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Corey Riley
Winthrop University

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Corey Riley[a]

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Rose-Hulman Institute of Technology
Department of Mathematics
Terre Haute, IN 47803
mathjournal@rose-hulman.edu
scholar.rose-hulman.edu/rhumj

[a]Winthrop University

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A MATHEMATICAL MODEL OF CARDIOVASCULAR AND RESPIRATORY DYNAMICS IN HUMANS WITH TRANSPOSITION OF THE GREAT ARTERIES

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Abstract. Transposition of the Great Arteries (TGA) is a congenital heart defect in humans in which the pulmonary artery and the aorta are transposed, causing oxygen-poor blood to bypass the lungs and be recirculated throughout the body. In many cases, an atrial and/or ventricular septal defect also forms to allow the oxygen-rich and oxygen-poor blood to mix in the heart, temporarily sustaining the patient's life. In this paper, we create a model of cardiovascular and respiratory dynamics for a human patient with TGA by extending a current model of normal heart function. The goal of this research is to predict blood-oxygen levels in critical organs such as the brain for patients with TGA and one or more septal defects. While we know a patient cannot survive long-term with TGA, an accurate prediction of blood-oxygen levels under a variety of defects and mixing circumstances can potentially help to establish optimal times for performing corrective surgery.

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1 Introduction

Congenital heart defects are conditions present from birth that affect the structure and function of a human baby's heart. Transposition of the Great Arteries (TGA) is one such defect in which the pulmonary artery and the aorta are transposed, causing oxygen-poor blood to recirculate throughout the body without receiving new oxygen from the lungs. According to the Centers for Disease Control and Prevention (CDC), TGA affects about 5 of every 10,000 babies born in the United States each year [2]. Since there is no way to prevent TGA (due to the cause of TGA being unknown), current research must aim to find the most efficient and effective way to correct the defects associated with TGA. Our hope is that this research could assist medical professionals in deciding on the optimal time to perform surgery to correct TGA.

In order to gain a better understanding of TGA's effect on a human patient, we aim to create a mathematical model of a human patient with TGA and compare findings from our model to findings from an existing model of a healthy patient. We build upon research done by Ellwein et. al. [3], utilizing a compartmental model of a cardiovascular and respiratory system in a normal patient. To display TGA in our model's patient, we will make necessary changes to the circulation pathway of blood in the system. We believe this will directly affect oxygen levels in the systemic and brain tissue compartments, demonstrating how TGA is fatal if left untreated.

Before understanding the model we used, it is first important to review basic anatomy of the human circulatory and respiratory systems. The human heart makes up just part of a larger circulatory system. In the heart, there are four chambers: the left ventricle, the right ventricle, the left atrium, and the right atrium. In a normal human circulatory system, oxygen-poor blood is pumped from the right side of the heart to the lungs through the pulmonary artery, where it is oxygenated. Then, the oxygen-rich blood returns to the left side of the heart and is pumped through the aorta and out to the body (including the brain and other organs). As the oxygen-rich blood travels through the body, the oxygen in the blood metabolizes and carbon dioxide is produced as a result of aerobic respiration. Finally, the now oxygen-poor blood returns to the right side of the heart to repeat the process. (see Figure 1). This process allows oxygen to diffuse throughout the body, which is necessary to sustain life.

The organization of the paper is as follows. In Section 2, we provide an overview of TGA as a medical condition. In Section 3, the model from Ellwein et. al. [3] is introduced, with the cardiovascular system described in Section 3.1 and the respiratory system described in Section 3.2. In Section 4, we modify this model to describe a human patient with TGA, both with and without a septal defect. In Section 5, we provide numerical simulations of the model under both normal and TGA conditions. Section 6 provides a discussion of our results, and Section 7 concludes with suggestions for future research on TGA in humans.

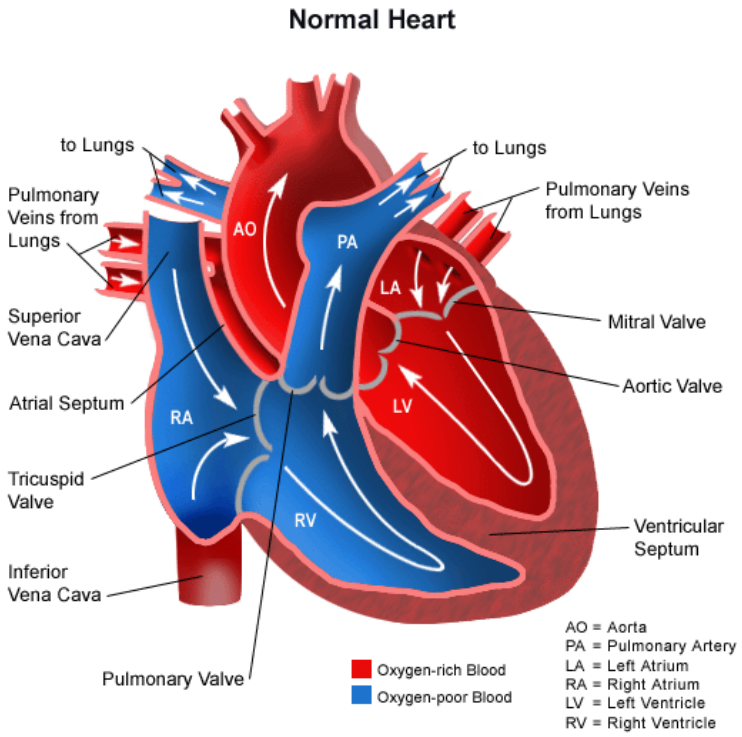

Figure 1: Normal heart structure [5].

2 Transposition of the Great Arteries

Transposition of the great arteries occurs when the pulmonary artery and the aorta are transposed. As a result of this transposition, the oxygen-rich blood that comes from the lungs to the left side of the heart is immediately circulated back to the lungs. Similarly, the oxygen-poor blood from the body returns to the right side of the heart, bypassing the lungs before being recirculated throughout the rest of the body. Thus, there are two circulatory paths instead of one as in Figure 2.

Symptoms for TGA include skin blueness, shortness of breath, and trouble feeding. The cause of TGA is unknown, but research has found some risk factors that may be associated with TGA, including the mother having a viral illness during pregnancy, the mother being older than 40, drinking alcohol excessively during pregnancy, the mother having poor nutrition, and others [2]. However, these aren't the only causes of TGA, and many cases occur without known cause.

Because oxygenated blood is not circulating throughout the body in a person with TGA, one cannot live without the defect being corrected. Essentially, TGA is fatal in the first 6 months of life [2]. In order for a fetus to come to full term during pregnancy, an arterial or septal defect (a hole) usually forms in the heart, allowing some of the oxygen-rich blood to mix with some of the oxygen-poor blood. This allows the fetus's brain to receive marginal

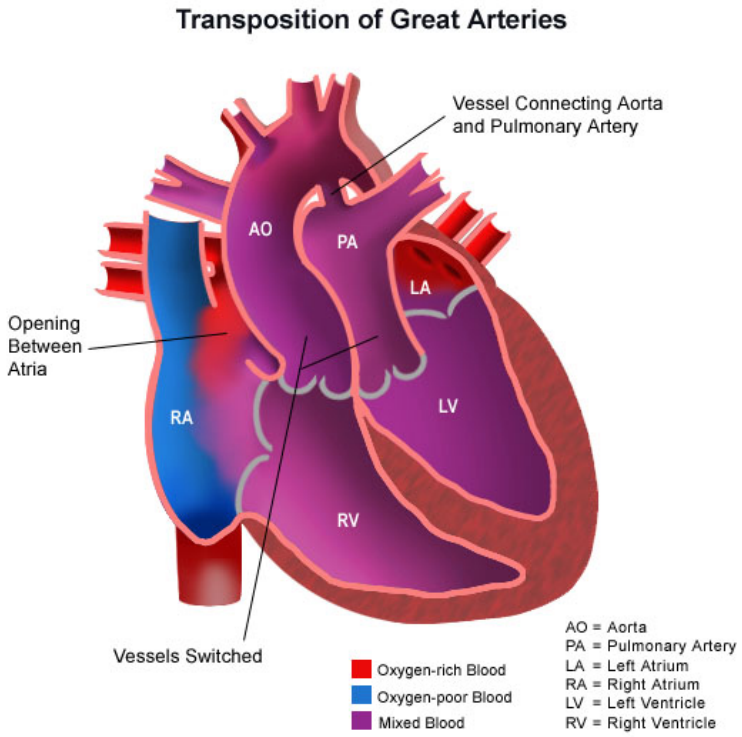

Figure 2: TGA heart structure [5].

amount of oxygen [5].

3 The Ellwein Model

Our model is adapted from a coupled cardiovascular and respiratory compartmental model from Ellwein et. al. [3] that measures blood pressure in different compartments of the circulatory system and gas concentration levels in the respiratory system. In their paper, Ellwein et. al. [3] use this coupled model and patient-specific data to predict cardiovascular and respiratory responses to hypercapnia in a patient with congestive heart failure. In the following two subsections, both the cardiovascular system and the respiratory system from this model are described. We refer the interested reader to the original Ellwein et. al. [3] model for a more detailed description.

In Figure 3, we have included a diagram of Ellwein's compartmental model. In this figure, L represents the lungs, B represents the brain tissue and components, and S represents the systemic tissue and components. v represents a collection of veins in the specified compartment, and a represents a collection of arteries in the specified compartment. For example, Ba would represent arteries in the brain, while Sv would represent systemic veins. lv and rv represent the left and right ventricles respectively. Pa and Pv represent pulmonary arteries and pulmonary veins respectively. $D1, D2$, and $D3$ represent dead-space volumes

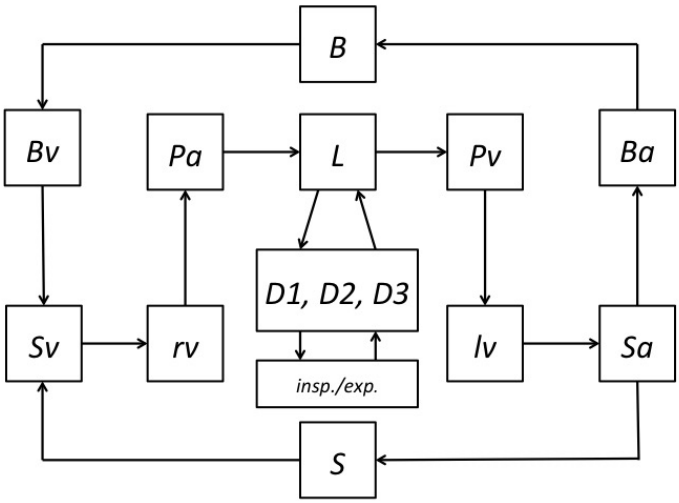

Figure 3: Ellwein's model for a normal patient.

(that is, regions where no gas exchange occurs) in the lungs. Inspiration and expiration is represented in the *insp./exp.* compartment. Lastly, arrows indicate the direction blood is moving through the system.

Since the model includes measurements of oxygen concentrations in both the body and brain tissues, we can compare a normal patient from the original model to an adapted model of a patient with TGA. By doing this, we can see how TGA affects blood oxygen concentration in the brain and systemic tissues.

3.1 Cardiovascular System

The cardiovascular system in this model is made up of eight compartments in a closed circuit: 3 arterial compartments, 3 venous compartments, and 2 ventricular compartments. The 6 arterial and venous compartments represent vessels in the brain and body, along with pulmonary arteries and veins. Flows between compartments are modeled using a volumetric flow rate $q(t)$ along with a constant resistance R [3].

An equation for partial pressure in a compartment of the form:

$$\frac{dp_i(t)}{dt} = \frac{q_{in}(t) - q_{out}(t)}{C_i} \tag{1}$$

is given to represent each compartment i, where the flow rates in and out of the compartment are given by:

$$q_{in} = \frac{p_{i-1}(t) - p_i(t)}{R_{in}}, \qquad q_{out} = \frac{p_i(t) - p_{i+1}(t)}{R_{out}},$$

and C_i is a compliance constant for that compartment. In both q_{in} and q_{out}, R is a constant

resistance for both the inflow and outflow of the corresponding compartment. It is also helpful to note that $i+1$ and $i-1$ denote compartments upstream and downstream in the circuit, respectively.

Equation 1 above holds for each compartment outside of the heart. Following Ellwein's approach, we divide the heart itself into two compartments (the left and right ventricles), and measure the blood volume in each using:

$$\frac{dV_{iv}(t)}{dt} = q_{in} - q_{out}, \qquad i = l, r, \tag{2}$$

with l and r denoting left and right ventricles respectively. The system of differential equations has 6 equations that measure change in partial pressure in different compartments and 2 equations that measure change in ventricular volumes over time for both the left and right ventricles. In order to calculate the pressure in each ventricle, Ellwein et. al. [3] give:

$$p_{iv}(t) = E_{iv}(t)[V_{iv}(t) - V_{id}], \qquad i = l, r, \tag{3}$$

again with l and r denoting left and right ventricles respectively. Note that V_{id} represents the volume at zero end-systolic pressure and $E_{iv}(t)$ is time-varying elastance (i.e. stiffness of the chamber wall). Ellwein et. al. [3] model time-varying elastance with a piecewise sinusoidal function:

$$E(t) = \begin{cases} (E_S - E_D)[1 - \cos(\frac{\pi t}{T_M})]/2 + E_D & 0 \le t \le T_M \\ (E_S - E_D)[\cos(\frac{\pi(t-T_M)}{T_R}) + 1]/2 + E_D & T_M \le t \le T_M + T_R \\ E_D & T_M + T_R \le t \le T, \end{cases} \tag{4}$$

with T_M and T_R denoting the time for end-systolic elastance (T_M) and the remaining time to relaxation (T_R).

Ellwein et. al. [3] state that the model includes four time-varying resistances, similar to previous studies. These resistances are defined by:

$$R_{valve}(t) = \min[R_{valve,o} + e^{-k(p_{in}(t) - p_{out}(t))}, R_{valve,c}], \qquad valve = mv, av, tv, pv, \tag{5}$$

where $R_{valve,o}$ is the resistance to flow out of the ventricle, k is the speed of the valve's transition from open to closed, and $R_{valve,c}$ is a value that is large enough to shut off flow through the valve. Note that mv is the mitral valve, av is the aortic valve, tv is the tricuspid valve, and pv is the pulmonary valve. Since the function $R_{valve}(t)$ is non-smooth, a smoothing function was used as in [3]. This smoothing function is defined as:

$$\min_\epsilon(x) = -\epsilon \log\left(\sum_i \exp(-x_i/\epsilon)\right)$$

where $\epsilon = 0.5$ denotes the degree of smoothness and x denotes the vector being minimized.

The input to the model is the period of one cardiac cycle (heartbeat) T. In the original model, T varies with each cardiac cycle based on a specific patient's data. In our model, since we lack patient-specific data, we shall use the mean heart rate $\overline{HR} = 62.5$ from the Ellwein et. al. model [3] to calculate an average period of $T = \frac{60}{\overline{HR}}$. Thus, $T = 0.96$ for our model.

3.2 Respiratory System

The respiratory model utilizes equations for both tissue (systemic and brain) and the lungs. Metabolism occurs in all tissue and organ compartments of this model. Ellwein et. al. [3] define metabolism as the consumption of oxygen and production of carbon dioxide. In total, the respiratory model contains compartments for the brain and systemic tissue and associated capillaries, an alveolar compartment within the lungs where gas exchange occurs, and three dead-space compartments as part of the lungs where no gas exchange occurs. The following two sections, Tissue Equations and Lung Equations, describe the separate parts of the respiratory system in this model.

Tissue Equations

In the tissue equations, various subscripts are used as follows. c denotes concentration of a gas. T denotes a generic tissue compartment that can either be systemic tissue (S) or brain tissue (B). Gas quantities (O_2 or CO_2) are represented by g and gas fractional amounts by F. Flows are denoted with v (venous) and a (arterial). Lastly, Ellwein et. al. [3] use the following: tissue regions $Ttis$ denoted as $Stis$ and $Btis$, and capillary compartments $Tcap$ denoted as $Scap$ and $Bcap$.

The quantity of gas (O_2 or CO_2) in a tissue region $A_{T,g}$ is defined as:

$$A_{T,g} = V_{T,g} c_{T,g}.$$

This equation describes the quantity as a product of the respective tissue volume V and concentration c of gas in that volume.

The change in the amount of gas in a tissue compartment depends on the amount of gas added or removed by diffusion with the capillary compartment and the amount of gas produced or consumed by metabolism M. The change in the amount of gas in a capillary compartment depends on the removal of gas by the bloodstream and gas removed or added through diffusion with the tissue compartment. Thus:

$$\frac{dA_{Ttis,g}}{dt} = \frac{dV_{Ttis,g}}{dt} c_{Ttis,g} + V_{Ttis,g} \frac{dc_{Ttis,g}}{dt} = M_{T,g} - D_{T,g}(c_{Ttis,g} - c_{Tcap,g}), \tag{6}$$

$$\frac{dA_{Tcap,g}}{dt} = \frac{dV_{Tcap,g}}{dt} c_{Tcap,g} + V_{Tcap,g} \frac{dc_{Tcap,g}}{dt} = q_{T,g}(c_{a,g} - c_{Tcap,g}) + D_{T,g}(c_{Ttis,g} - c_{Tcap,g}). \tag{7}$$

In Equations 6 and 7, $D_{T,g}$ denotes the diffusion capacity for a gas in a given tissue. $V_{Ttis,g}$ and $V_{Tcap,g}$ represent effective tissue volume for a gas and effective capillary blood volume

for a gas respectively. Also, $q_{T,g}$ is the volumetric blood flow rate through the capillary compartment and $c_{a,g}$ denotes arterial concentration in both systemic and brain arteries.

As in Ellwein et. al. [3], we assume that the effective tissue volume $V_{T,g}$ for a gas will be constant, i.e. $\frac{dV_{T,g}}{dt} = 0$. Equations 6 and 7 then become:

$$V_{Ttis,g}\frac{dc_{Ttis,g}}{dt} = M_{T,g} - D_{T,g}(c_{Ttis,g} - c_{Tcap,g}),$$

$$V_{Tcap,g}\frac{dc_{Tcap,g}}{dt} = q_{T,g}(c_{a,g} - c_{Tcap,g}) + D_{T,g}(c_{Ttis,g} - c_{Tcap,g}).$$

The gas concentration $c_{v,g}$ in the systemic venous return is defined as:

$$c_{v,g} = \frac{c_{Stis,g}q_S + c_{Btis,g}q_{Bv}}{q_S + q_{Bv}},$$

where $c_{S,g}$ and $c_{B,g}$ are systemic and cerebral concentrations of each gas exiting the capillary compartments.

Lung Equations

This model describes the lungs using five compartments: pulmonary capillaries, alveolar space, and three dead space compartments that represent the bronchial airways. The compartment representing alveolar space has a dynamic volume in which O_2 and CO_2 are exchanged between the lungs and pulmonary capillaries. The amount of alveolar gas is defined as:

$$V_{A,g} = V_A F_{A,g},$$

where A denotes the alveolar compartment, V_A denotes alveolar volume, and $F_{A,g}$ denotes gas fraction.

The bronchial airways are modeled with three dead space compartments that connect the alveolar space to the space outside of the body (allowing respiration to occur). These dead space compartments of equal volume are denoted $D1$, $D2$, and $D3$. The model states that $D1$ is the compartment located closest to the mouth, while $D3$ is the compartment located closest to the alveolar space. In this model, gas concentrations and partial pressures are predicted in all compartments. The mass balance equation for the alveolar compartment is expressed as:

$$\frac{dV_{A,g}}{dt} = F_{A,g}\frac{dV_A}{dt} + V_A\frac{dF_{A,g}}{dt} = \frac{dV_A}{dt}F_{i,g} + q_P(c_{v,g} - c_{a,g}). \tag{8}$$

Note that in the lung equations, $c_{v,g}$ and $c_{a,g}$ are used to denote pulmonary arterial and venous concentrations respectively. In Equation 8 above, subscript P denotes the pulmonary compartment and $F_{i,g}$ is the fraction of gas in the air that is either inspired or expired into the alveolar compartment: $i = D_3$ during inspiration and $i = A$ during expiration. With this condition in place, Equation 8 becomes:

$$\frac{dV_{A,g}}{dt} = \begin{cases} \frac{dV_A}{dt}(F_{D_3,g} - F_{A,g}) + q_P(c_{v,g} - c_{a,g}), & \text{inspiration} \\ q_P(c_{v,g} - c_{a,g}), & \text{expiration.} \end{cases}$$

By converting the gas fractions to partial pressures and accounting for other unit conversions, the final alveolar equations are given by:

$$V_A \frac{dp_{a,g}}{dt} = \begin{cases} \frac{dV_A}{dt}(p_{D_3,g} - p_{a,g}) + 0.98 \cdot 863 q_P (c_{v,g} - c_{a,g}), & \text{inspiration} \\ 0.98 \cdot 863 q_P (c_{v,g} - c_{a,g}), & \text{expiration.} \end{cases} \tag{9}$$

During inspiration and expiration, each of the three dead space compartment partial pressures are governed by differential equations as follows:

Inspiration:

$$V_{D_1} \frac{dp_{D_1,g}}{dt} = \frac{dV_A}{dt}(p_{I,g} - p_{D_1,g}), \tag{10}$$

$$V_{D_i} \frac{dp_{D_i,g}}{dt} = \frac{dV_A}{dt}(p_{D_{i-1},g} - p_{D_i,g}), \qquad i = 2, 3 \tag{11}$$

Expiration:

$$V_{D_i} \frac{dp_{D_i,g}}{dt} = \frac{dV_A}{dt}(p_{D_i,g} - p_{D_{i+1},g}), \qquad i = 1, 2 \tag{12}$$

$$V_{D_3} \frac{dp_{D_3,g}}{dt} = \frac{dV_A}{dt}(p_{D_3,g} - p_{a,g}). \tag{13}$$

In Equation 10, $p_{I,g}$ denotes partial pressure of the gas in inspired air.

It is also important to note the following additional aspects about the respiratory model. This model uses gas dissociation laws presented by Batzel et. al. [1] to convert alveolar gas pressures to blood gas concentrations. These dissociation laws are as follows:

$$c_{T,CO_2} = K_{CO_2} p_{T,CO_2} + k_{CO_2},$$
$$c_{T,O_2} = K_{O_2}(1 - e^{-k_{O_2} p_{T,O_2}})^2.$$

Furthermore, inputs for the respiratory model are heart rate, flows predicted by the cardiovascular model, and inspired volumetric airflow $\dot{V}_{IE}$ that Ellwein et. al. [3] measured in experimentation. The flows that are fed into this part of the model are average flow rates over time, which we calculated. It is important to know that $\dot{V}_{IE}$ is equivalent to the rate at which alveolar volume changes. Alveolar volume is defined as:

$$V_A = \int \dot{V}_{IE} dt.$$

As above, since we lack patient-specific data as in the Ellwein et. al. [3] model, we simulate V_A and $\dot{V}_{IE}$ based on estimated normal breathing patterns as follows:

$$V_A = \begin{cases} V_{min} + (V_{max} - V_{min}) \cdot [1 - \cos(\frac{\pi t}{T_I})]/2, & 0 \le t \le T_I \\ V_{min} + (V_{max} - V_{min}) \cdot [\cos(\frac{\pi (t - T_I)}{T_E}) + 1]/2, & T_I \le t \le T_I + T_E \\ V_{min}, & T_I + T_E \le t \le T, \end{cases} \tag{14}$$

$$\dot{V}_{IE} = \begin{cases} (V_{max} - V_{min}) \cdot [\sin(\frac{\pi t}{T_I}) \cdot \frac{\pi}{T_I}]/2, & 0 \le t \le T_I, \\ -(V_{max} - V_{min}) \cdot [\sin(\frac{\pi(t-T_I)}{T_E}) + 1] \cdot \frac{\pi}{T_E}/2, & T_I \le t \le T_I + T_E \\ 0, & T_I + T_E \le t \le T, \end{cases} \tag{15}$$

where T is the total time for inspiration and expiration, subscript I represents inspiration, subscript E represents expiration. Also, note that V_{min} denotes minimum alveolar air volume and V_{max} denotes maximum alveolar air volume. The total model for a normal heart is summarized below in Appendix B.

4 The TGA Model

We developed a model for a patient with TGA by changing the circulation path of the original Ellwein et. al. [3] model. Since the pulmonary artery and the aorta are transposed, blood now travels in two closed cycles: one throughout the body and the other throughout the lungs. We know intuitively that eventually all oxygen in the oxygen-poor body circuit will be consumed, causing the patient to die.

In order to sustain life, a septal defect usually forms between either the ventricles or atria of the heart. As previously mentioned, oxygen-poor blood will continuously circulate in the body without this defect. The defect allows oxygen-poor blood to mix with oxygen-rich blood so that some oxygen is able to diffuse throughout the body. We altered our model to display patients with and without defects, i.e. with and without mixing of oxygen-rich and oxygen-poor blood. Each patient (the healthy patient, the TGA patient without a septal defect, and the TGA patient with a septal defect) has an individual model simulation that we will compare. In the following two sections, our models for both patients with TGA are described. We describe the changes we made to the original model in order to create a model showing TGA both with and without a septal defect. To maintain simplicity as well as to adhere closely to the model we utilized, this research will only consider a septal defect forming between the left and right ventricles.

4.1 Without Mixing

Since TGA in itself is simply the transposition of the pulmonary artery and the aorta, we first model TGA with no septal defect. As described above, the patient will not survive unless a septal defect forms. In Figure 4, changes that we made to Figure 3 to reflect the new TGA system are shown.

With the aorta and pulmonary arteries transposed, blood now flows from the right ventricle through the aorta and out to the systemic arteries (to the body and brain). Blood returns to the right ventricle and repeats the process, never gaining oxygen in the lungs to provide to the body. Similarly, blood flows from the left ventricle to the lungs through the transposed pulmonary artery. The blood is then oxygenated and returns to the left ventricle, never passing through the body for the oxygen to be metabolized.

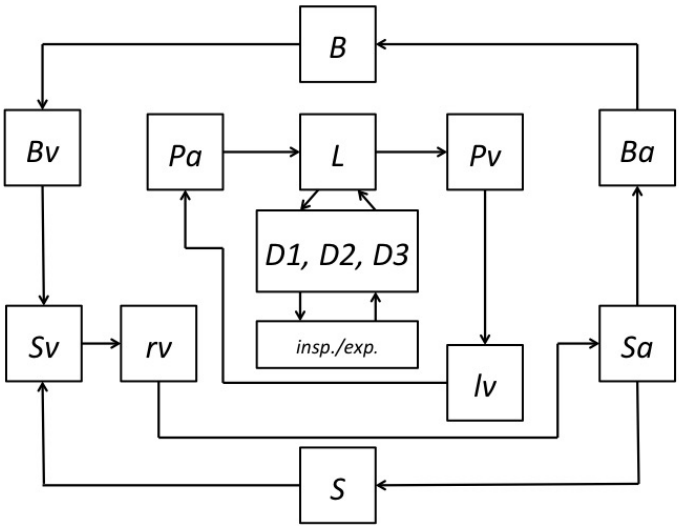

Figure 4: Ellwein's model under TGA.

Cardiovascular system. Appendix B.1 below describes the complete cardiovascular system for the normal model, and we now outline the changes made to derive the cardiovascular system for the TGA model with no mixing found in Appendix C.1. Specifically, we adjusted $\frac{dp_{Pa}}{dt}$, $\frac{dp_{Sa}}{dt}$, $\frac{dV_{lv}}{dt}$, and $\frac{dV_{rv}}{dt}$ to reflect the changes made in the path that blood flows through the system. In the Pa compartment, blood now flows in from lv instead of rv. Thus p_{lv} replaces p_{rv} in the $\frac{dp_{Pa}}{dt}$ equation. Since blood is flowing out of the lv compartment to the Pa compartment instead of the Sa compartment, p_{Sa} is replaced with p_{Pa} in $\frac{dV_{lv}}{dt}$. Similarly, blood now flows into the Sa compartment from rv. Thus p_{rv} replaces p_{lv} in $\frac{dp_{Sa}}{dt}$. Since blood is flowing out of rv to Sa, we let p_{Sa} replace p_{Pa} in $\frac{dV_{rv}}{dt}$.

Respiratory system. In a TGA system, since oxygen-rich blood circulates through the lungs and heart but bypasses the rest of the body whereas oxygen-poor blood circulates through the body and heart but bypasses the lungs, our model must be modified to show the lack of oxygenated blood in the body and excess of oxygenated blood in the lungs.

As above, the reader may similarly compare the changes to the respiratory systems for the normal model and TGA model with no mixing in Appendices B.2 and C.2. In the systemic tissue and brain tissue equations, we made changes to reflect the lack of oxygen entering the body and brain. The changes for $\frac{dc_{Ttis,g}}{dt}$ are different for each gas. In $\frac{dc_{Ttis,CO_2}}{dt}$, we now have:

$$\frac{dc_{Ttis,CO_2}}{dt} = (M_{T,CO_2}(c^I_{Ttis,CO_2} + c^I_{Ttis,O_2} - c_{Ttis,CO_2}) - D_{T,CO_2}(c_{Ttis,CO_2} - c_{Tcap,CO_2}))/V_{Ttis,CO_2},$$

where the I denotes the initial concentration of the gas in the tissue compartment. Originally, metabolism in the brain and systemic tissues was constant, causing carbon dioxide concentration to grow without bound. In the case of TGA, this concentration will be bounded

because there is not a continuous supply of oxygen flowing in. In $\frac{dc_{Ttis,O_2}}{dt}$, we now have:

$$\frac{dc_{Ttis,CO_2}}{dt} = (-M_{T,O_2} \cdot c_{Ttis,O_2} - D_{T,O_2}(c_{Ttis,O_2} - c_{Tcap,O_2}))/V_{Ttis,O_2}.$$

This change, similar to that of CO_2, causes oxygen concentration to remain bounded. For the $\frac{dc_{Tcap,g}}{dt}$ equations, $c_{a,g}$ is replaced with $c_{v,g}$. Since $c_{a,g}$ represents systemic arterial return, we can no longer utilize this value in the TGA system. With TGA, the blood in the systemic and brain tissue never passes through the lungs. This means that the concentration of the systemic venous return $c_{v,g}$ remains the same as it passes through the heart and returns back to the systemic and brain tissues.

In the inspiration and expiration equations, a change is made in $\frac{dp_{a,g}}{dt}$. In contrast to the change made in $\frac{dc_{Tcap,g}}{dt}$, $c_{v,g}$ is replaced with $c_{a,g}$. This is because the concentration of the systemic arterial return never leaves the lungs and heart circuit. Thus, the inspiration equations are defined as:

$$\frac{dp_{a,g}}{dt} = 863 \cdot 0.98 \cdot qp(c_{a,g} - c_{a,g}) + \dot{V}_{IE}(p_{D3,g} - p_{a,g})/V_A = 0 + \dot{V}_{IE}(p_{D3,g} - p_{a,g})/V_A,$$

and expiration equations are defined as:

$$\frac{dp_{a,g}}{dt} = 863 \cdot 0.98 \cdot qp(c_{a,g} - c_{a,g})/V_A = 0/V_A = 0.$$

4.2 With Mixing

In Figure 5, the previous TGA model is given. With this model, however, a septal defect is created. This defect is shown as a dashed line in Figure 5. The defect is a hole that forms between the left ventricle and the right ventricle. Oxygen-rich blood is able to mix with oxygen-poor blood through this hole in a bidirectional manner. In this section, the changes made to the TGA model to accommodate the septal defect are described below.

Cardiovascular system. The cardiovascular system in this model must be altered to account for the additional flow between the left and right ventricular compartments (see complete list of equations in Appendix D.1). In the ventricular volume equations, a new term is added to account for this flow. This term exhibits the flow between the rv and lv compartments with a small flow rate of $R_{sd} = 0.001$. This flow rate was chosen to align with the estimated resistances from Ellwein et. al. [3] for the other heart valves in an "open" state. These equations are now defined as:

$$\frac{dV_{lv}}{dt} = \frac{p_{Pv} - p_{lv}}{R_{mv}} - \frac{p_{lv} - p_{Pa}}{R_{av}} - \frac{p_{lv} - p_{rv}}{R_{sd}},$$

$$\frac{dV_{rv}}{dt} = \frac{p_{Sv} - p_{rv}}{R_{tv}} + \frac{p_{lv} - p_{rv}}{R_{sd}} - \frac{p_{rv} - p_{Sa}}{R_{pv}}.$$

Respiratory system. We present the equations for the respiratory model for TGA with a septal defect in Appendix D.2. Since a septal defect allows for mixing of oxygen-rich and

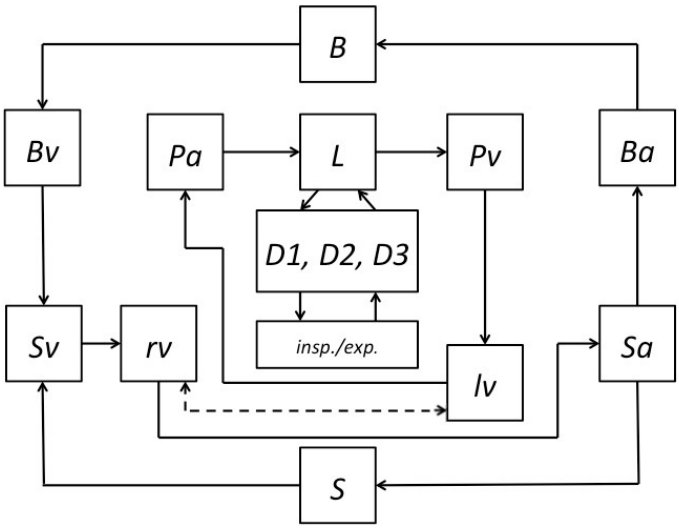

Figure 5: Ellwein's model under TGA with a septal defect.

oxygen-poor blood between the ventricles of the heart, neither $c_{a,g}$ nor $c_{v,g}$ will be used in the systemic and brain tissue equations. We define a new value $c_{mix,g}$ to model concentration of mixed blood that occurs due to the septal defect between the left and right ventricles as:

$$c_{mix,g} = \frac{c_{v,g} \cdot q_{sv} + c_{a,g} \cdot q_{lv}}{q_{sv} + q_{lv}}. \tag{16}$$

Equation 16 is simply an average of the concentration in each ventricle. This new value will replace $c_{v,g}$ in the $\frac{dc_{Tcap,g}}{dt}$ equations. The inspiration and expiration equations will remain the same as in the TGA model without a septal defect.

5 Simulations

Our model is simulated using Wolfram Mathematica 10 using parameter values found in Appendix A below. For each model, the system of equations is solved all at once and we produce plots of particular compartments of interest.

Using the model for a normal heart, we first compute the partial pressure in the systemic arteries p_{Sa} from the cardiovascular model and the partial pressure in the dead space compartment closest to the mouth p_{D1,CO_2} from the respiratory model. Simulations for each partial pressure are given in Figures 6 and 7, respectively. We note that each of these plots agree strongly with the results presented in the findings from Ellwein et. al. [3].

The most critical function in our model is the measure of oxygen concentration in the brain tissue c_{Btis,O_2}. The brain is an organ that must receive oxygen for the patient to remain alive. A plot of this function will show how TGA affects oxygen circulation throughout the body. We know that oxygen will deplete and eventually not be present anywhere in the body

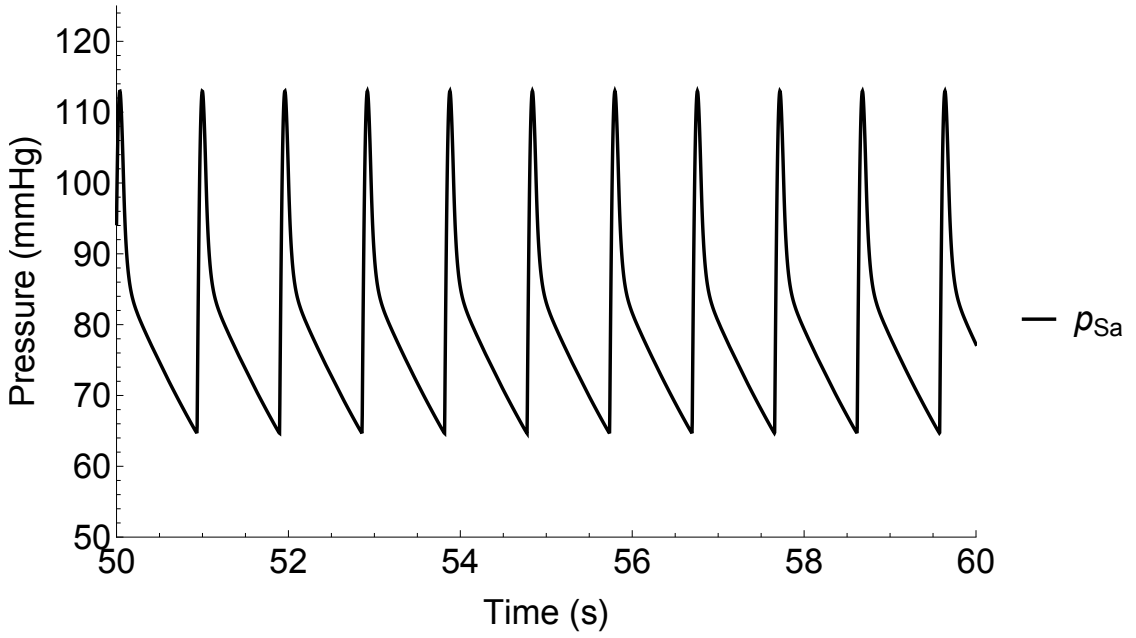

Figure 6: p_{Sa} for normal model.

in the system with TGA and no septal defect. We are particularly interested in the oxygen concentration in the brain when the septal defect forms. More importantly, we want to show how this concentration behaves as the flow through this septal defect changes.

In Figure 8, it is shown that the concentration of oxygen in the brain tissue of a healthy patient approaches approximately 0.15 ml_{STPD}/ml and then remains constant. Similarly, in the case of TGA with no septal defect, the concentration of oxygen in the brain approaches 0 ml_{STPD}/ml due to the fact that no oxygenated blood is leaving the lungs and heart. When the septal defect is formed in the TGA model, the concentration levels off at approximately 0.07 ml_{STPD}/ml over time.

6 Discussion

Our research shows that without a septal defect, the oxygen concentration in the brain of a patient with TGA will decrease to 0 over time. Since we want to explore how our research could be applied in assisting medical professionals in better deciding a treatment route for TGA, we wanted to examine what would happen to oxygen concentration in the brain as the septal defect changed size. We have the flow rate q_{lv} denoting the flow between the two ventricles of the heart. In our model, this value is set at 1.7 ml/s. We computed this value as the average flow rate over time. Intuitively, as this flow rate gets larger, the septal defect has become larger. As q_{lv} gets larger, the value of $c_{mix,g}$ approaches the value of $c_{a,g}$. Thus:

$$\lim_{q_{lv}\to\infty} c_{mix,g} = c_{a,g},$$

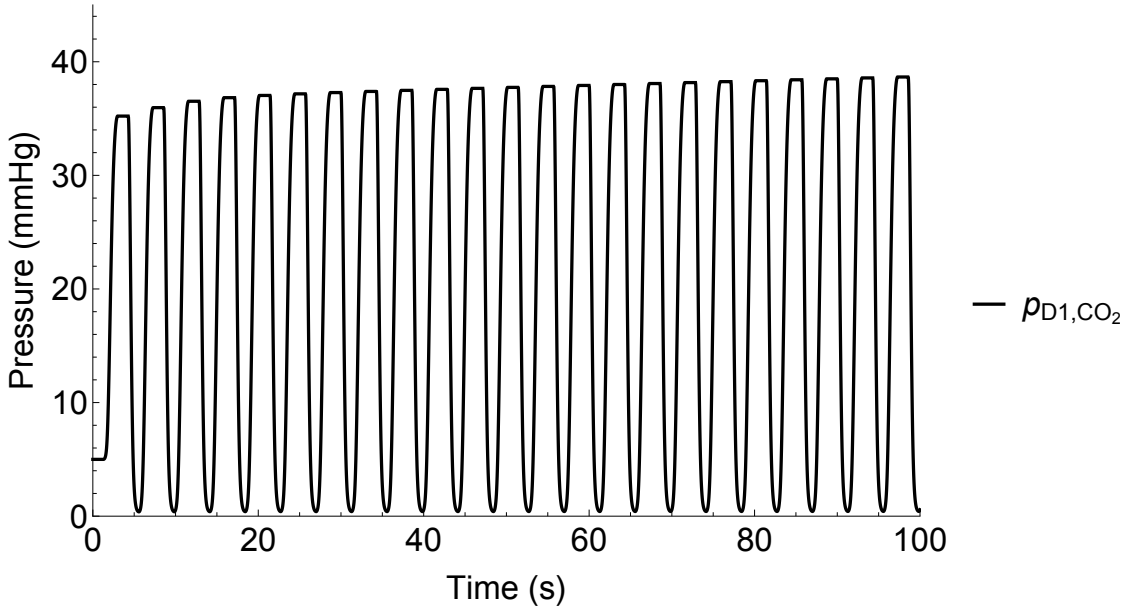

Figure 7: p_{D1,CO_2} for normal model.

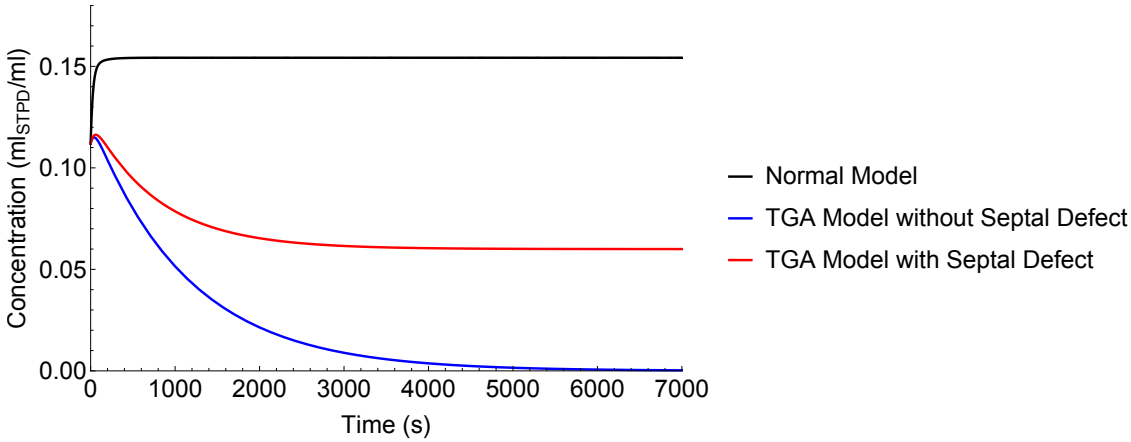

Figure 8: c_{Btis,O_2} compared in each model.

which can be justified in Figure 9. Figure 9 shows the concentration of oxygen in the brain c_{Btis,O_2} as the flow through the septal defect increases (as the size of the hole increases). Larger values of q_{lv} will thus allow more time before surgical intervention is required.

7 Future Research

In the future, our research could be extended to be more specific for an infant with TGA. The original model from Ellwein et. al. [3] is a patient-specific model where the patient is

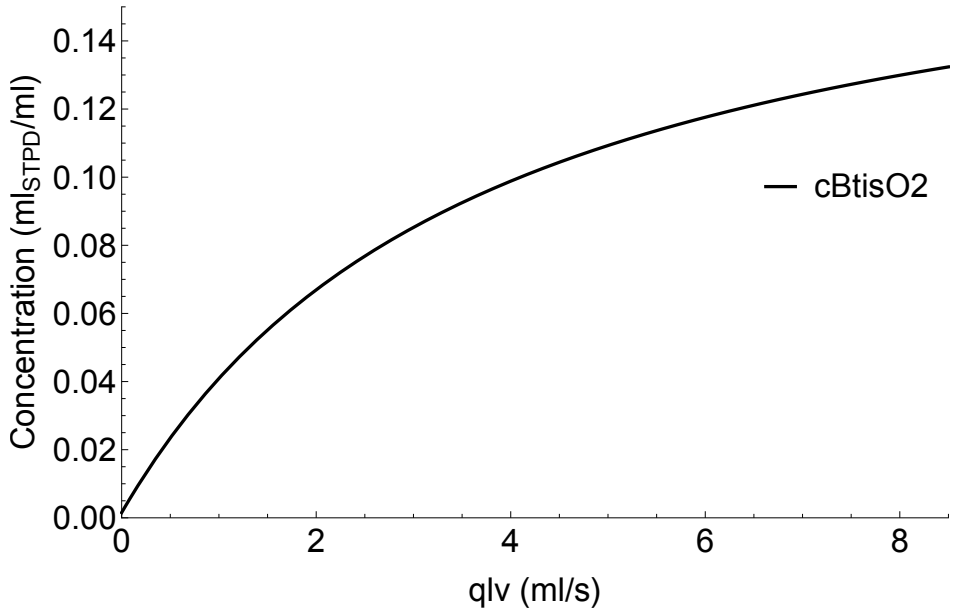

Figure 9: Change in blood oxygen concentration in the brain, c_{Btis,O_2} as q_{lv} changes.

178 centimeters tall and weighs 82 kilograms. All of the parameters in the current model are for that same adult patient. Since TGA must be corrected for an infant to survive in the long run, we know this adult patient may not be the most realistic representation of an actual patient with TGA. Our hope is that making the model more specific for an infant patient would give more accurate insight into TGA. Conducting a sensitivity analysis on the model would reveal which changes to parameters would lead to the largest differences in the model's predictions.

Also, since infants have TGA, we know that their bodies are constantly growing. Thus, their tissue volumes would be changing over time, instead of remaining constant as in our model. Our model holds tissue volumes constant (since an adult is no longer growing), but in a model that would be more representative of an infant, these volumes would need to be more dynamic.

Nevertheless, our model is able to capture the qualitative differences in brain oxygen concentration with three different patients: one healthy patient, one with non-mixing TGA, and one with mixing TGA. Our model recognizes that a patient with TGA and no mixing will not be able to survive long-term while a patient with TGA and mixing can sustain life at lower oxygen levels until corrective surgery can be performed. Furthermore, our model shows that as the flow rate through the septal defect increases (i.e. the defect gets larger to allow for more mixing), the concentration of oxygen in the blood that circulates throughout the brain approaches that of a normal system.

A Parameters

A.1 Cardiovascular Parameters

Parameter	Physiological Description	Value
W[kg]	Weight	82.3
H[cm]	Height	178
EF	Ejection fraction	0.26
SV[ml]	Stroke volume	81.1
ESV_l	End-systolic volume (left ventricle)	231
ESV_r	End-systolic volume (right ventricle)	18.9
$\overline{HR}$[bpm]	Mean heart rate	62.5
CO[l/min]	Cardiac output	5.07
$E_{D,l}$[mmHg/ml]	Left ventricular diastolic elastance	0.0135
$E_{D,r}$[mmHg/ml]	Right ventricular diastolic elastance	0.0167
$E_{S,l}$[mmHg/ml]	Left ventricular systemic elastance	0.507
$E_{S,r}$[mmHg/ml]	Right ventricular systemic elastance	3.38
$p_{l,sys}$[mmHg]	Systemic left ventricular pressure	120
$p_{r,sys}$[mmHg]	Systemic left ventricular pressure	30
$p_{l,dia}$[mmHg]	Diastolic left ventricular pressure	3
$p_{r,dia}$[mmHg]	Diastolic right ventricular pressure	6
p^I_{Pa}[mmHg]	Initial pulmonary arterial pressure	20
p^I_{Pv}[mmHg]	Initial pulmonary venous pressure	3.3
p^I_{Sa}[mmHg]	Initial systemic arterial pressure	79.5
p^I_{Sv}[mmHg]	Initial systemic venous pressure	6.6
p^I_{Ba}[mmHg]	Initial cerebral arterial pressure	78.7
p^I_{Bv}[mmHg]	Initial cerebral venous pressure	7
q_S[ml/s]	Mean systemic flow	79.6
q_{Ba}[ml/s]	Mean cerebral arterial flow	27.0
q_{Bv}[ml/s]	Mean cerebral venous flow	27.2
q_B[ml/s]	Mean cerebral flow	27.0
q_{Pa}[ml/s]	Mean pulmonary arterial flow	106.3
q_{Pv}[ml/s]	Mean pulmonary venous flow	106.3
q_P[ml/s]	Mean pulmonary flow	106.3
R_{sd}[mmHg s/ml]	Septal defect resistance	0.001
$R_{i,o}$[mmHg s/ml]	Open valve resistance $i = mv, ao, tv, pv$	0.001
$R_{i,c}$[mmHg s/ml]	Closed valve resistance $i = mv, ao, tv, pv$	20
R_S[mmHg s/ml]	Systemic resistance	0.934
R_B[mmHg s/ml]	Cerebral resistance	2.69
R_{Ba}[mmHg s/ml]	Cerebral arterial resistance	0.0471
R_{Bv}[mmHg s/ml]	Cerebral venous resistance	0.0237
R_P[mmHg s/ml]	Pulmonary resistance	0.198
T[s]	Cardiac cycle period	0.96
T_M[s]	Time for end-systolic elastance	0.132
T_R[s]	Remaining time to relaxation	0.168
V_t[ml]	Total blood volume	5408

Parameter	**Physiological Description**	**Value**
C_{Sa}[ml/mmHg]	Systemic arterial compliance	0.989
C_{Sv}[ml/mmHg]	Systemic venous compliance	39.9
C_{Ba}[ml/mmHg]	Cerebral arterial compliance	3.18
C_{Bv}[ml/mmHg]	Cerebral venous compliance	5.95
C_{Pa}[ml/mmHg]	Pulmonary arterial compliance	4.52
C_{Pv}[ml/mmHg]	Pulmonary venous compliance	22.4
V_{Sa}[ml]	Mean systemic arterial blood volume	637
V_{Sv}[ml]	Mean systemic venous blood volume	3294
V_{Ba}[ml]	Mean cerebral arterial blood volume	128
V_{Bv}[ml]	Mean cerebral venous blood volume	521
V_{Pa}[ml]	Mean pulmonary arterial blood volume	156
V_{Pv}[ml]	Mean pulmonary venous blood volume	1672
V_{dl}[ml]	Zero left ventricular end-diastolic volume	90
V_{dr}[ml]	Zero right ventricular end-diastolic volume	10
V_{lv}^{I}[mmHg]	Initial left ventricular volume	312
V_{rv}^{I}[mmHg]	Initial right ventricular volume	100

A.2 Respiratory Parameters

Parameter	Physiological Description	Value
T[s]	Time of respiration cycle	4.286
T_I[s]	Time of inspiration	1.29
T_E[s]	Time for expiration	1.71
V_{min}[ml]	Minimum alveolar volume	2447
V_{max}[ml]	Maximum alveolar volume	2750
M_{CO_2}[ml_{stpd}/s]	Body CO_2 tissue metabolism	4.89
M_{O_2}[ml_{stpd}/s]	Body O_2 tissue metabolism	5.2
V_{CO_2}[ml_{stpd}]	Body CO_2 tissue volume	15,000
V_{O_2}[ml_{stpd}]	Body O_2 tissue volume	6,000
M_{B,CO_2}[ml_{stpd}/s]	Brain CO_2 tissue metabolism	1.24
M_{B,O_2}[ml_{stpd}/s]	Brain O_2 tissue metabolism	1.04
M_{S,CO_2}[ml_{stpd}/s]	Systemic CO_2 tissue metabolism	3.38
M_{S,O_2}[ml_{stpd}/s]	Systemic O_2 tissue metabolism	4.16
V_{Btis,CO_2}[ml_{stpd}]	Cerebral tissue CO_2 volume	900
V_{Btis,O_2}[ml_{stpd}]	Cerebral tissue O_2 volume	855
V_{Stis,CO_2}[ml_{stpd}]	Systemic tissue CO_2 volume	14,100
V_{Stis,O_2}[ml_{stpd}]	Systemic tissue O_2 volume	5,000
V_{Bcap,CO_2}[ml_{stpd}]	Cerebral capillary CO_2 volume	9
V_{Bcap,O_2}[ml_{stpd}]	Cerebral capillary O_2 volume	10
V_{Scap,CO_2}[ml_{stpd}]	Systemic capillary CO_2 volume	141
V_{Scap,O_2}[ml_{stpd}]	Systemic capillary O_2 volume	50
V_D[ml_{stpd}]	Total dead space volume	201
V_{Di}[ml_{stpd}]	Dead space volume $i = 1, 2, 3$	67
K_{O_2}[ml_{stpd}/ml]	O_2 dissociation coefficient	0.200
k_{O_2}[mmHg^{-1}]	O_2 dissociation coefficient	0.046
K_{CO_2}[ml_{stpd}/mmHg/ml]	CO_2 dissociation coefficient	0.0065
k_{CO_2}[ml_{stpd}/ml]	CO_2 dissociation coefficient	0.244
$\tilde{K}_{O_2}$[ml_{stpd}/mmHg/ml]	O_2 linearized dissociation coefficient	0.0025
D_{T,CO_2}[ml/s]	CO_2 diffusion coefficient $T = B, S$	1899
D_{T,O_2}[ml/s]	O_2 diffusion coefficient $T = B, S$	4938
$f_{V,cap}$[N.D.]	Tissue-capillary volume fraction	0.01
p^I_{D1,CO_2}[mmHg]	Initial CO_2 partial pressure dead space 1	5
p^I_{D1,O_2}[mmHg]	Initial O_2 partial pressure dead space 1	159
p^I_{D2,CO_2}[mmHg]	Initial CO_2 partial pressure dead space 2	6
p^I_{D2,O_2}[mmHg]	Initial O_2 partial pressure dead space 2	158
p^I_{D3,CO_2}[mmHg]	Initial CO_2 partial pressure dead space 3	7
p^I_{D3,O_2}[mmHg]	Initial O_2 partial pressure dead space 3	157
p^I_{a,CO_2}[mmHg]	Initial systemic arterial CO_2 partial pressure	40
p^I_{a,O_2}[mmHg]	Initial systemic artierial O_2 partial pressure	100
p_{I,CO_2}[mmHg]	Inspired air CO_2 partial pressure	0
p_{I,O_2}[mmHg]	Inspired air O_2 partial pressure	159

Parameter	Physiological Description	Value
q_S[ml/s]	Mean systemic flow	79.6
q_{Ba}[ml/s]	Mean cerebral arterial flow	27.0
q_{Bv}[ml/s]	Mean cerebral venous flow	27.2
q_B[ml/s]	Mean cerebral flow	27.0
q_{Pa}[ml/s]	Mean pulmonary arterial flow	106.3
q_{Pv}[ml/s]	Mean pulmonary venous flow	106.3
q_P[ml/s]	Mean pulmonary flow	106.3
c^I_{Stis,CO_2}[ml_{stpd}/ml]	Initial systemic tissue CO_2 concentration	0.543
c^I_{Stis,O_2}[ml_{stpd}/ml]	Initial systemic tissue O_2 concentration	0.128
c^I_{Stis,CO_2}[ml_{stpd}/ml]	Initial brain tissue CO_2 concentration	0.569
c^I_{Stis,O_2}[ml_{stpd}/ml]	Initial brain tissue O_2 concentration	0.112
c^I_{Stis,CO_2}[ml_{stpd}/ml]	Initial systemic capillary CO_2 concentration	0.541
c^I_{Stis,O_2}[ml_{stpd}/ml]	Initial systemic capillary O_2 concentration	0.127
c^I_{Stis,CO_2}[ml_{stpd}/ml]	Initial cerebral capillary CO_2 concentration	0.568
c^I_{Stis,O_2}[ml_{stpd}/ml]	Initial cerebral capillary O_2 concentration	0.111

A.3 Changes in Parameters in Our Models

In both TGA models in our research, the flow rates are changed. In the TGA model with a septal defect, a new flow rate (the flow through the septal defect) is formed. This rate, q_{lv} will be assigned a value below. Also, a flow rate q_{Sv} is defined.

Parameter	Physiological Description	Normal	TGA(no mixing)	TGA(mixing)
q_S[ml/s]	Mean systemic flow	79.6	64.9	57.4
q_{Sv}[ml/s]	Mean systemic venous flow	N/A	N/A	57.4
q_{Ba}[ml/s]	Mean cerebral arterial flow	27.0	22.0	19.4
q_{Bv}[ml/s]	Mean cerebral venous flow	27.2	22.3	19.4
q_B[ml/s]	Mean cerebral flow	27.0	22.0	19.4
q_{Pa}[ml/s]	Mean pulmonary arterial flow	106.3	25.6	160.5
q_{Pv}[ml/s]	Mean pulmonary venous flow	106.3	25.6	160.5
q_P[ml/s]	Mean pulmonary flow	106.3	25.6	160.5
q_{lv}[ml/s]	Mean septal defect flow	N/A	N/A	1.7

B Normal Model

B.1 Cardiovascular System

Blood pressures, ventricular volumes, and intrathoracic pressure

$$\frac{dp_{Pa}}{dt} = (\frac{p_{rv} - p_{Pa}}{R_{pv}} - \frac{p_{Pa} - p_{Pv}}{R_P})/C_{Pa}$$

$$\frac{dp_{Pv}}{dt} = (\frac{p_{Pa} - p_{Pv}}{R_P} - \frac{p_{Pv} - p_{lv}}{R_{mv}})/C_{Pv}$$

$$\frac{dp_{Sa}}{dt} = (\frac{p_{lv} - p_{Sa}}{R_{av}} - \frac{p_{Sa} - p_{Sv}}{R_S} - \frac{p_{Sa} - p_{Ba}}{R_{Ba}})/C_{Sa}$$

$$\frac{dp_{Sv}}{dt} = (\frac{p_{Sa} - p_{Sv}}{R_S} + \frac{p_{Bv} - p_{Sv}}{R_{Bv}} - \frac{p_{Sv} - p_{rv}}{R_{tv}})/C_{Sv}$$

$$\frac{dp_{Ba}}{dt} = (\frac{p_{Sa} - p_{Ba}}{R_{Ba}} - \frac{p_{Ba} - p_{Bv}}{R_B})/C_{Ba}$$

$$\frac{dp_{Bv}}{dt} = (\frac{p_{Ba} - p_{Bv}}{R_B} - \frac{p_{Bv} - p_{Sv}}{R_{Bv}})/C_{Bv}$$

$$\frac{dV_{lv}}{dt} = \frac{p_{Pv} - p_{lv}}{R_{mv}} - \frac{p_{lv} - p_{Sa}}{R_{av}}$$

$$\frac{dV_{rv}}{dt} = \frac{p_{Sv} - p_{rv}}{R_{tv}} - \frac{p_{rv} - p_{Pa}}{R_{pv}}$$

Heart valves

$$R_{av} = \min[R_{av,o} + e^{-2(p_{lv} - p_{Sa})}, R_{av,c}]$$
$$R_{mv} = \min[R_{mv,o} + e^{-2(p_{Pv} - p_{lv})}, R_{mv,c}]$$
$$R_{pv} = \min[R_{pv,o} + e^{-2(p_{rv} - p_{Pa})}, R_{pv,c}]$$
$$R_{tv} = \min[R_{tv,o} + e^{-2(p_{Sv} - p_{rv}}, R_{tv,c}]$$

Ventricular pressures

$$p_{lv}(t) = E_{lv}(t)[V_{lv}(t) - V_{ld}]$$
$$p_{rv}(t) = E_{rv}(t)[V_{rv}(t) - V_{rd}]$$

where

$$E_{lv}(t) = \begin{cases} E_{D,l} + (E_{S,l} - E_{D,l})[1 - \cos(\frac{\pi t}{T_M})]/2 & 0 \le t \le T_M \\ E_{D,l} + (E_{S,l} - E_{D,l})[\cos(\frac{\pi(t-T_M}{T_R}) + 1]/2 & T_M \le t \le T_M + T_R \\ E_{D,l} & T_M + T_R \le t \le T, \end{cases}$$

$$E_{rv}(t) = \begin{cases} E_{D,r} + (E_{S,r} - E_{D,r})[1 - \cos(\frac{\pi t}{T_M})]/2 & 0 \le t \le T_M \\ E_{D,r} + (E_{S,r} - E_{D,r})[\cos(\frac{\pi(t-T_M)}{T_R}) + 1]/2 & T_M \le t \le T_M + T_R \\ E_{D,r} & T_M + T_R \le t \le T \end{cases}$$

B.2 Respiratory System

Systemic tissue

$$\frac{dc_{Stis,CO_2}}{dt} = (M_{S,CO_2} - D_{S,CO_2}(c_{Stis,CO_2} - c_{Scap,CO_2}))/V_{Stis,CO_2}$$

$$\frac{dc_{Scap,CO_2}}{dt} = (q_S(c_{a,CO_2} - c_{Scap,CO_2}) + D_{S,CO_2}(c_{Stis,CO_2} - c_{Scap,CO_2}))/V_{Scap,CO_2}$$

$$\frac{dc_{Stis,O_2}}{dt} = (-M_{S,O_2} - D_{S,O_2}(c_{Stis,O_2} - c_{Scap,O_2}))/V_{Stis,O_2}$$

$$\frac{dc_{Scap,O_2}}{dt} = (q_S(c_{a,O_2} - c_{Scap,O_2}) + D_{S,O_2}(c_{Stis,O_2} - c_{Scap,O_2}))/V_{Scap,O_2}$$

Brain tissue

$$\frac{dc_{Btis,CO_2}}{dt} = (M_{B,CO_2} - D_{B,CO_2}(c_{Btis,CO_2} - c_{Bcap,CO_2}))/V_{Btis,CO_2}$$

$$\frac{dc_{Bcap,CO_2}}{dt} = (q_{Bv}(c_{a,CO_2} - c_{Bcap,CO_2}) + D_{B,CO_2}(c_{Btis,CO_2} - c_{Bcap,CO_2}))/V_{Bcap,CO_2}$$

$$\frac{dc_{Btis,O_2}}{dt} = (-M_{B,O_2} - D_{B,O_2}(c_{Btis,O_2} - c_{Bcap,O_2}))/V_{Btis,O_2}$$

$$\frac{dc_{Bcap,O_2}}{dt} = (q_{Bv}(c_{a,O_2} - c_{Bcap,O_2}) + D_{B,O_2}(c_{Btis,O_2} - c_{Bcap,O_2}))/V_{Bcap,O_2}$$

Inspiration

$$\frac{dp_{D1,CO_2}}{dt} = \dot{V}_{ie}(p_{I,CO_2} - p_{D1,CO_2})/V_{D1}$$

$$\frac{dp_{D1,O_2}}{dt} = \dot{V}_{ie}(p_{I,O_2} - p_{D1,O_2})/V_{D1}$$

$$\frac{dp_{D2,CO_2}}{dt} = \dot{V}_{ie}(p_{D1,CO_2} - p_{D2,CO_2})/V_{D2}$$

$$\frac{dp_{D2,O_2}}{dt} = \dot{V}_{ie}(p_{D1,O_2} - p_{D2,O_2})/V_{D2}$$

$$\frac{dp_{D3,CO_2}}{dt} = \dot{V}_{ie}(p_{D2,CO_2} - p_{D3,CO_2})/V_{D3}$$

$$\frac{dp_{D3,O_2}}{dt} = \dot{V}_{ie}(p_{D2,O_2} - p_{D3,O_2})/V_{D3}$$

$$\frac{dp_{a,CO_2}}{dt} = 863 \cdot 0.98 \cdot q_P(c_{v,CO_2} - c_{a,CO_2}) + \dot{V}_{ie}(p_{D3,CO_2} - p_{a,CO_2})/V_A$$

$$\frac{dp_{a,O_2}}{dt} = 863 \cdot 0.98 \cdot q_P(c_{v,O_2} - c_{a,O_2}) + \dot{V}_{ie}(p_{D3,O_2} - p_{a,O_2})/V_A$$

Expiration

$$\frac{dp_{D1,CO_2}}{dt} = \dot{V}_{ie}(p_{D1,CO_2} - p_{D2,CO_2})/V_{D1}$$

$$\frac{dp_{D1,O_2}}{dt} = \dot{V}_{ie}(p_{D1,O_2} - p_{D2,O_2})/V_{D1}$$

$$\frac{dp_{D2,CO_2}}{dt} = \dot{V}_{ie}(p_{D2,CO_2} - p_{D3,CO_2})/V_{D2}$$

$$\frac{dp_{D2,O_2}}{dt} = \dot{V}_{ie}(p_{D2,O_2} - p_{D3,O_2})/V_{D2}$$

$$\frac{dp_{D3,CO_2}}{dt} = \dot{V}_{ie}(p_{D3,CO_2} - p_{a,CO_2})/V_{D3}$$

$$\frac{dp_{D3,O_2}}{dt} = \dot{V}_{ie}(p_{D3,O_2} - p_{a,O_2})/V_{D3}$$

$$\frac{dp_{a,CO_2}}{dt} = 863 \cdot 0.98 \cdot q_P(c_{v,CO_2} - c_{a,CO_2}))/V_A$$

$$\frac{dp_{a,O_2}}{dt} = 863 \cdot 0.98 \cdot q_P(c_{v,O_2} - c_{a,O_2}))/V_A$$

C TGA Model Without Mixing

C.1 Cardiovascular Model with TGA

Blood pressures, ventricular volumes, and intrathoracic pressure

$$\frac{dp_{Pa}}{dt} = (\frac{p_{lv} - p_{Pa}}{R_{av}} - \frac{p_{Pa} - p_{Pv}}{R_P})/C_{Pa}$$

$$\frac{dp_{Pv}}{dt} = (\frac{p_{Pa} - p_{Pv}}{R_P} - \frac{p_{Pv} - p_{lv}}{R_{mv}})/C_{Pv}$$

$$\frac{dp_{Sa}}{dt} = (\frac{p_{rv} - p_{Sa}}{R_{Pv}} - \frac{p_{Sa} - p_{Sv}}{R_S} - \frac{p_{Sa} - p_{Ba}}{R_{Ba}})/C_{Sa}$$

$$\frac{dp_{Sv}}{dt} = (\frac{p_{Sa} - p_{Sv}}{R_S} + \frac{p_{Bv} - p_{Sv}}{R_{Bv}} - \frac{p_{Sv} - p_{rv}}{R_{tv}})/C_{Sv}$$

$$\frac{dp_{Ba}}{dt} = (\frac{p_{Sa} - p_{Ba}}{R_{Ba}} - \frac{p_{Ba} - p_{Bv}}{R_B})/C_{Ba}$$

$$\frac{dp_{Bv}}{dt} = (\frac{p_{Ba} - p_{Bv}}{R_B} - \frac{p_{Bv} - p_{Sv}}{R_{Bv}})/C_{Bv}$$

$$\frac{dV_{lv}}{dt} = \frac{p_{Pv} - p_{lv}}{R_{mv}} - \frac{p_{lv} - p_{Pa}}{R_{av}}$$

$$\frac{dV_{rv}}{dt} = \frac{p_{Sv} - p_{rv}}{R_{tv}} - \frac{p_{rv} - p_{Sa}}{R_{pv}}$$

Heart valves

$$R_{av} = \min[R_{av,o} + e^{-2(p_{lv} - p_{Sa})}, R_{av,c}]$$
$$R_{mv} = \min[R_{mv,o} + e^{-2(p_{Pv} - p_{lv})}, R_{mv,c}]$$
$$R_{pv} = \min[R_{pv,o} + e^{-2(p_{rv} - p_{Pa})}, R_{pv,c}]$$
$$R_{tv} = \min[R_{tv,o} + e^{-2(p_{Sv} - p_{rv})}, R_{tv,c}]$$

Ventricular pressures

$$p_{lv}(t) = E_{lv}(t)[V_{lv}(t) - V_{ld}]$$
$$p_{rv}(t) = E_{rv}(t)[V_{rv}(t) - V_{rd}]$$

where

$$E_{lv}(t) = \begin{cases} E_{D,l} + (E_{S,l} - E_{D,l})[1 - \cos(\frac{\pi t}{T_M})]/2 & 0 \le t \le T_M \\ E_{D,l} + (E_{S,l} - E_{D,l})[\cos(\frac{\pi(t-T_M}{T_R}) + 1]/2 & T_M \le t \le T_M + T_R \\ E_{D,l} & T_M + T_R \le t \le T, \end{cases}$$

$$E_{rv}(t) = \begin{cases} E_{D,r} + (E_{S,r} - E_{D,r})[1 - \cos(\frac{\pi t}{T_M})]/2 & 0 \le t \le T_M \\ E_{D,r} + (E_{S,r} - E_{D,r})[\cos(\frac{\pi(t-T_M}{T_R}) + 1]/2 & T_M \le t \le T_M + T_R \\ E_{D,r} & T_M + T_R \le t \le T \end{cases}$$

C.2 Respiratory System

Systemic tissue

$$\frac{dc_{Stis,CO_2}}{dt} = (M_{S,CO_2}(c^I_{Stis,CO_2} + c^I_{Stis,O_2} - c_{Stis,CO_2}) - D_{S,CO_2}(c_{Stis,CO_2} - c_{Scap,CO_2}))/V_{Stis,CO_2}$$

$$\frac{dc_{Scap,CO_2}}{dt} = (q_S(c_{v,CO_2} - c_{Scap,CO_2}) + D_{S,CO_2}(c_{Stis,CO_2} - c_{Scap,CO_2}))/V_{Scap,CO_2}$$

$$\frac{dc_{Stis,O_2}}{dt} = (-M_{S,O_2} \cdot c_{Stis,O_2} - D_{S,O_2}(c_{Stis,O_2} - c_{Scap,O_2}))/V_{Stis,O_2}$$

$$\frac{dc_{Scap,O_2}}{dt} = (q_S(c_{v,O_2} - c_{Scap,O_2}) + D_{S,O_2}(c_{Stis,O_2} - c_{Scap,O_2}))/V_{Scap,O_2}$$

Brain tissue

$$\frac{dc_{Btis,CO_2}}{dt} = (M_{B,CO_2}(c^I_{Btis,CO_2} + c^I_{Btis,O_2} - c_{Btis,CO_2}) - D_{B,CO_2}(c_{Btis,CO_2} - c_{Bcap,CO_2}))/V_{Btis,CO_2}$$

$$\frac{dc_{Bcap,CO_2}}{dt} = (q_{Bv}(c_{v,CO_2} - c_{Bcap,CO_2}) + D_{B,CO_2}(c_{Btis,CO_2} - c_{Bcap,CO_2}))/V_{Bcap,CO_2}$$

$$\frac{dc_{Btis,O_2}}{dt} = (-M_{B,O_2} \cdot c_{Btis,O_2} - D_{B,O_2}(c_{Btis,O_2} - c_{Bcap,O_2}))/V_{Btis,O_2}$$

$$\frac{dc_{Bcap,O_2}}{dt} = (q_{Bv}(c_{v,O_2} - c_{Bcap,O_2}) + D_{B,O_2}(c_{Btis,O_2} - c_{Bcap,O_2}))/V_{Bcap,O_2}$$

Inspiration

$$\frac{dp_{D1,CO_2}}{dt} = \dot{V}_{ie}(p_{I,CO_2} - p_{D1,CO_2})/V_{D1}$$

$$\frac{dp_{D1,O_2}}{dt} = \dot{V}_{ie}(p_{I,O_2} - p_{D1,O_2})/V_{D1}$$

$$\frac{dp_{D2,CO_2}}{dt} = \dot{V}_{ie}(p_{D1,CO_2} - p_{D2,CO_2})/V_{D2}$$

$$\frac{dp_{D2,O_2}}{dt} = \dot{V}_{ie}(p_{D1,O_2} - p_{D2,O_2})/V_{D2}$$

$$\frac{dp_{D3,CO_2}}{dt} = \dot{V}_{ie}(p_{D2,CO_2} - p_{D3,CO_2})/V_{D3}$$

$$\frac{dp_{D3,O_2}}{dt} = \dot{V}_{ie}(p_{D2,O_2} - p_{D3,O_2})/V_{D3}$$

$$\frac{dp_{a,CO_2}}{dt} = \dot{V}_{ie}(p_{D3,CO_2} - p_{a,CO_2})/V_A$$

$$\frac{dp_{a,O_2}}{dt} = \dot{V}_{ie}(p_{D3,O_2} - p_{a,O_2})/V_A$$

Expiration

$$\frac{dp_{D1,CO_2}}{dt} = \dot{V}_{ie}(p_{D1,CO_2} - p_{D2,CO_2})/V_{D1}$$

$$\frac{dp_{D1,O_2}}{dt} = \dot{V}_{ie}(p_{D1,O_2} - p_{D2,O_2})/V_{D1}$$

$$\frac{dp_{D2,CO_2}}{dt} = \dot{V}_{ie}(p_{D2,CO_2} - p_{D3,CO_2})/V_{D2}$$

$$\frac{dp_{D2,O_2}}{dt} = \dot{V}_{ie}(p_{D2,O_2} - p_{D3,O_2})/V_{D2}$$

$$\frac{dp_{D3,CO_2}}{dt} = \dot{V}_{ie}(p_{D3,CO_2} - p_{a,CO_2})/V_{D3}$$

$$\frac{dp_{D3,O_2}}{dt} = \dot{V}_{ie}(p_{D3,O_2} - p_{a,O_2})/V_{D3}$$

$$\frac{dp_{a,CO_2}}{dt} = 0$$

$$\frac{dp_{a,O_2}}{dt} = 0$$

D TGA Model With Mixing

D.1 Cardiovascular Model with TGA

Blood pressures, ventricular volumes, and intrathoracic pressure

$$\frac{dp_{Pa}}{dt} = (\frac{p_{lv} - p_{Pa}}{R_{av}} - \frac{p_{Pa} - p_{Pv}}{R_P})/C_{Pa}$$

$$\frac{dp_{Pv}}{dt} = (\frac{p_{Pa} - p_{Pv}}{R_P} - \frac{p_{Pv} - p_{lv}}{R_{mv}})/C_{Pv}$$

$$\frac{dp_{Sa}}{dt} = (\frac{p_{rv} - p_{Sa}}{R_{Pv}} - \frac{p_{Sa} - p_{Sv}}{R_S} - \frac{p_{Sa} - p_{Ba}}{R_{Ba}})/C_{Sa}$$

$$\frac{dp_{Sv}}{dt} = (\frac{p_{Sa} - p_{Sv}}{R_S} + \frac{p_{Bv} - p_{Sv}}{R_{Bv}} - \frac{p_{Sv} - p_{rv}}{R_{tv}})/C_{Sv}$$

$$\frac{dp_{Ba}}{dt} = (\frac{p_{Sa} - p_{Ba}}{R_{Ba}} - \frac{p_{Ba} - p_{Bv}}{R_B})/C_{Ba}$$

$$\frac{dp_{Bv}}{dt} = (\frac{p_{Ba} - p_{Bv}}{R_B} - \frac{p_{Bv} - p_{Sv}}{R_{Bv}})/C_{Bv}$$

$$\frac{dV_{lv}}{dt} = \frac{p_{Pv} - p_{lv}}{R_{mv}} - \frac{p_{lv} - p_{Pa}}{R_{av}} - \frac{p_{lv} - p_{rv}}{0.001}$$

$$\frac{dV_{rv}}{dt} = \frac{p_{Sv} - p_{rv}}{R_{tv}} + \frac{p_{lv} - p_{rv}}{0.001} - \frac{p_{rv} - p_{Sa}}{R_{pv}}$$

Heart valves

$$R_{av} = \min[R_{av,o} + e^{-2(p_{lv} - p_{Sa})}, R_{av,c}]$$
$$R_{mv} = \min[R_{mv,o} + e^{-2(p_{Pv} - p_{lv})}, R_{mv,c}]$$
$$R_{pv} = \min[R_{pv,o} + e^{-2(p_{rv} - p_{Pa})}, R_{pv,c}]$$
$$R_{tv} = \min[R_{tv,o} + e^{-2(p_{Sv} - p_{rv})}, R_{tv,c}]$$

Ventricular pressures

$$p_{lv}(t) = E_{lv}(t)[V_{lv}(t) - V_{ld}]$$
$$p_{rv}(t) = E_{rv}(t)[V_{rv}(t) - V_{rd}]$$

where

$$E_{lv}(t) = \begin{cases} E_{D,l} + (E_{S,l} - E_{D,l})[1 - \cos(\frac{\pi t}{T_M})]/2 & 0 \le t \le T_M \\ E_{D,l} + (E_{S,l} - E_{D,l})[\cos(\frac{\pi(t-T_M}{T_R}) + 1]/2 & T_M \le t \le T_M + T_R \\ E_{D,l} & T_M + T_R \le t \le T, \end{cases}$$

$$E_{rv}(t) = \begin{cases} E_{D,r} + (E_{S,r} - E_{D,r})[1 - \cos(\frac{\pi t}{T_M})]/2 & 0 \le t \le T_M \\ E_{D,r} + (E_{S,r} - E_{D,r})[\cos(\frac{\pi(t-T_M}{T_R}) + 1]/2 & T_M \le t \le T_M + T_R \\ E_{D,r} & T_M + T_R \le t \le T \end{cases}$$

D.2 Respiratory System

Systemic tissue

$$\frac{dc_{Stis,CO_2}}{dt} = (M_{S,CO_2}(c^I_{Stis,CO_2} + c^I_{Stis,O_2} - c_{Stis,CO_2}) - D_{S,CO_2}(c_{Stis,CO_2} - c_{Scap,CO_2}))/V_{Stis,CO_2}$$

$$\frac{dc_{Scap,CO_2}}{dt} = (q_S(c_{mix,CO_2} - c_{Scap,CO_2}) + D_{S,CO_2}(c_{Stis,CO_2} - c_{Scap,CO_2}))/V_{Scap,CO_2}$$

$$\frac{dc_{Stis,O_2}}{dt} = (-M_{S,O_2} \cdot c_{Stis,O_2} - D_{S,O_2}(c_{Stis,O_2} - c_{Scap,O_2}))/V_{Stis,O_2}$$

$$\frac{dc_{Scap,O_2}}{dt} = (q_S(c_{mix,O_2} - c_{Scap,O_2}) + D_{S,O_2}(c_{Stis,O_2} - c_{Scap,O_2}))/V_{Scap,O_2}$$

Brain tissue

$$\frac{dc_{Btis,CO_2}}{dt} = (M_{B,CO_2}(c^I_{Btis,CO_2} + c^I_{Btis,O_2} - c_{Btis,CO_2}) - D_{B,CO_2}(c_{Btis,CO_2} - c_{Bcap,CO_2}))/V_{Btis,CO_2}$$

$$\frac{dc_{Bcap,CO_2}}{dt} = (q_{Bv}(c_{mix,CO_2} - c_{Bcap,CO_2}) + D_{B,CO_2}(c_{Btis,CO_2} - c_{Bcap,CO_2}))/V_{Bcap,CO_2}$$

$$\frac{dc_{Btis,O_2}}{dt} = (-M_{B,O_2} \cdot c_{Btis,O_2} - D_{B,O_2}(c_{Btis,O_2} - c_{Bcap,O_2}))/V_{Btis,O_2}$$

$$\frac{dc_{Bcap,O_2}}{dt} = (q_{Bv}(c_{mix,O_2} - c_{Bcap,O_2}) + D_{B,O_2}(c_{Btis,O_2} - c_{Bcap,O_2}))/V_{Bcap,O_2}$$

Inspiration

$$\frac{dp_{D1,CO_2}}{dt} = \dot{V}_{ie}(p_{I,CO_2} - p_{D1,CO_2})/V_{D1}$$

$$\frac{dp_{D1,O_2}}{dt} = \dot{V}_{ie}(p_{I,O_2} - p_{D1,O_2})/V_{D1}$$

$$\frac{dp_{D2,CO_2}}{dt} = \dot{V}_{ie}(p_{D1,CO_2} - p_{D2,CO_2})/V_{D2}$$

$$\frac{dp_{D2,O_2}}{dt} = \dot{V}_{ie}(p_{D1,O_2} - p_{D2,O_2})/V_{D2}$$

$$\frac{dp_{D3,CO_2}}{dt} = \dot{V}_{ie}(p_{D2,CO_2} - p_{D3,CO_2})/V_{D3}$$

$$\frac{dp_{D3,O_2}}{dt} = \dot{V}_{ie}(p_{D2,O_2} - p_{D3,O_2})/V_{D3}$$

$$\frac{dp_{a,CO_2}}{dt} = \dot{V}_{ie}(p_{D3,CO_2} - p_{a,CO_2})/V_A$$

$$\frac{dp_{a,O_2}}{dt} = \dot{V}_{ie}(p_{D3,O_2} - p_{a,O_2})/V_A$$

Expiration

$$\frac{dp_{D1,CO_2}}{dt} = \dot{V}_{ie}(p_{D1,CO_2} - p_{D2,CO_2})/V_{D1}$$

$$\frac{dp_{D1,O_2}}{dt} = \dot{V}_{ie}(p_{D1,O_2} - p_{D2,O_2})/V_{D1}$$

$$\frac{dp_{D2,CO_2}}{dt} = \dot{V}_{ie}(p_{D2,CO_2} - p_{D3,CO_2})/V_{D2}$$

$$\frac{dp_{D2,O_2}}{dt} = \dot{V}_{ie}(p_{D2,O_2} - p_{D3,O_2})/V_{D2}$$

$$\frac{dp_{D3,CO_2}}{dt} = \dot{V}_{ie}(p_{D3,CO_2} - p_{a,CO_2})/V_{D3}$$

$$\frac{dp_{D3,O_2}}{dt} = \dot{V}_{ie}(p_{D3,O_2} - p_{a,O_2})/V_{D3}$$

$$\frac{dp_{a,CO_2}}{dt} = 0$$

$$\frac{dp_{a,O_2}}{dt} = 0$$

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