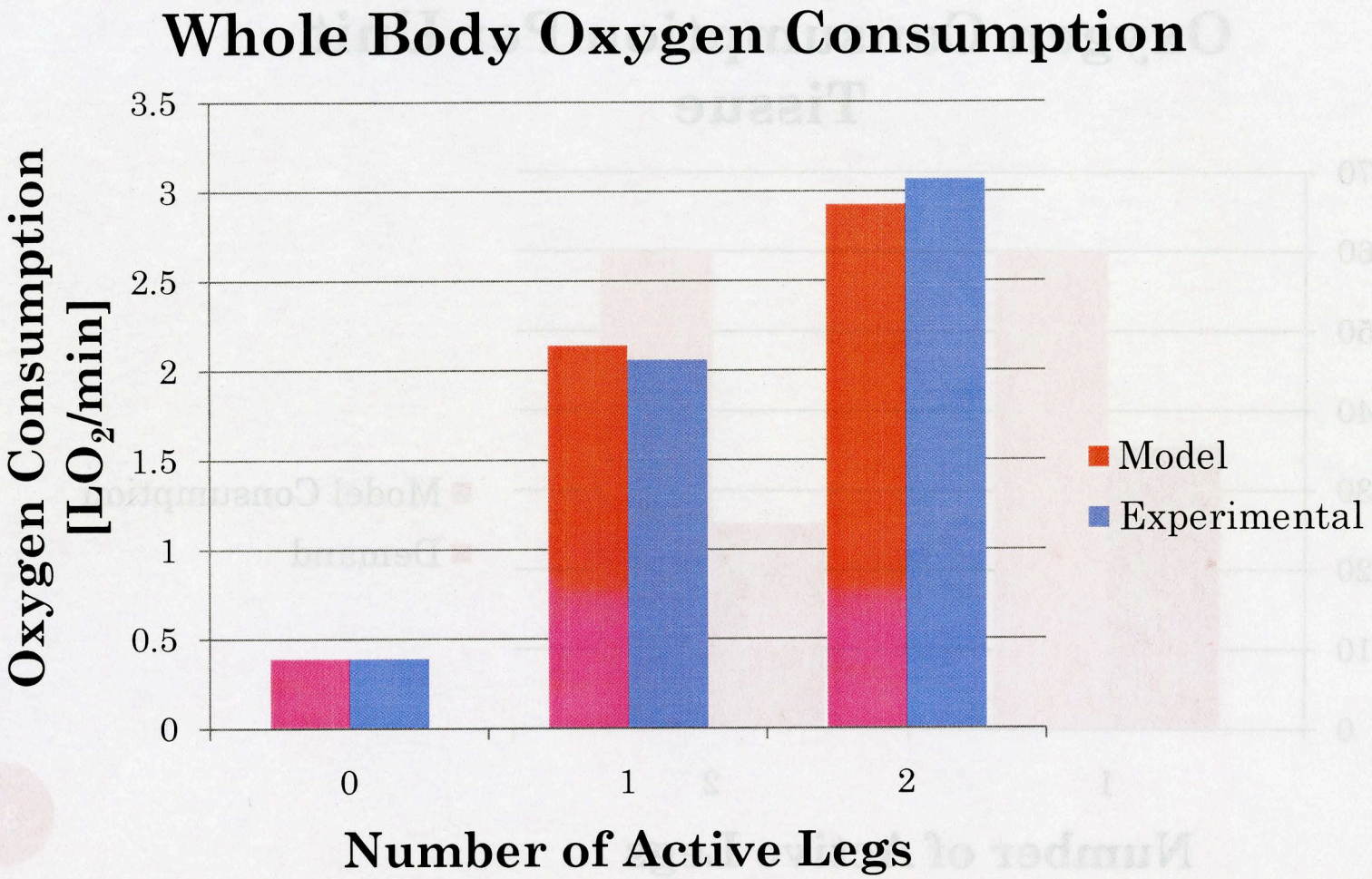
Results
Systemic



Results
Capillary Level



Results
Systemic



Results
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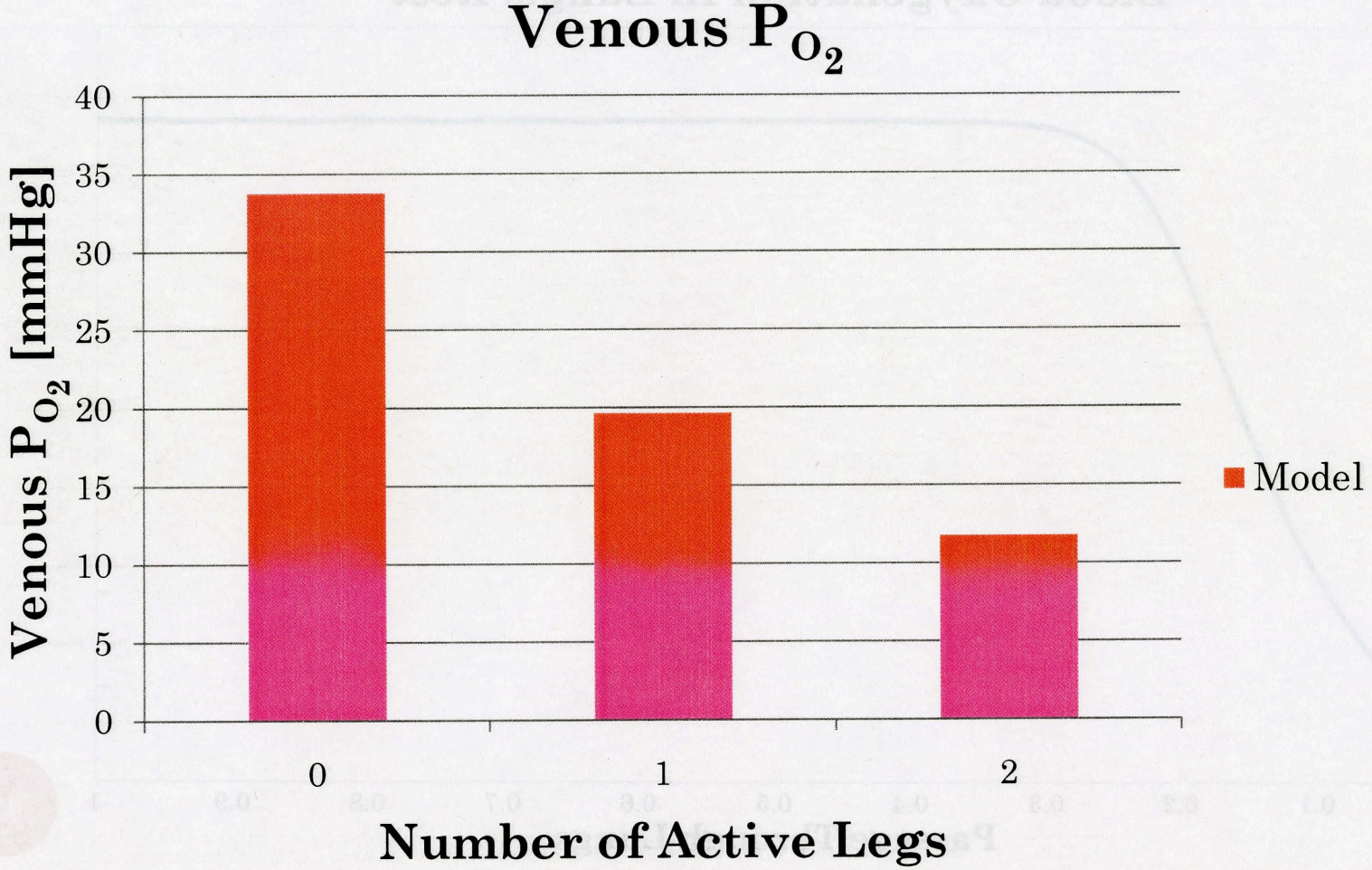

Results
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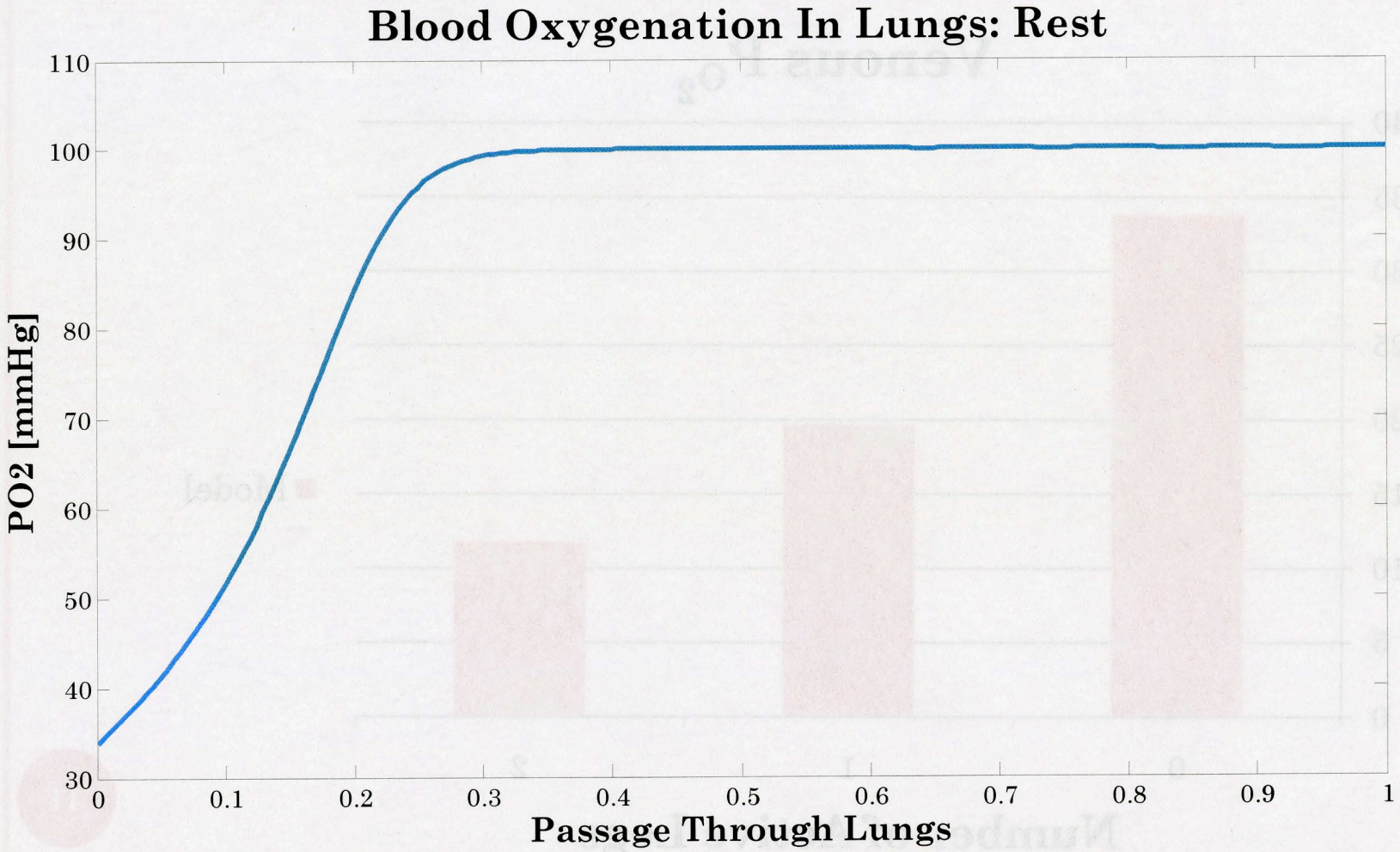

Results
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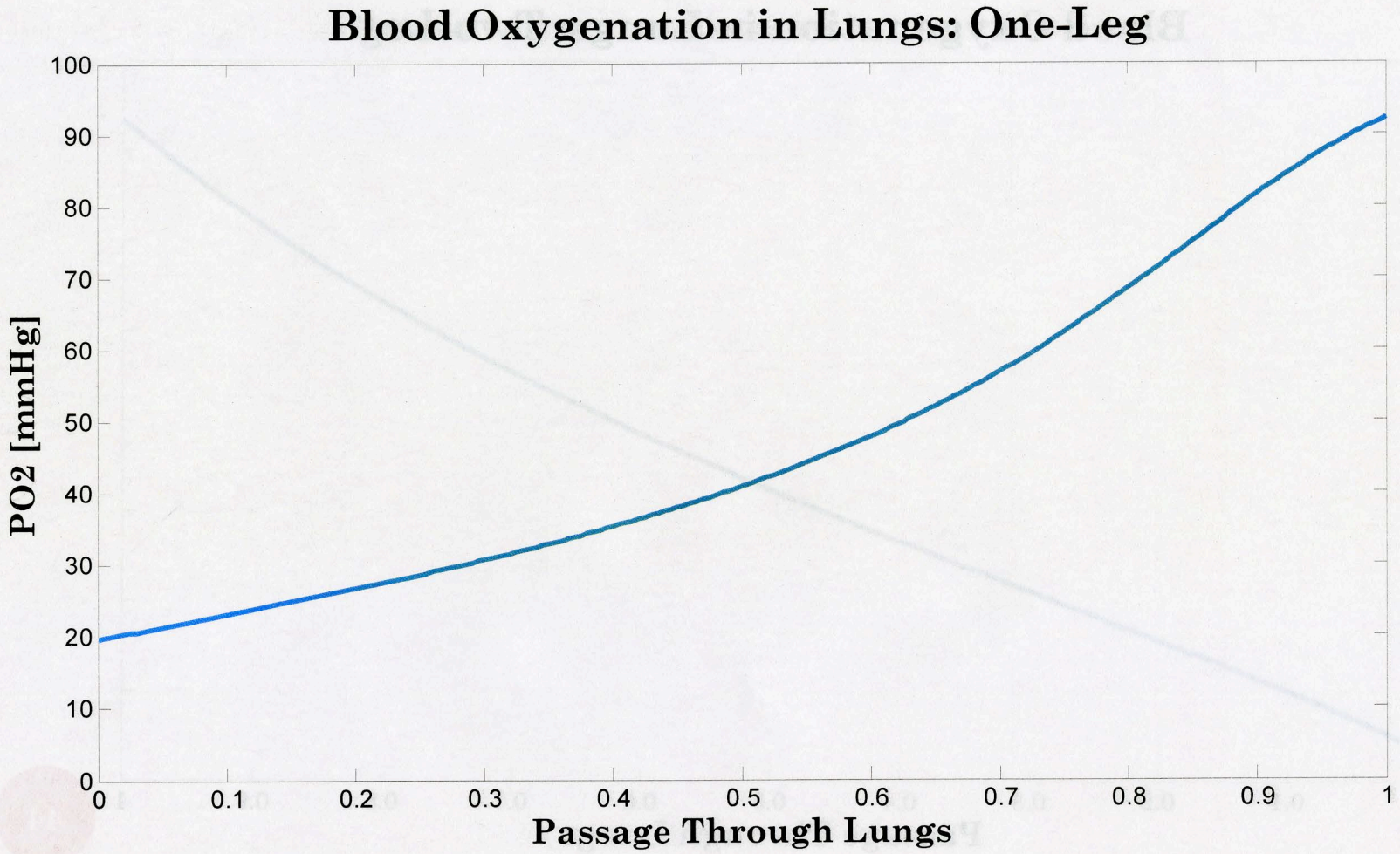

Results
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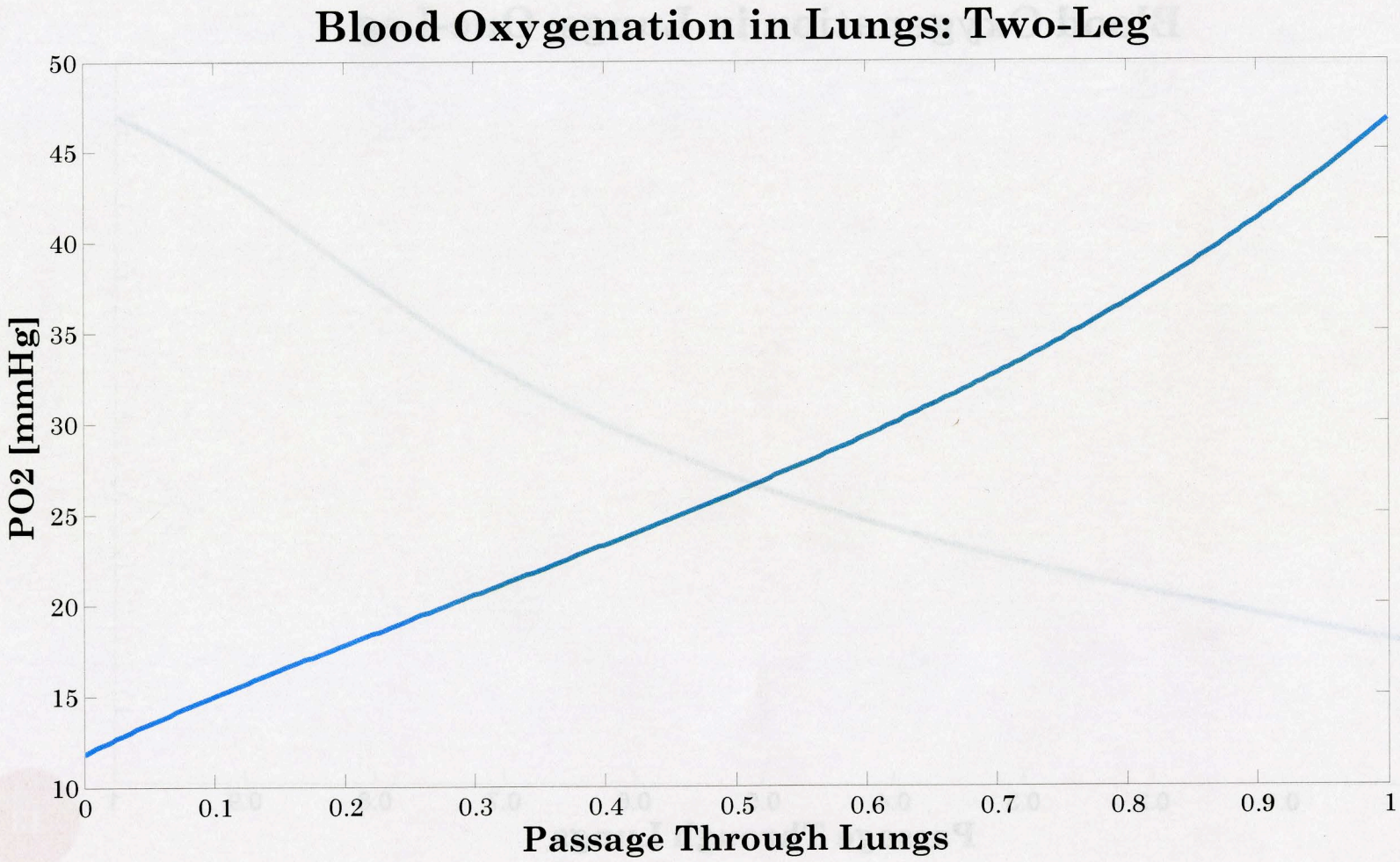

Results
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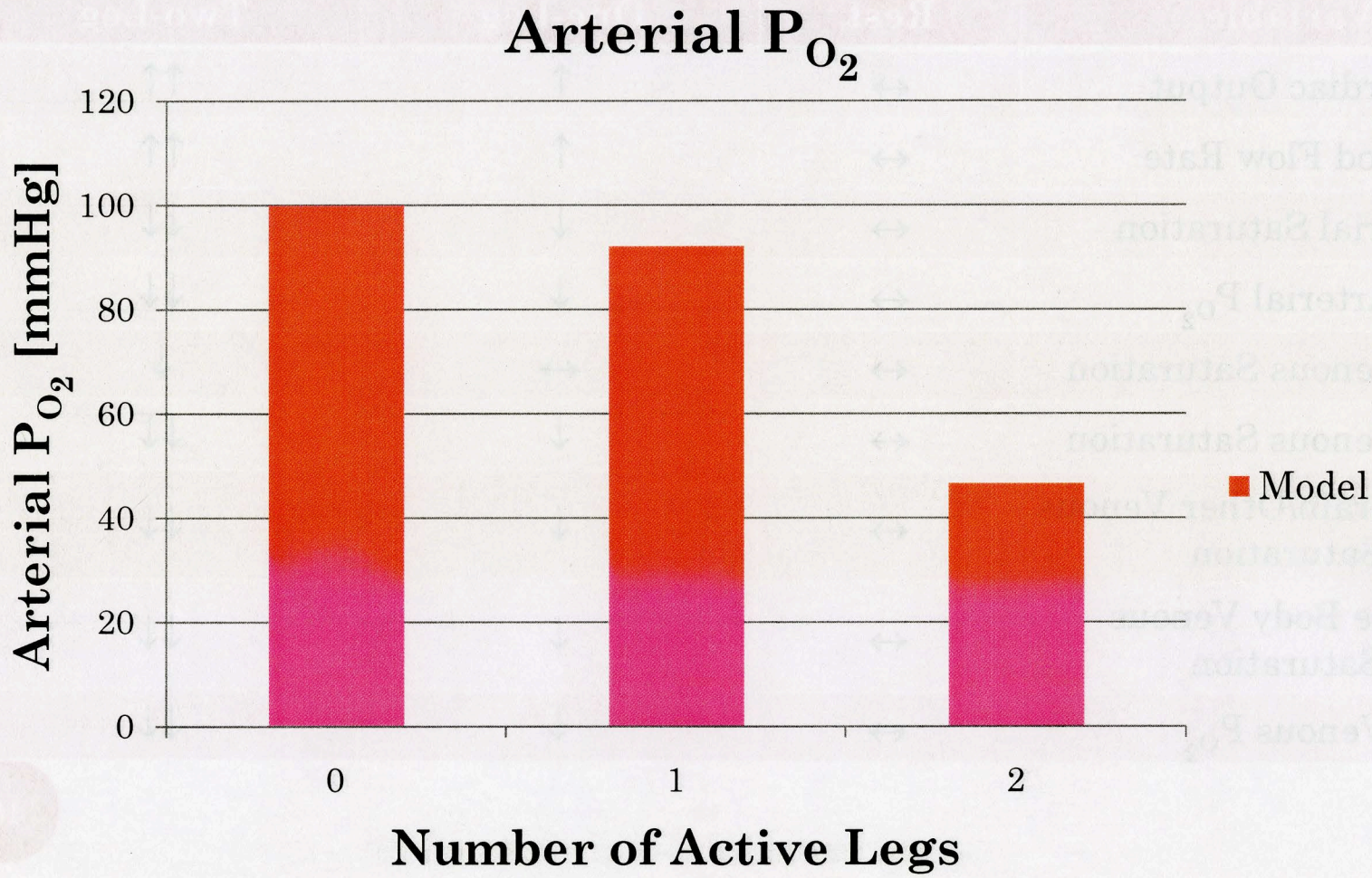

Results Summary

Variable	Rest	One-Leg	Two-Leg
Cardiac Output	↔	↑	↑↑
Blood Flow Rate	↔	↑	↑↑
Arterial Saturation	↔	↓	↓↓
Arterial P_{O_2}	↔	↓	↓↓
Leg 1 Venous Saturation	↔	↔	↓
Leg 2 Venous Saturation	↔	↓	↓↓
Kidney/Brain/Other Venous Saturation	↔	↓	↓↓
Whole Body Venous Saturation	↔	↓	↓↓
Venous P_{O_2}	↔	↓	↓↓

Conclusion

Conclusion

- What are the limitations on oxygen consumption at the systemic and capillary levels?

Conclusion
Systemic

Increased activity means....

- Greater cardiac output
- Higher blood flow rate
- Less blood-tissue contact time
- Decreased arterial oxygen saturation
- Reduced blood oxygen content
- Reduced oxygen delivery to tissue

Conclusion
Capillary Level

In two-leg exercise…

- Decreased blood flow to each leg
- Reduced oxygen delivery to tissue
- Combined effect: increased hypoxia
- Reduced consumption rate per unit tissue

Future Directions

- Different oxygen environments
  - What happens to this model under hypoxic conditions?

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