Pulmonary Vascular Resistance as a Predictor for Survival in Premature Babies

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Abstract

Pulmonary hypertension (PH) is a significant cause of morbidity and mortality in premature infants, and is strongly associated with elevated pulmonary vascular resistance (PVR). PVR impedes the flow of blood through the lung circulation. Elevated PVR leads to higher pressure in the pulmonary arteries, making it more difficult for the heart to pump blood through the lungs, and affecting the circulatory system as a whole.

In this thesis we also present a generalization of the PVR concept by incorporating the impact of the vessel wall compliance, resulting in the impedance Z. We thus examine the concept of PVZ as a new clinical index for assessing the degree of the pathology.

This thesis presents two computational approaches to investigate the impacts of PVR and PVZ on the blood circulation in newborns with PH: a 0D electrical circuit model and a 2D computational fluid dynamics (CFD) simulation. The 0D model provides a simplified representation of the circulatory system, enabling rapid evaluation of PVR changes across normal and pathological ranges and can be used to guide the more elaborate simulations. The 2D CFD model offers detailed insights into pressure and velocity distributions within the pulmonary and systemic circulations.

Results are consistent with clinical observations that elevated PVR leads to higher pulmonary arterial pressure and significant changes in right ventricular function. Together, these models contribute to understanding the hemodynamic impacts of PVR and offer tools for predicting outcomes and optimizing clinical management in preterm infants at risk of PH.

Résumé

L’hypertension (HP) est une cause importante de morbidité et de mortalité chez les enfants prématurés et est fortement corrélé avec l’élévation de la résistance vasculaire pulmonaire (PVR). La PVR limite l’écoulement normal du sang de la circulation pulmonaire. Des valeurs élevées de PVR mènent à des pressions augmentées dans les artères pulmonaires, ce qui rend plus difficile pour le coeur de pomper le sang au travers les poumons et affecte la circulation globalement.

Dans cette thèse, nous présentons également une généralisation du concept PVR en incorporant l'impact de la compliance de la paroi vasculaire, résultant en l'impédance Z. Nous examinons ainsi le concept de PVZ comme un nouvel indice clinique pour évaluer le degré de la pathologie.

Cette thèse présente deux approches informatiques pour investiguer les impacts de la PVR: un modèle 0D utilisant un analogue électrique et un modèle 2D utilisant des simulations de la dynamiques des fluides (CFD). Le modèle 0D fournit une représentation simplifiée du système circulatoire et permet une évaluation rapide des changements de PVR pour des cas normaux et pathologiques. La modélisation par CFD offre une compréhension détaillée pour les pressions et les distributions de vitesses pour les circulations pulmonaires et systémiques.

Les résultats montrent que des valeurs élevées de PVR mènent à des pressions artérielles plus élevées et causent des changements importants de la fonction ventriculaire droite. Ces modèles combinés permettent de mieux comprendre les impacts hémodynamiques de la PVR et offrent

des outils pour prédire ses conséquences et optimiser la gestion clinique des enfants prématurés et les risques de l'hypertension.

Acknowledgements

I would like to express my deepest gratitude to my supervisor, Prof. Rosaire Mongrain, for his invaluable guidance, encouragement, and support throughout the last two years. His expertise and patience have been instrumental in helping me navigate the challenges of this project. I also want to thank Hristo Valtchanov for his assistance in setting up the 2D simulations. His technical input and advice was essential to the development of this aspect of my work.

Lastly, I would like to acknowledge my parents for their unwavering support, encouragement and belief in me, which has been a constant throughout this process.

Contributions of Authors

Morgan Chapados designed and developed all of the models and performed all of the experiments and analysis shown within this work, with assistance from Hristo Valtchnov in setting up the 2D simulations. All figures and graphics not otherwise indicated were created by M. Chapados. Dr. Rosaire Mongrain provided guidance and feedback on model development and experiments. This thesis was written by M. Chapados with feedback, editing, and suggestions by R. Mongrain.

Lists of Figures and Tables

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List of Abbreviations

BPD: bronchopulmonary dysplasia

BSA: body surface area

CFD: computational fluid dynamics

CO: cardiac output

HRF: hypoxemic respiratory failure

mPAP: mean pulmonary arterial pressure

PAH: pulmonary arterial hypertension

PCWP: pulmonary capillary wedge pressure

PH: pulmonary hypertension

PPHN: persistent pulmonary hypertension of the newborn

PVC: pulmonary vascular compliance

PVD: pulmonary vascular disease

PVR: pulmonary vascular resistance

PVZ: pulmonary vascular impedance

SVR: systemic vascular resistance

WU: Wood units

1 Introduction

Premature infants are 3.5 times more likely to die than infants born at term[1], and a significant cause of these deaths is acute respiratory illness. One study[2] found this category to be the most common cause of death in the lowest gestational age group (22-25 weeks) and the second most common overall. Pulmonary hypertension (PH), in particular, affects up to 23% of premature infants[3]. This condition is characterized by higher than normal pulmonary vascular resistance (PVR)[4]. Understanding and managing PVR is essential for improving outcomes in this vulnerable population.

PVR impedes the flow of blood through the lungs. Elevated PVR leads to higher pressure in the pulmonary arteries, making it more difficult for the heart to pump blood through the lungs. This increased workload on the heart can result in right heart failure and significantly impact the overall circulatory system. Therefore, monitoring and managing PVR is critical for predicting survival and managing treatment in premature infants with PH.

The relationship between PVR and pulmonary vascular impedance (PVZ), which takes the vessel wall compliance into consideration, is also important. Previous studies[5][6] have found that this value, more so than PVR alone, is instrumental in determining the severity of PH in its early stages.

By exploring how the values of PVR and PVZ impact the overall circulatory system through predictive models, clinicians can gain valuable insights into the prognosis and potential

outcomes for affected patients. These models can help clinicians anticipate the progression of the disease, adjust treatment strategies, and ultimately improve patient prognosis.

The goal of this thesis is to create a simplified numerical model of the circulatory system that can accurately represent the effects of varying PVR both within and outside of normal physiological ranges. This model aims to show how changes in PVR and PVZ influence other components of the circulatory system, providing a comprehensive understanding of the condition's impact.

Chapter 2 presents the clinical background associated with the function of the cardiovascular system, the characterization and effects of pulmonary hypertension in premature babies, a review of previous computational models that have been developed to study this disease, and technical background for electrical circuit analogies.

Chapters 3 and 4 present the two models that were developed for this thesis: a 0D electrical circuit model and a 2D computational fluid dynamics (CFD) model, with the parameters and boundary conditions given for both models in Chapter 3 and the simulation results presented in Chapter 4.

Chapter 5 discusses the clinical and physiological relevance of the models, comparisons with previous studies, strengths and limitations of the models, and suggestions for future work.

Finally, the last chapter concludes the thesis and summarizes the relevance of the findings.

2 Literature Review

2.1 The Heart as a System

The heart is a physiological system comprised of two interacting loops: the systemic circulation and the pulmonary circulation. Figure 2.1 shows a visual representation of the circulatory flow.

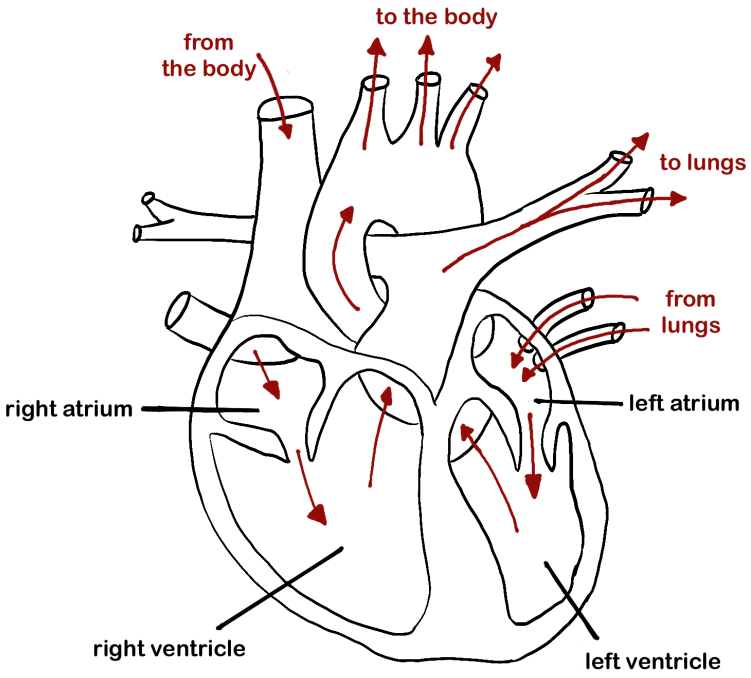

Figure 2.1: Diagram of the heart showing how blood flows through the circulatory loops

Pulmonary Circulation

Deoxygenated blood returning from the body enters the heart via the right atrium, which contracts and pushes blood into the right ventricle. The right ventricle then pumps blood into the

pulmonary arteries, where it must overcome pulmonary vascular resistance (PVR) to reach the lungs. After gas exchange occurs, oxygenated blood returns to the heart through the pulmonary veins, entering the left atrium.

Systemic Circulation

From the left atrium, oxygenated blood flows into the left ventricle, which then pumps the blood through the aorta and out to the body for the systemic circulation, where it encounters systemic vascular resistance.

2.2 Pulmonary Hypertension in Premature Babies

Pre-capillary pulmonary hypertension (PH) is generally characterized by PVR >= 3 Wood units (WU) (1 WU = 1 mmHg min/L) and mean pulmonary arterial pressure (mPAP) >= 20 mmHg[4]. These criteria, however, come from studies of PH in adults. In pediatric patients, and especially in newborns, the circulatory system is significantly smaller, and absolute resistance values are not directly comparable to those in adults; therefore, del Cerro et al.[7] suggest that pediatric PH be defined by mPAP > 25 mmHg and PVR indexed to body surface area (BSA) > 3 WU m^2.

By this definition, before birth, the fetus is technically in a state of pulmonary hypertension. PVR and blood pressure are high and pulmonary blood flow is low, while the fetus receives oxygenated blood from the placenta. In the fetal circulatory system, the ductus arteriosus and foramen ovale are open, shunting blood across from right to left. At birth, the initiation of breathing fills the lungs with air, which causes the lungs to expand and significantly increases

blood oxygen levels and triggers dilation of the pulmonary vessels. The removal of the placenta from the circulation increases systemic vascular resistance (SVR) and redirects blood flow toward the lungs. These processes rapidly lower PVR during the first few days of life. Pulmonary blood flow increases by a factor of eight, and the shunts at the foramen ovale and ductus arteriosus decrease and eventually reverse direction[1][7][8].

When this normal transition fails, it leads to persistent pulmonary hypertension of the newborn (PPHN), which often appears as severe hypoxemic respiratory failure (HRF) due to the blood shunting away from the lung circulation[1][8].

Infants born pre-term are especially at risk of developing PH and HRF, particularly when there is a deficiency of amniotic fluid in the womb and the lungs are underdeveloped[1][7][8]. PPHN in premature infants is heavily associated with low gestational age[1][2][8]. PH in the first few days of life leads to an increased risk of developing bronchopulmonary dysplasia (BPD), especially severe BPD, and death before 36 weeks gestational age.

PH or pulmonary vascular disease (PVD) in premature infants can look different, vary in severity, timing of onset, and other factors[1], so early diagnosis and treatment is essential to improve these patients' survival.

2.3 Computational Models

Blood flow in the circulatory system is very similar to electric conduction in a circuit[9]; blood pressure drives flow against hydraulic impedance caused by frictional loss, elasticity of vessel walls, and blood inertia, while voltage drives current against electric impedance caused by

resistance (R), capacitance (C), and inductance (L). Therefore, the circulatory system can be represented by a simplified 0D electrical circuit model.

The simplest form of these models is the two-element (RC) Windkessel model (shown in Figure 2.2), which consists of a single resistor and capacitor wired in parallel[9]. Adding a second resistor to separate the pulmonary and systemic resistances can improve accuracy.

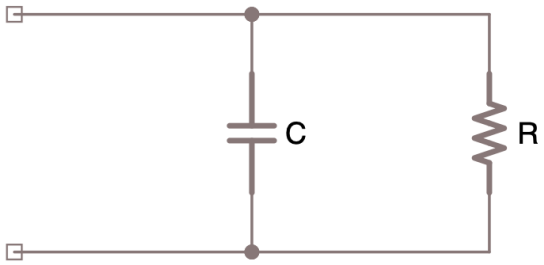

Figure 2.2: The simplest Windkessel circuit model

More comprehensive models have been developed with many more compartments representing each part of the system. Because the heart valves work to prevent backflow of blood from the ventricles to the atria or from the aorta or pulmonary artery into the ventricles, these are usually modeled as diodes. Figure 2.3 shows an example of a multi-compartment 0D model that represents the entire circulatory system. The heart is represented by diodes for each of the atria and ventricles. The pulmonary and systemic loops are each modeled by resistors, capacitors, and inductors representing the arteries, arterioles, capillaries, and veins.

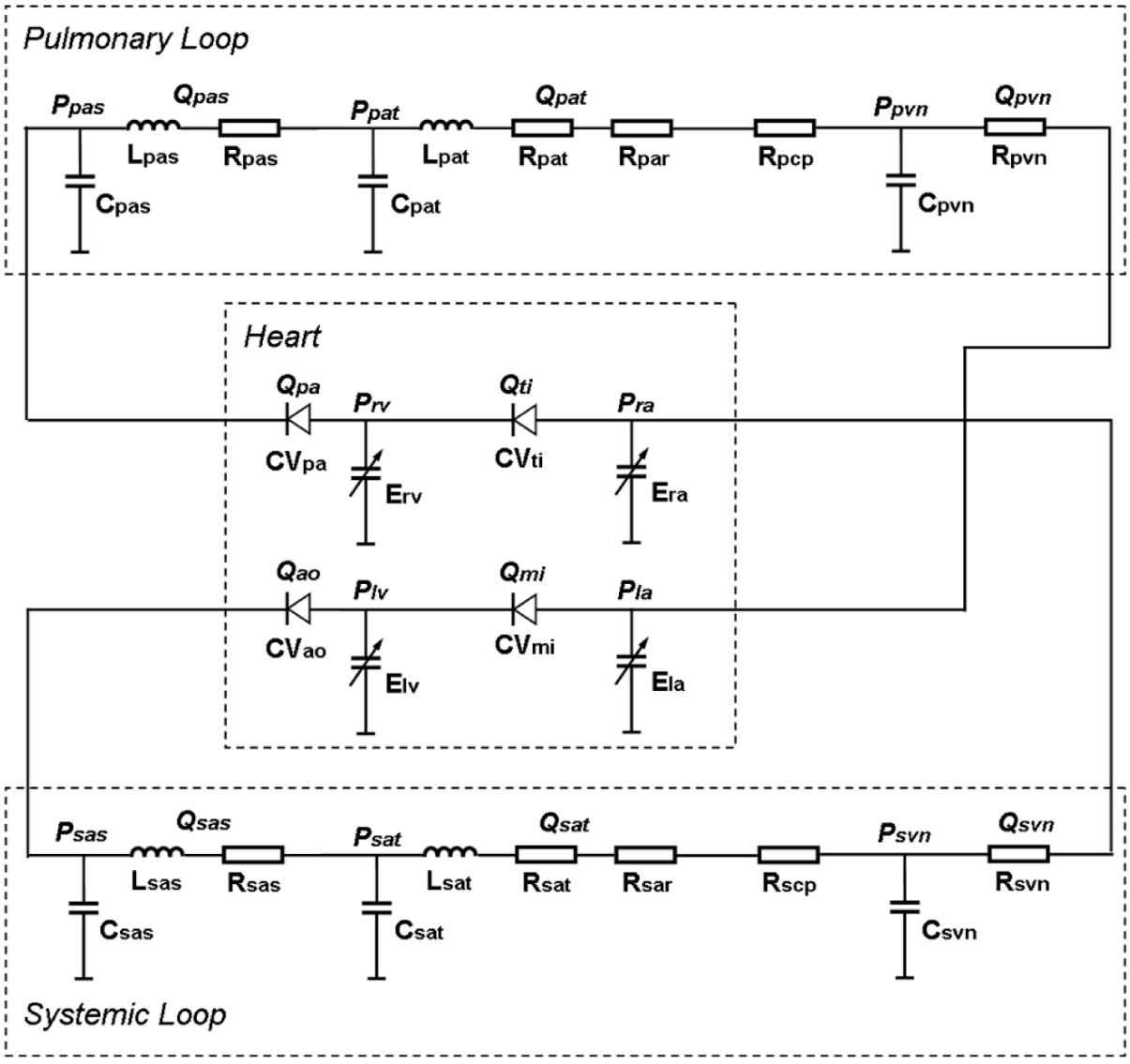

Figure 2.3: A sample circuit representing the entire circulatory system[9] *Reproduced with Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0)*

The biggest challenge with these model is obtaining accurate parameters. The measurement procedures for many cardiovascular variables are invasive, and available data often only provide part of the necessary information, especially as models become more complex. In practice, parameters are often estimated through manual trial-and-error, where values are adjusted iteratively to match physiological data, which is time-consuming and may not always lead to

accurate results. Additionally, model structure and purpose heavily influence parameter selection. A model designed to simulate fetal circulation, for instance, will require different resistances and compliances than one representing adult hypertension. This variability leads to a wide range of published parameter values across the literature, making direct comparisons between studies difficult.

Component variables in 0D models are generally treated as constants, although real physiological parameters can be subject to nonlinearities and frequency dependance, which cannot be represented by the circuit analogy. The impact of these nonlinearities is however quite small, and therefore reasonable to neglect, but they can be represented by higher dimensional models[9].

1D pulse wave transmission models often use pressure, flow, and area as parameters, and can show the pressure and flow changes along the full length of a vessel. 2D and 3D computational fluid dynamics (CFD) models can show detailed pressure and velocity distributions, but these are computationally expensive and so they are often not feasible to use for more than a small part of the system being studied.

Because of these limitations, 0D models are often coupled with 1D, 2D, and/or 3D models in order to represent the whole circulatory system, with a higher-dimensional model used for the part of interest and a 0D or 1D model used to provide the boundary conditions. This section will examine three different computational blood flow models developed to simulate the effects of pulmonary hypertension on the circulatory system and study its impact on hemodynamic parameters. While previous studies have explored computational models of the heart in pediatric populations[10][11][12][13], these have not specifically addressed pulmonary hypertension. The

models reviewed in this thesis were developed with adult patients in mind; however, they were selected for their closer alignment with the pathophysiological focus of this work.

The first model, developed by Marcinno et al. (2023)[14], used a geometric multiscale approach: a detailed 3D computational fluid dynamics (CFD) model for the part of interest (in this case, the pulmonary arteries), coupled with a scaled-down closed-loop 0D model for the remaining parts of the cardiovascular system.

The 0D model used electrical analogies, with voltage representing pressure, current representing blood flow, resistance accounting for the effect of blood viscosity, capacity for wall compliance, and inductance for the inertial effects of blood flow. The four heart valves were modeled as non-ideal diodes, with the pump function accomplished through time dependent elastances. Ohm's law was used to calculate pressure.

For the CFD simulation, blood was modeled as an incompressible, homogenous Newtonian fluid, with density of $1.06 * 10^3$ kg/m^3 and viscosity of $3.5 * 10^3$ Pa s. The model produced a 0D inlet flow rate of 0.23 L/s, 3D inlet mean pressure of 21 mmHg, and 0D right ventricular pressure of 30 mmHg.

The closed-0D model was almost perfectly accurate for the mean quantities, with no difference in flow rate and only a small difference in the pressures at systolic peak and deceleration. A 3D-0D coupled model was, however, needed to provide details of blood flow, localized pressures, the velocity field, and wall shear stress.

Comparing the healthy base case to the simulation of pulmonary arterial hypertension (PAH), the model showed higher velocity and lower pressure in the pulmonary artery of the healthy case, with the pressure at systolic peak being almost 1.5 times higher in the unhealthy case. This

suggests that PAH causes an increase in working pressure of the right ventricle, which could lead to hypertrophy and eventual right heart failure.

In the treatment of pulmonary arterial hypertension, it is important to consider the relationship between PVR and pulmonary compliance (PVC), which are related by an inverse hyperbolic function: when PVR decreases, PVC increases[5]. De Lazzari et al. (2019)[5] developed a model with the pulmonary circulation represented in three parts: the main pulmonary artery, the small pulmonary artery, and the pulmonary arteriole and capillary compartments. The behaviour of the pulmonary arteries was modeled with resistance, inertance, and compliance. Right atrial pressure and pulmonary capillary wedge pressure (PCWP) were modeled with two fixed pressure generators.

This model was tested using clinical data from one adult patient with PAH. The model successfully reproduced the patient's basal conditions, and again six months after the patient began treatment. The model showed that the decrease in PVR resulting from treatment also causes an increase in PVC; this increase is significant in mild cases of PH, but negligible in severe cases. This study explains why patients with mild PH show more improvement from treatment than those with more severe PH, even if PVR decreases by the same amount: the compliance is the more important measure.

The third model, developed by Acosta et al. (2017)[6] used 1D equations to represent the major vessels as elastic tubes, coupled with 0D equations for the organs and left and right sides of the heart, with the goal being to create a high-fidelity mathematical model of the hemodynamics associated with PH.

The 0D model, similarly to Marcinno et al.[14], used an electrical circuit analogy. Each chamber of the heart was modeled using three variables: pressure, momentum, and volume.

For the 1D model, blood was modeled as a Newtonian fluid with density of 1.06 g/cm^3 and viscosity of $3.20 * 10^{-2}$ g/cm/s.

Acosta[6] considered in particular the stiffening of the pulmonary vessels. Because both PVR and the higher pressures caused by PH can lead to a decrease in cardiac output, physiological reflexes often attempt to compensate by increasing the heart rate and myocardial contractility. This model simulated both the scenario with complete cardiac compensation, where normal cardiac output is maintained, and the scenario with no compensation at all.

The model effectively showed that increasing stiffness corresponds to an increase in PAP and a decrease in blood flow rate in systole, while diastole was unaffected, which is consistent with clinical data. As in [5], this model also showed an inverse relationship between PVR and PVC; PVR increases with the stiffness, while PVC decreases. Cardiac compensation did not have a significant impact in the simulation of the early stages of PH; it showed no impact on PVR at any stage, and only a small impact on PVC at later stages.

Acosta et al.[6] also concluded that PVC may be the more useful parameter for early detection of PH, and is also a stronger predictor of mortality, compared to other biomarkers such as cardiac output, right atrial pressure, mPAP, and PVR. However, while PVR alone was not found to be highly sensitive to the pulmonary arterial stiffening in early PH, the RC time constant (PVR * PVC) was found to be more sensitive, and RC can be estimated non-invasively, so this measure may be more clinically useful overall.

Shi et al.[9] concluded that the more complex models do not always lead to more accurate results, and emphasized the importance of correct parameter setting. Shi et al.[9] also argued that 0D models, which are currently more prevalent in research than in clinical practice, could be very useful for patient-specific analysis if the parameters are personalized.

2.4 Electrical Circuits

The electrical circuit analogy used in this thesis is primarily based on Ohm's law, which states that the voltage difference across a resistor is equal to the product of the current flow and the resistance[15]:

$$\Delta V = IR \tag{2.1}$$

Current (I) is related to blood flow (CO), where 1 A (1 Coulomb/s) is analogous to 1 L/s. From Kirchhoff's loop law, we know that the sum of all the voltages around a loop in the circuit should be zero, and we also consider Kirchhoff's junction law; when a wire (analogous to a vein) splits, the amount of current going in to the junction must be the same as the amount leaving the junction[15]:

$$I_{total} = I_1 + I_2 \tag{2.2}$$

Resistance (R) in a circuit is analogous to vascular resistance (PVR and SVR) in the circulatory system, with 1 Ω (1 V/A) analogous to 1 mmHg s/L. The potential difference (ΔV) is analogous to blood pressure, where 1 V is analogous to 1 mmHg. Pulmonary vascular compliance (PVC) is represented by capacitance (C), with 1 F (1 Coulomb/V) analogous to 1 L/

mmHg. The magnitude of the capacitive reactance is calculated using the angular frequency ω = 2π*f*:

$$X_C = \frac{1}{\omega C} \tag{2.3}$$

It is important to note that 1 F is actually a very large amount of capacitance, so the value of C should be very small[15].

The heart's pumping action can be modeled as a sine wave. This means that the currents (blood flows) going through each resistor and the voltage (pressure) drops across the resistors should be in phase with each other, but for the capacitor, the currents and voltage drops should be 2π radians out of phase, with the current being ahead of the voltage drop[15].

When we have a resistor and capacitor wired in parallel, we combine the resistance and capacitance into one total impedance[15][16] (the pulmonary vascular impedance—PVZ), resulting in:

$$Z = \frac{1}{\frac{1}{R} + j\omega C} \tag{2.4}$$

Thus, Ohm's law to calculate the voltage change across a parallel resistor and capacitor is:

$$\Delta V = IZ = \frac{I}{\frac{1}{R} + j\omega C} \tag{2.5}$$

2.5 Reference Values

Table 2.1 shows the normal reference values for hemodynamic parameters used in this thesis. Values from [17] were measured in neonates; those from [18] and [19] were measured in

children (3 months to 18 years). The range for PVR shown in the table was measured in children diagnosed with pulmonary hypertension; a normal healthy range in children would be less than 3 Wood units m^2 BSA [7].

Table 2.1: Hemodynamic Reference Values

	Range	Mean	Conversion	Converted Mean
Heart Rate (bpm) [17]	137.6 - 160.4	149	/60	2.483 bps
Cardiac Output (L/min) [17]	0.20 - 0.26	0.23	/60	$3.833*10^{-3}$ L/s
Systemic Vascular Resistance (dyn s/cm^5) [17]	10271 - 17241	13756	/80 * 60	10320 mmHg s/L
Pulmonary Vascular Resistance (mmHg min/L) [18]	3.5 - 18.4	5.4	* 60	324 mmHg s/L
Pulmonary Arterial Compliance (ml/mmHg/m^2 BSA) [19]	0.75 - 2.97	1.53	/1000 * BSA	$2.601*10^{-4}$ L/ mmHg (calculated with mean BSA)
Body Surface Area (m^2) [17]	0.10 - 0.26	0.17		

3 Methodology

3.1 Electrical Circuit Analogy and Simulation

The circulatory system is modeled as an electrical circuit with the following components: two sinusoidal voltage sources representing the left and right ventricles, two resistors representing the systemic and pulmonary vascular resistances, and one capacitor representing the pulmonary compliance. Figure 3.1 shows the model created using iCircuit (Krueger Systems, Inc., https://icircuitapp.com/). All files used for these simulations are available at: https://github.com/mchapados/heart-simulation.

AC Sources / Heart Ventricles

The function of each ventricle is modeled as a sine wave, with frequency (Hz) corresponding to the heart rate (beats per second). For the iCircuit model, source amplitude (V) is calculated from the total resistance and current (cardiac output) using Ohm's law (given in Section 2.4).

Resistors and Capacitor / Pulmonary Vascular Resistance and Compliance

Electrical resistance (Ω) corresponds directly to vascular resistance (mmHg s/L), and the capacitance value (F) relates to the pulmonary arterial compliance (L/mmHg).

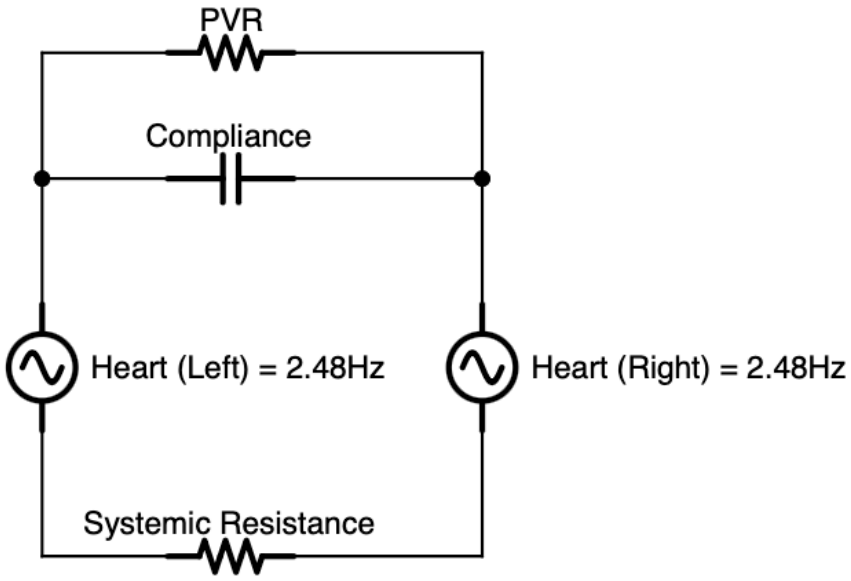

Figure 3.1: Circuit diagram created using iCircuit

This model was replicated using Python to validate the results and better understand the calculations. All of the input parameters are the same, except the source amplitude uses the peak cardiac output directly. The Python model uses three main functions calculated at each time step: the total blood flow, the systemic circulation, and the pulmonary circulation. The detailed script is provided in Appendix A.1.

Total Blood Flow

This function replicates the AC sources used in the iCircuit model. The total blood flow (CO) is given by Equation 3.1 and illustrated in the code snippet below:

$$CO(t) = CO_{peak} \cdot sin(\omega t) \tag{3.1}$$

Corresponding Python code:

```
def blood_flow(t: float) -> float:
    return cardiac_output * np.sin(angular_freq * t)
```

Systemic Circulation

This function, shown below, calculates the blood flow and pressure change from the left ventricle across the systemic vascular resistance. The blood flow is the same as given above. The pressure change is calculated by Equation 3.2:

$$\Delta P_s(t) = CO(t) \cdot R_s \tag{3.2}$$

Corresponding Python code:

```
def systemic_circulation(t: float) -> Tuple[float, float]:

    blood_flow_total  = blood_flow(t)
    pressure_change   = blood_flow_total * systemic_resistance
    return blood_flow_total, pressure_change
```

Pulmonary Circulation

Because the right ventricle is pumping blood through the lungs circulation and the capacitor in parallel, the total blood flow, which is inversely proportional to the systemic circulation, is split between them. The pressure change across each is given by Equation 3.3:

$$\Delta P_p(t) = \frac{-CO(t)}{\frac{1}{R_p} + j\omega C_p} \tag{3.3}$$

Since blood flow can be calculated from the pressure and resistance, and we know that the pressure change across both components is the same, we can use this to determine the blood flow across each separate component. This is given by Equations 3.4 and 3.5:

$$CO(t)_{PVR} = -\frac{P_p}{R_p} \cdot sin(\omega t) \tag{3.4}$$

$$CO(t)_C = -(P_p \omega C_p) \cdot sin(\omega t + \frac{\pi}{2}) \tag{3.5}$$

The code block below shows the complete pulmonary circulation function.

```
def pulmonary_circulation(t: float) -> Tuple[float, float, float]:

    pressure_change   = -blood_flow(t) / ((1/pulmonary_resistance) +
(angular_freq * compliance))
    peak_pressure     = cardiac_output / ((1/pulmonary_resistance) +
(angular_freq * compliance))
    peak_blood_flow_R = peak_pressure / pulmonary_resistance
    blood_flow_R      = -peak_blood_flow_R * np.sin(angular_freq * t)
    peak_blood_flow_C = peak_pressure * angular_freq * compliance
    blood_flow_C      = -peak_blood_flow_C * np.sin(angular_freq * t +
np.pi/2)
    return blood_flow_R, blood_flow_C, pressure_change
```

Simulation and Analysis

To run simulations on the 0D model, all parameters other than the PVR were fixed to the averages given in Table 2.1. The PVR was then set to each test value (both normal and higher-than-normal values were tested), and output data were obtained from each model using iCircuit's simulation engine and the Python code. Both models were then compared and analyzed using Python and the Matplotlib library. Code for these analyses is provided in Appendix A.2.

For most simulations, the blood flow was fixed and the primary variable being observed was the change in pressure. To gain a more complete understanding of the model, one additional set of simulations was done using a fixed value of 20 mmHg for the input pressure, with the primary variable then being the blood flow.

3.2 CFD Flow Simulation

The simplified 2D heart geometry was created in Ansys SpaceClaim, then meshed (Figure 3.2) in Ansys Mechanical. Simulations were then run using Ansys Fluent 2024 R2 (ANSYS, Inc).

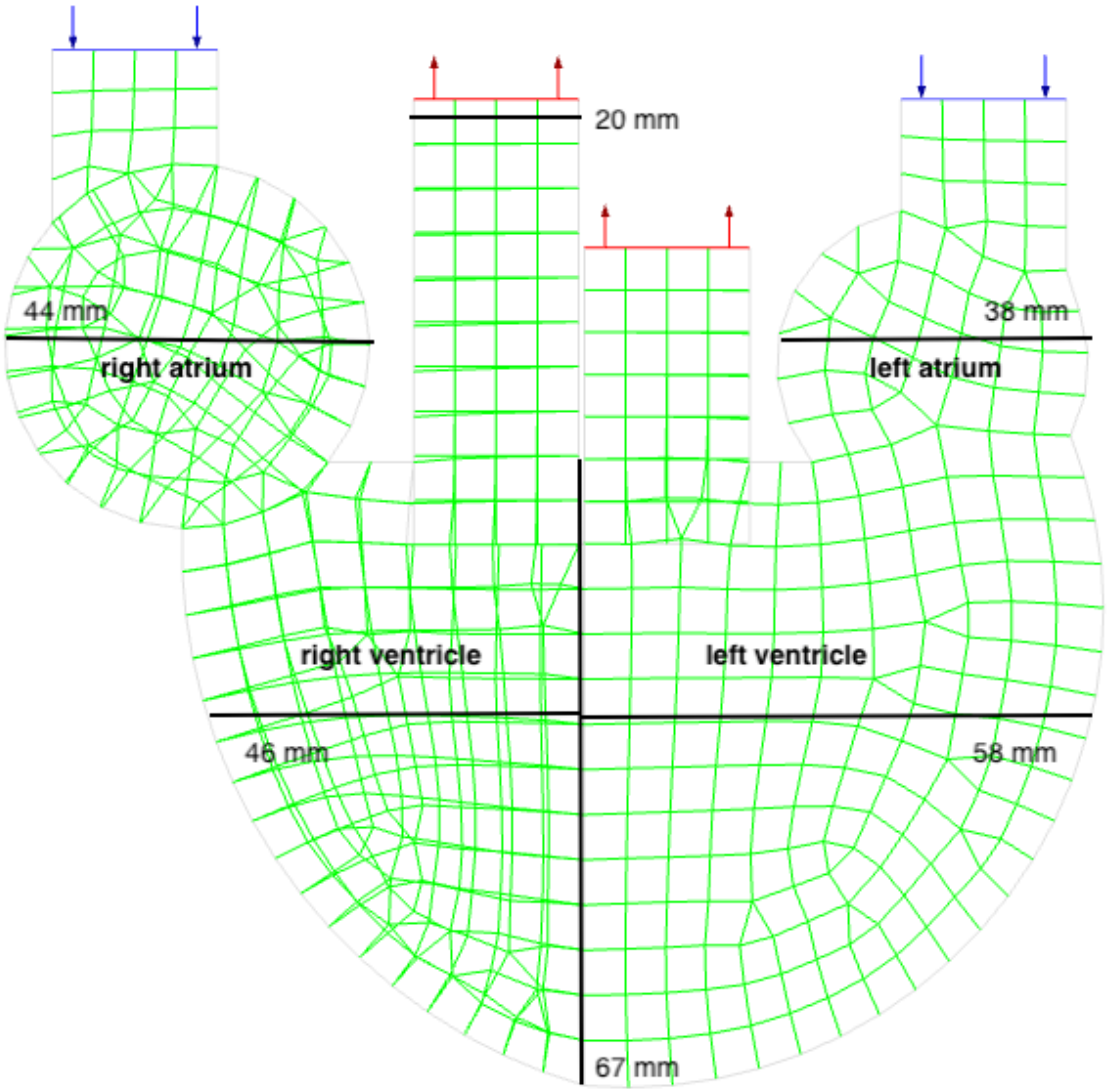

Figure 3.2: 2D model mesh of the circulatory loops

General Settings

To capture the complexities of the flow observed in cardiovascular fluid mechanics, the SST (Shear Stress Transport) k-ω turbulence model was employed. This turbulence model combines the near-wall accuracy of the standard k-ω model with the free-stream robustness of the k-ε model, ensuring accurate predictions in regions characterized by high velocity gradients, turbulence, and flow separation, which are common conditions in cardiovascular flows[20].

These settings were chosen to ensure a robust and reliable representation of the flow physics relevant to the cardiovascular system.

Fluid Settings

Blood was modeled as a Newtonian fluid with a density of 1024 kg/m^3 and viscosity of 0.0035 kg/m s. Ansys Fluent applies these fluid properties uniformly over an assumed unit depth of 1 m for computational convenience, which is a common approach in 2D CFD modeling.

Inlet and Outlet Settings

Both inlets are mass-flow inlets, with a mass flow rate given by Equation 3.6, simulating the heart contractions as a sine function:

$$\text{mass\_inflow}(t) = CO \cdot 1024 \cdot \frac{sin(\omega t) + 1}{2} \qquad (3.6)$$

The simulation was also run using velocity inlets, with velocity given by Equation 3.7:

$$\text{velocity}(t) = \frac{CO}{A} \cdot \frac{sin(\omega t) + 1}{2} \qquad (3.7)$$

Both outlets are pressure outlets with initial gauge pressure specified by Equation 3.8 (resistance (R) is multiplied by 133.3224 to convert from mmHg to Pa, which is the standard unit used by Ansys Fluent):

$$\text{pressure}(t) = CO \cdot R \cdot 133.3224 \cdot \frac{sin(\omega t) + 1}{2} \qquad (3.8)$$

These simulations used a cardiac output (CO) of 0.23 L/min (a typical flow rate for premature babies, as given in Table 2.1) and a heart rate of 150 bpm. Area (A) for the velocity calculation was determined using the width of the inlets (0.02 m).

Resistance values were taken from Table 2.1. The periodic component in all of these equations is adjusted (by adding 1 then dividing by 2) to give a range between 0 and 1. All other settings were kept to their default values.

4 Results

4.1 Electrical Circuit Simulation

Simulations were run with a range of PVR between 1 and 20 WU, incrementing by 1 WU, and 0.2 WU. Four specific values of PVR within this range were selected to look at the simulation more closely: 0.2 WU (below normal range), 2 WU (within normal range), 5 WU (slightly above normal range), and 20 WU (far above normal range).

Blood Flow

Figure 4.1 shows the profiles of blood flow over time across each resistor and the capacitor for each of the four selected PVR values. The systemic blood flow remains the same in every simulation. In the pulmonary circulation, as PVR increases, the blood flow through the resistor decreases, and the blood flow through the capacitor (compliance) increases. We also observe that the total pulmonary and systemic blood flows are inversely proportional to each other.

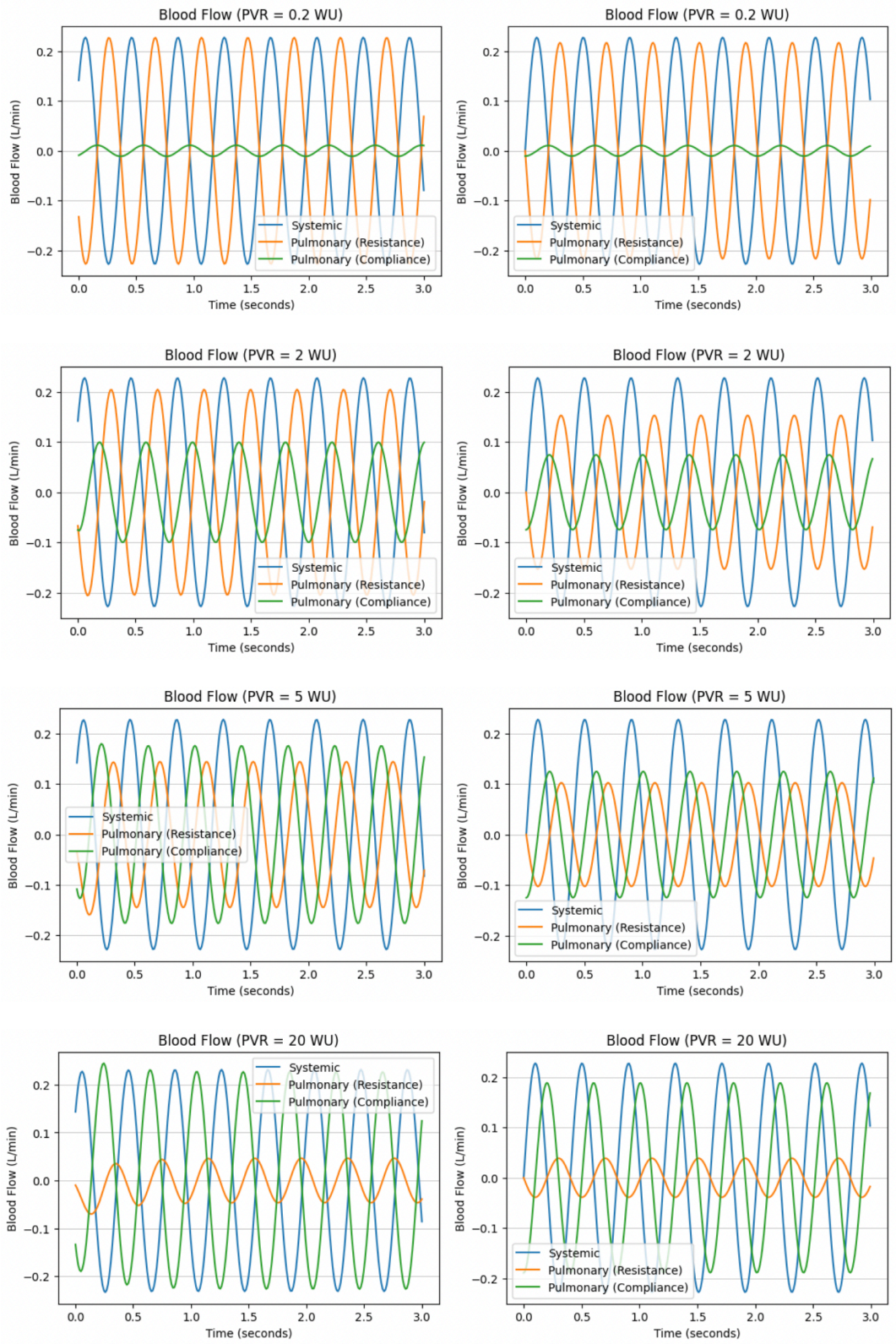

Figure 4.1: Blood flow plots from iCircuit simulation (left) and Python simulation (right) for comparison

Although the systemic blood flow peaks at the same value (0.23 L/min) in both models, there is a discrepancy between the models in the values for the pulmonary circulation. This is due to the phase differences. As shown in Figure 4.2, in the Python model, the phase differences between each component remain constant no matter the PVR. However, in the iCircuit model, only the phase difference between the two components of the pulmonary circulation is constant, while the phase difference between the pulmonary and systemic resistors increases with PVR. Because the total pulmonary and systemic blood flow must be the exact inverse of each other at each point in time, this leads to a difference in the Python model. Thus the iCircuit model is more physiologically accurate; this increase in phase difference is consistent with clinical observations of pulmonary hypertension, where elevated resistance and reduced compliance cause blood flow in the pulmonary circulation to lag behind the systemic circulation.

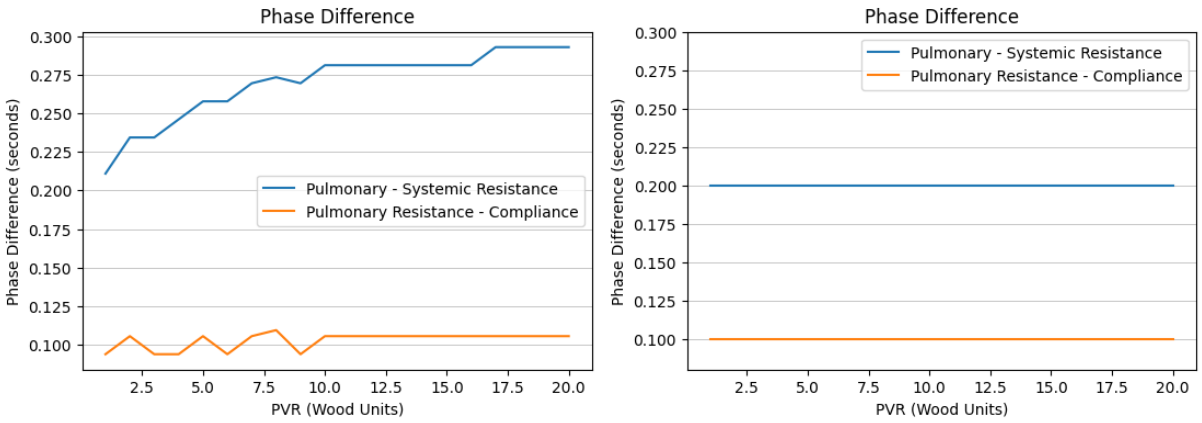

Figure 4.2: Plots showing the phase difference based on PVR from iCircuit simulation (left) and Python simulation (right)

Figure 4.3 shows that we also observe a similar increase or decrease in the phase difference between the pulmonary and systemic resistors when changing the compliance in the iCircuit model.

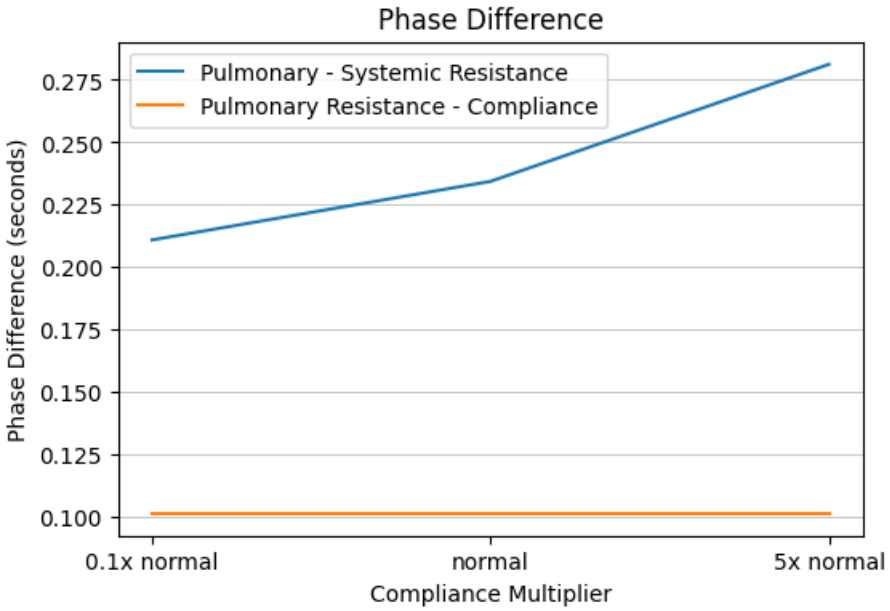

Figure 4.3: Plot showing the phase difference based on factors of the normal mean compliance from iCircuit simulation

Pressure Change

Like the blood flow, the systemic pressure change is not dependant on PVR, as shown in Figure 4.4. In the pulmonary circulation, while the blood flow through the resistor decreases with higher PVR, the pressure change increases. We again observe a slight difference in the pressure change magnitudes between the two models, with the Python model being an average of 18.8% lower, which can again be attributed to the increasing phase that is only shown in the iCircuit model, because the pressure change is calculated from the blood flow which is fixed.

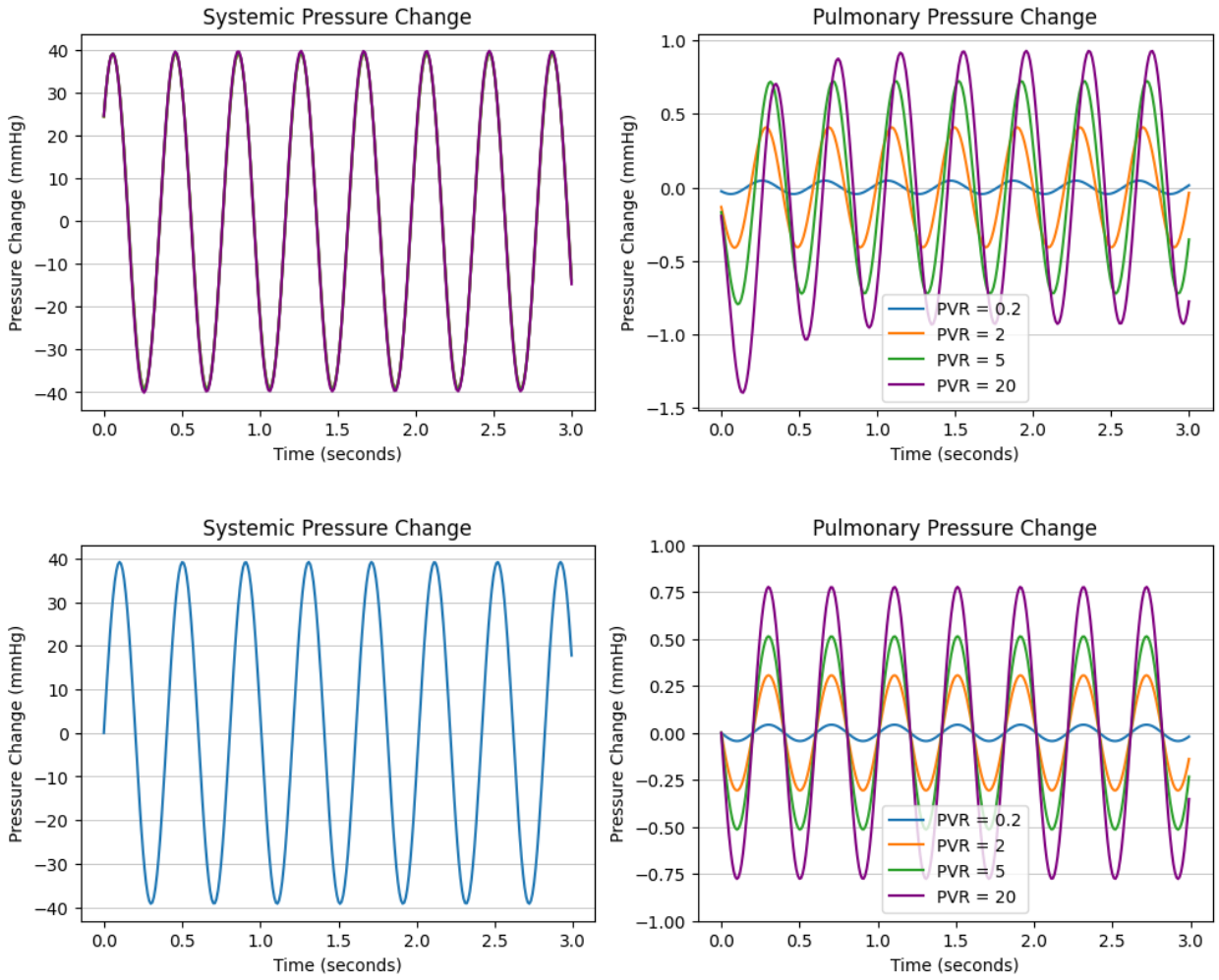

Figure 4.4: Pressure change plots from iCircuit simulation (top) and Python simulation (bottom) for comparison

Peak Blood Flow and Pressure Change

Figure 4.5 shows how the peak blood flow and pressure change with increasing PVR. The peak systemic blood flow remains constant, again suggesting that the systemic circulation is not impacted by changes in PVR, and is the same in both models.

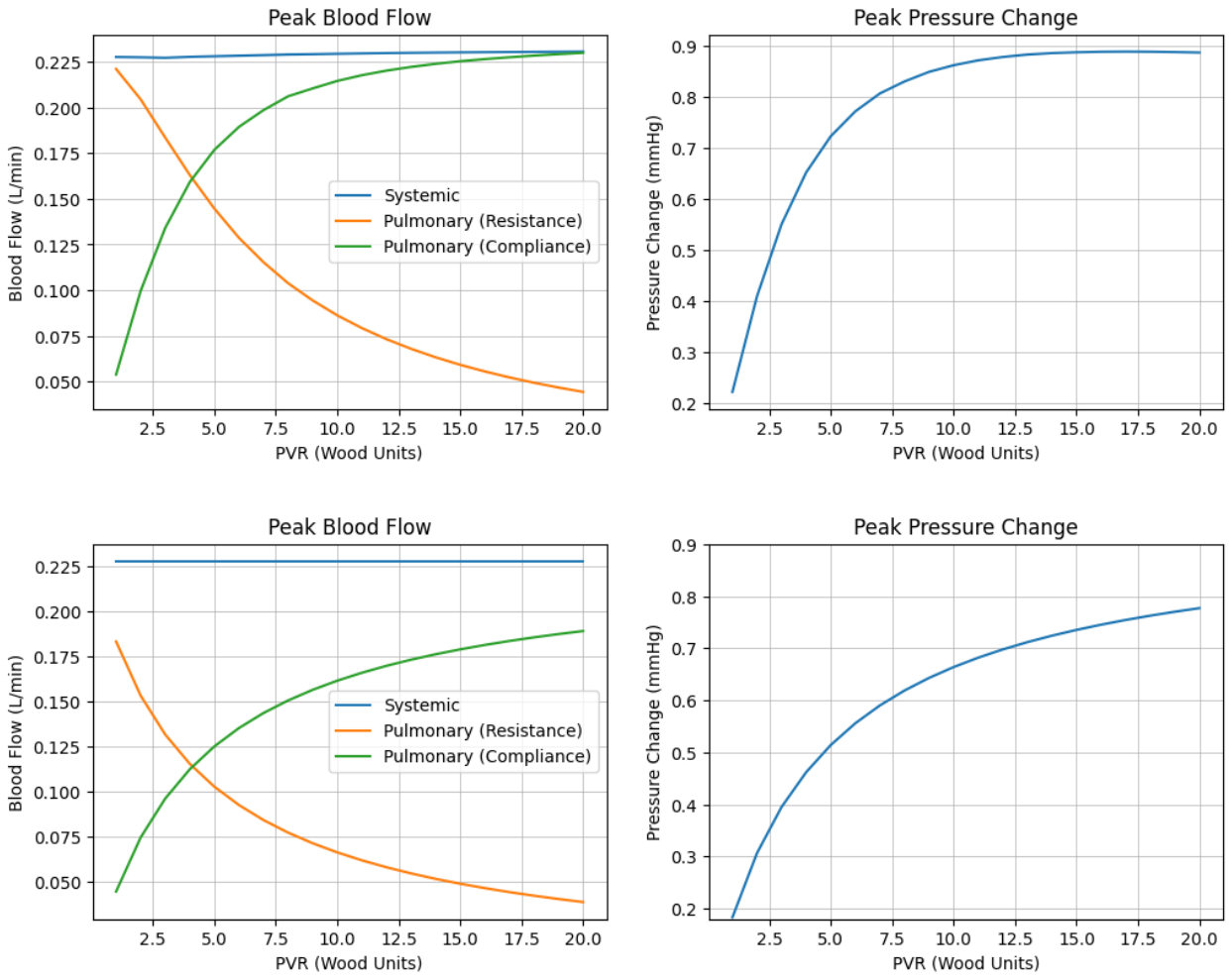

Figure 4.5: Peak blood flow and pulmonary pressure change plots from iCircuit simulation (top) and Python simulation (bottom) for comparison

Although the pulmonary circulation values differ between the two models, we observe in both blood flow plots that the flow through the compliance surpasses that through the resistance with values of PVR higher than 4 WU. Pulmonary blood flow through the resistance exhibits a negative correlation with PVR, with an increase in PVR resulting in a steep decline in blood flow initially, which then flattens at higher PVR values. Conversely, blood flow through the compliance demonstrates a positive correlation with PVR, where blood flow increases rapidly up to a PVR of about 7.5 WU but the rate of increase slows at higher PVR values.

Similarly, the relationship between PVR and peak pulmonary pressure change is characterized by an initial rapid increase followed by a gradual leveling off. At lower PVR values (up to 7.5 WU), there is a significant increase in pressure change, indicating a strong positive correlation. However, as PVR increases further, the rate of pressure change diminishes, and beyond approximately 15 Wood Units in the iCircuit model, the pressure change remains at around 0.9 mmHg.

Fixed Pressure

Figures 4.6 and 4.7 show how the model behaves when the input pressure (the right ventricle source amplitude) is fixed at 20 mmHg, rather than being calculated from the cardiac output and total pulmonary resistance. These simulations were only done with the iCircuit model for further validation of the model's accuracy.

While the observed values differ, we see that the model behaviour is similar to that of the simulations where the blood flow is fixed and the pressure is calculated.

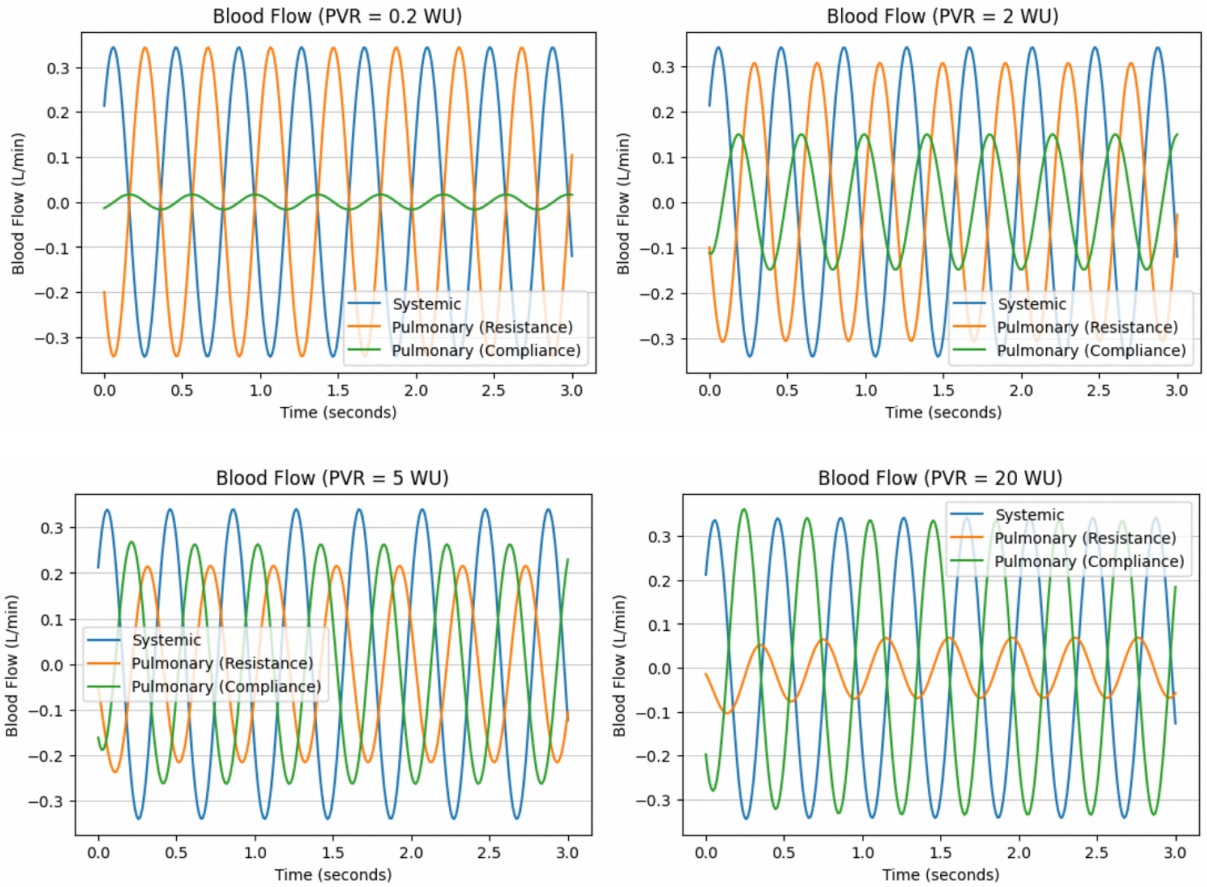

Figure 4.6: Blood flow plots from iCircuit simulation with pulmonary pressure fixed to 20 mmHg

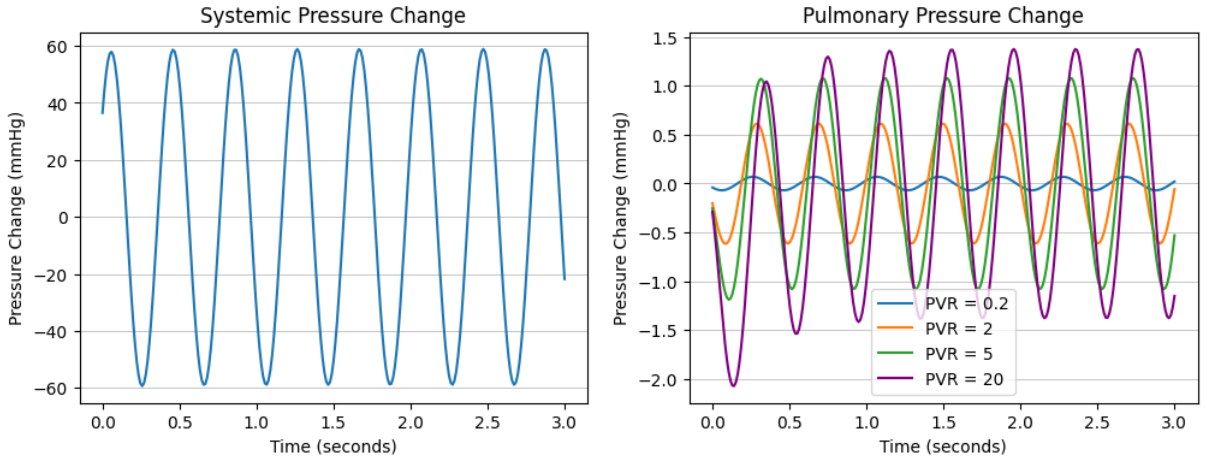

Figure 4.7: Pressure change plots from iCircuit simulation with pulmonary pressure fixed to 20 mmHg

4.2 CFD Flow Simulation

All CFD results were identical whether the simulation used velocity inlets or mass-flow inlets.

Mass Flow Rate

Figure 4.8 shows the mass flow rate throughout the simulation, measured at the inlets. This is synonymous with the blood flow, so a flow rate of 0.0038 kg/s (cardiac output of 0.23 L/min) is expected.

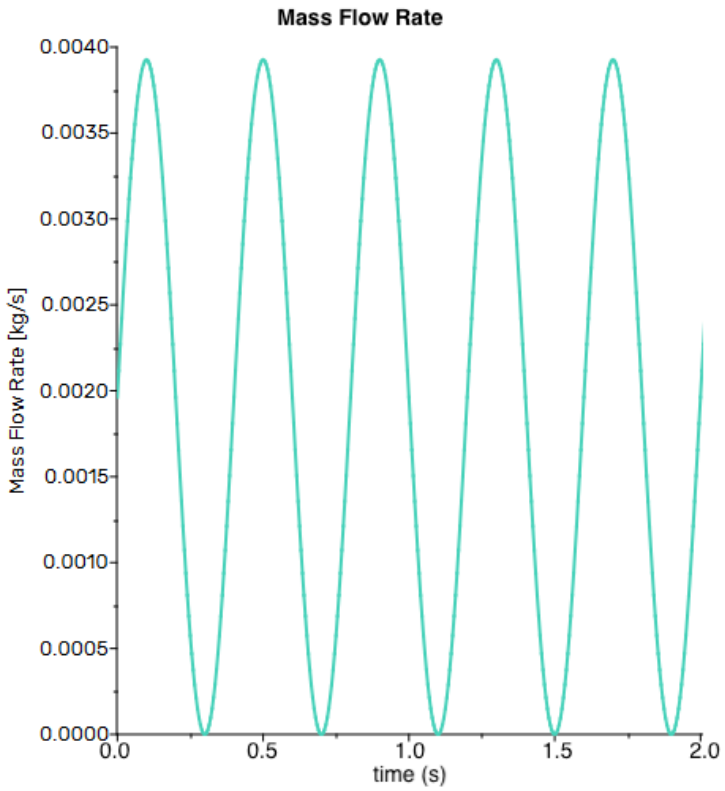

Figure 4.8: Plot of inlet mass flow rate, showing peak flow of 0.0038 kg/s (equivalent to blood flow in L/s)

Pressure

Inlet and outlet pressure for each of the pulmonary and systemic circulations is shown in Figure 4.9. In both plots, we observe identical pressures at each inlet and its corresponding outlet. Using Ohm's Law, a cardiac output of 0.23 L/min, pulmonary pressure of 1.242 mmHg, and systemic pressure of 39.55 mmHg gives a PVR of 5.4 WU and SVR of 171.95 WU. This is consistent with the average reference values shown in Table 2.1.

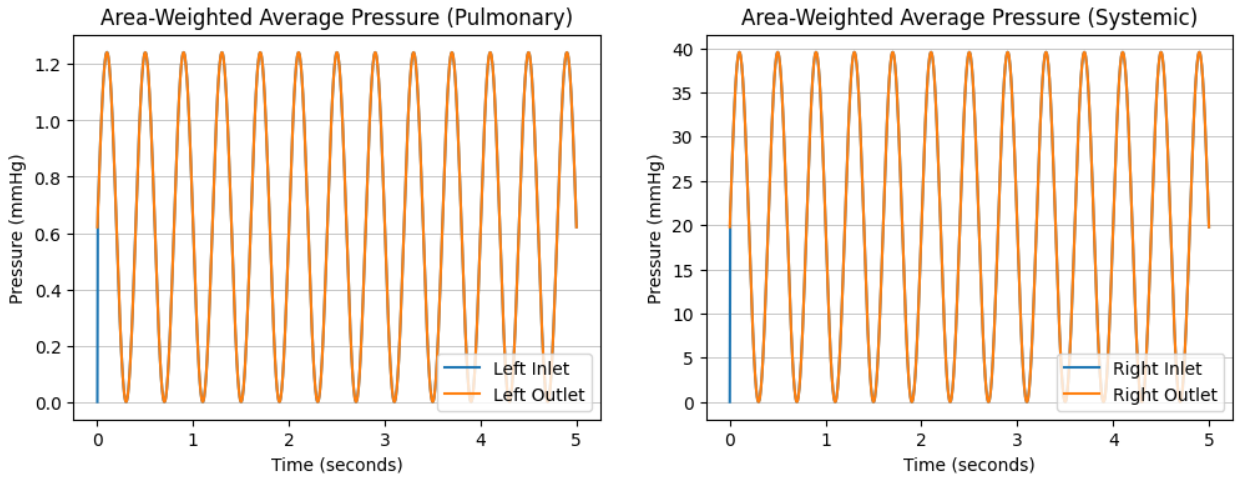

Figure 4.9: Area-weighted average pressure plots during the simulation, measured at each inlet and each outlet. The blue and orange curves are identical and are superimposed.

Contours of static pressure within the model are shown in Figure 4.10. Here we observe that the pressure is significantly higher in the right chambers (which receive blood from the systemic circulation and pump blood into the lungs) than in the left chambers (which receive blood from the pulmonary circulation). On the right side of the heart, we also observe that the pressure is higher near the inlet and outlet, and lower within the chambers. This is expected on the left side as well, but it is difficult to see due to the lower overall pressure.

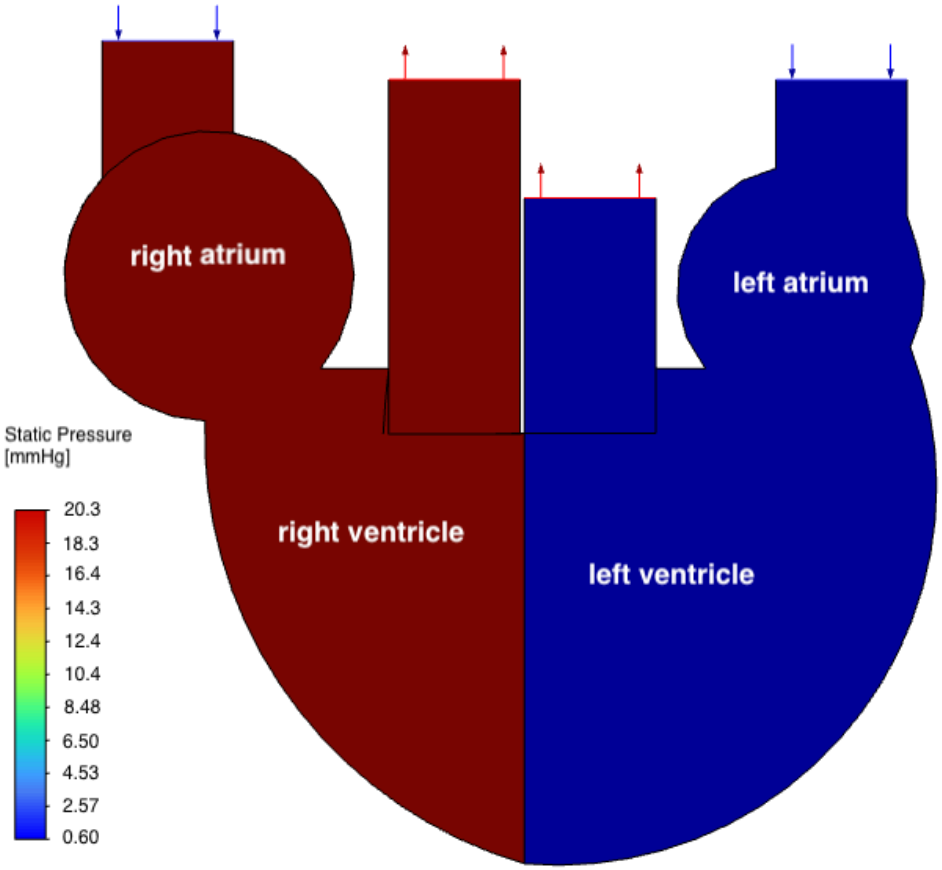

Figure 4.10: Contours showing static pressure within the heart model

Velocity

Figure 4.11 shows the velocity vectors indicating the direction of blood flow within the heart model. The flow is clearly pressure-driven, with velocity increasing near the outlets. There are regions of significant flow complexity and turbulence, primarily due to simplifications inherent in the geometry and boundary conditions, such as the absence of heart valves and dynamic chamber wall movements. While these complexities may exaggerate turbulent phenomena and recirculation compared to real physiological flows, the model successfully demonstrates directional flow patterns from the inlets to the outlets.

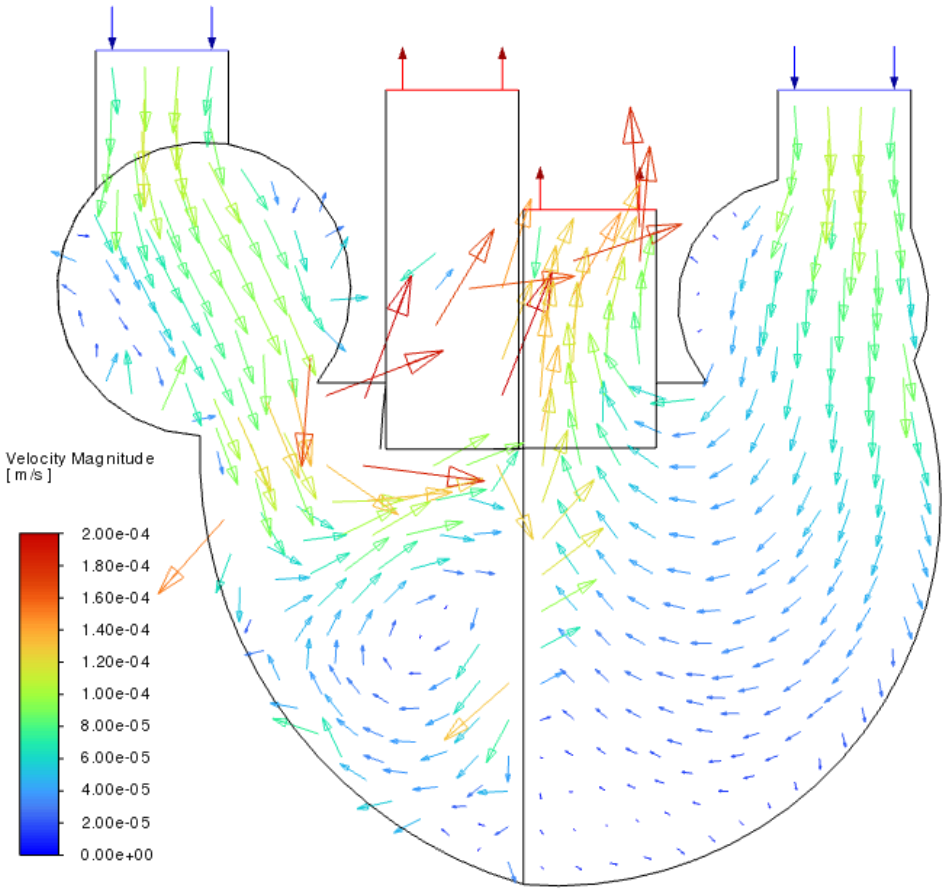

Figure 4.11: Velocity vectors showing magnitude and direction of blood flow through the simulation

5 Discussion

The main focus of this thesis was to develop a simplified 0D electrical circuit model to simulate the circulatory system and analyze the effects of pulmonary hypertension (PH) in premature infants—a population with distinct physiology, including smaller heart size, smaller vessel sizes, lower compliance, and unique hemodynamic challenges compared to adults. Due to the limitations of the 0D model in capturing spatial variations, we also created a 2D CFD model to study localized pressure and velocity changes.

The 0D model was tested across a range of pulmonary vascular resistance (PVR) values, keeping all other parameters at normal levels. Results showed no significant impact on the systemic circulation but highlighted clear changes in the pulmonary circulation:

- Increased PVR led to higher pressure changes and a noticeable phase difference between pulmonary and systemic blood flow.
- Pulmonary blood flow through the resistor decreased, while flow through the capacitor increased, consistent with the inverse relationship between PVR and compliance (PVC).

The 2D CFD model was tested with a PVR of 5.4 WU, simulating early-stage PH. Results for inlet and outlet pressures and mass flow rate closely aligned with the 0D model, providing additional confidence in the findings. Both models showed minimal noise, with the Python-based simulations producing clean deterministic results and iCircuit simulations stabilizing quickly after initial transients. Artificial white noise could have been added to more realistically represent the physiology but is not needed for accurate analysis.

5.1 Comparison with Previous Studies

In our circuit model, the ventricles were represented as AC sources without diodes to mimic the function of the heart valves. This simplification introduced a backflow effect, as shown by the negative flow values, which are not physiologically accurate. However, this does not affect the analysis or the trends observed. Similarly, the 2D geometry does not include valves, but backflow appears minimal in the velocity vectors (Figure 4.11), likely due to the impact of gravity in the simplified setup. In the clinical setting, especially for supine premature infants, gravity plays a relatively minor role in intracardiac flow dynamics.

The positive correlation between PVR and pulmonary pressure aligns with the literature, and is expected due to Ohm's law ($\Delta V = IR$). As resistance (R) increases with fixed flow (I), the pressure difference (ΔV) increases accordingly. However, unlike real physiology, the total flow remains constant in the circuit due to Kirchhoff's loop law. Because the resistor and the capacitor in the pulmonary loop are wired in parallel, the total current will be divided between the two. So instead of an overall reduction in pulmonary blood flow, we observed a redistribution: flow through the capacitor increased, while flow through the resistor decreased.

Additionally, most computational models of PH are designed for adult patients, where the pulmonary vasculature is larger, more mature, and subject to different pathological processes. In contrast, premature infants have underdeveloped lungs and vessels, which significantly alters PVC and its relationship with PVR. Our study highlights these distinctions, particularly the steep compliance drop observed at lower PVR values, which may be more clinically relevant in this population.

5.2 Clinical and Physiological Relevance

The results support the established inverse relationship between PVR and PVC. When PVR is low, arterial compliance is very high, but as PVR increases, compliance drops very rapidly. Our model shows this effect in Figure 4.5, where we see the same inverse hyperbolic relationship between PVR and peak blood flow through the pulmonary resistor and the opposite through the capacitor. With PVR at healthy levels, there is more blood flowing through the resistor (representing the pulmonary arteries) than the capacitor. However, as PVR increases beyond 4 WU—indicative of early-stage PH—the flow through the capacitor (compliance) becomes dominant. This reflects how vessel stiffening forces the system to accommodate flow differently. We also observe that in the early stages of pulmonary hypertension, with PVR up to about 7.5 WU, the change in compliance is significant, but as the disease progresses, the difference becomes smaller and starts to level off at around 12 WU of PVR.

The increasing phase difference between pulmonary and systemic blood flow as PVR rises is another key finding. Under normal conditions (PVR $\leq$ 2 WU), the flows are tightly coupled and in phase, reflecting the heart's synchronized function. However, as PVR increases, and similarly when PVR is fixed and the compliance is changed instead, the pulmonary circulation lags behind. This behaviour highlights the increased workload on the right ventricle as it struggles to pump blood into the stiffened pulmonary vasculature. As the severity of pulmonary hypertension increases and PVR gets even higher (>10 WU), this lag becomes more pronounced, aligning with clinical observations of right ventricular strain and eventual right heart failure if left untreated.

The 2D model further supports these findings, showing increases in pressure within the right heart chambers (Figure 4.10). This reinforces the clinical need for early detection and intervention to prevent progression to severe PH and eventual death.

This is particularly interesting when considering premature infants, as their right heart is not yet fully developed. Unlike adults, whose hearts may adapt to chronic PH over time, premature infants are far more vulnerable to acute increases in PVZ and subsequent right ventricular strain. This distinction is clinically significant because the early compliance drop observed in our model could help to identify PH in its initial phases, enabling intervention before irreversible right heart damage occurs.

5.3 Strengths of the Models

The main strength of these models is their simplicity. Prior studies have used highly complex models with many components (such as the example shown in Figure 2.3), which can be more accurate, but are not always so, and increased complexity comes with corresponding difficulty in determining correct model parameters. Our 0D circuit model consists of only five components and a relatively small set of parameters. Despite this simplicity, the model provides meaningful insights into PVR's effects on hemodynamics. The 2D CFD model complements this by offering additional details, while maintaining computational efficiency.

The simplicity of the 0D model also makes it particularly relevant for premature infants, where parameter estimation is challenging due to the scarcity of clinical data and the small size of the pulmonary vasculature. Our streamlined approach may be better suited to representing

neonatal physiology than the more complex models that are based on adult physiology. This model could be integrated into clinical decision-support tools to predict circulatory changes in real time based on patient-specific parameters.

5.4 Limitations and Future Directions

These models do have limitations. First, we assumed that all variables other than the PVR would be average values for a healthy newborn, which may not hold true in real patients, especially those who are born many weeks premature and may have co-morbidities. In reality, pulmonary blood flow often decreases with increased PVZ, even though the heart attempts to compensate to maintain normal levels of flow.

The 2D CFD model is also highly simplified, with approximate geometries and rigid vessel walls. A more detailed model, incorporating dynamic wall motion and more realistic heart chamber shapes, could provide greater physiological accuracy.

Lastly, although the model parameters were sourced from measurements taken in real patients, and the results align with trends seen in the literature, the models were not validated against real patient data, which limits their clinical applicability at this stage.

Another limitation is the lack of directly comparable studies. While our results align qualitatively with adult models, further research is needed to validate the specific hemodynamic responses observed in premature infants.

Future work could address these limitations by comparing our model results to clinical data from premature infants to refine the parameters and validate the findings. Further, simulating the

effects of common treatments such as inhaled nitric oxide[1], or adapting more complete adult models to newborns could also yield interesting results.

6 Conclusion

This thesis presents a computational investigation into the hemodynamic impacts of pulmonary hypertension (PH) in premature infants using two complementary modeling approaches: a 0D electrical circuit model and a 2D CFD model. The 0D model offers a simplified, system-wide view of the circulatory system, allowing for efficient analysis of PVZ and its effects on pulmonary and systemic blood flow. The 2D model provides localized insights into pressure and velocity distributions, complementing the 0D results and validating trends observed in the simulations. Together, these models demonstrate the relationship between PVR and PVC, and highlight the dynamic changes in flow and pressure as PH progresses.

The results of this study emphasize the significant physiological differences between PH in premature infants and in adults, with compliance changes occurring at lower PVR thresholds in neonates. These findings reinforce the need for early detection and intervention, as even moderate increases in PVR can cause substantial hemodynamic changes, leading to increased right ventricular workload, eventual right heart failure, and death. While the models presented are simplified, they provide valuable insights and a foundation for future work, including incorporating patient-specific data. Ultimately, this research contributes to a better understanding of the circulatory dynamics in premature infants with PH, offering tools to improve clinical prediction and treatment strategies.

References

[1] S. H. Abman, “Characterization of Early Pulmonary Hypertension in Infants Born Preterm: A Key Step Toward Improving Outcomes,” *The Journal of Pediatrics*, vol. 251, pp. 44–46, Dec. 2022, doi: 10.1016/j.jpeds.2022.09.006.

[2] T. Schindler, L. Koller-Smith, K. Lui, B. Bajuk, and S. Bolisetty, New South Wales and Australian Capital Territory Neonatal Intensive Care Units’ Data Collection, “Causes of death in very preterm infants cared for in neonatal intensive care units: a population-based retrospective cohort study,” *BMC Pediatr*, vol. 17, no. 1, p. 59, Dec. 2017, doi: 10.1186/s12887-017-0810-3.

[3] S. Vyas-Read, U. Kanaan, P. Shankar, J. Stremming, C. Travers, D. P. Carlton, and A. Fitzpatrick, “Early characteristics of infants with pulmonary hypertension in a referral neonatal intensive care unit,” *BMC Pediatr*, vol. 17, no. 1, p. 163, Dec. 2017, doi: 10.1186/s12887-017-0910-0.

[4] G. Simonneau, D. Montani, D. S. Celermajer, C. P. Denton, M. A. Gatzoulis, M. Krowka, P. G. Williams, and R. Souza, “Haemodynamic definitions and updated clinical classification of pulmonary hypertension,” *Eur Respir J*, vol. 53, no. 1, p. 1801913, Jan. 2019, doi: 10.1183/13993003.01913-2018.

[5] C. De Lazzari, S. Marconi, M. Capoccia, S. Papa, R. Badagliacca, and C. D. Vizza, “A 0-D model to predict the relationship between resistance and compliance in pulmonary arterial hypertension,” in *The European Modeling and Simulation Symposium*, Cal-Tek srl, Sep. 2019, pp. 23–28. doi: 10.46354/i3m.2019.emss.004.

[6] S. Acosta, C. Puelz, B. Rivière, D. J. Penny, K. M. Brady, and C. G. Rusin, “Cardiovascular mechanics in the early stages of pulmonary hypertension: a computational study,” *Biomech Model Mechanobiol*, vol. 16, no. 6, pp. 2093–2112, Dec. 2017, doi: 10.1007/s10237-017-0940-4.

[7] M. J. del Cerro, S. Abman, G. Diaz, A. H. Freudenthal, F. Freudenthal, S. Harikrishnan, S. G. Haworth, D. Ivy, A. A. Lopes, J. U. Raj, J. Sandoval, K. Stenmark, and I. Adatia, “A Consensus Approach to the Classification of Pediatric Pulmonary Hypertensive Vascular Disease: Report from the PVRI Pediatric Taskforce, Panama 2011,” *Pulm. circ.*, vol. 1, no. 2, pp. 286–298, Apr. 2011, doi: 10.4103/2045-8932.83456.

[8] B. Mathew and S. Lakshminrusimha, “Persistent Pulmonary Hypertension in the Newborn,” *Children*, vol. 4, no. 8, p. 63, Jul. 2017, doi: 10.3390/children4080063.

[9] Y. Shi, P. Lawford, and R. Hose, “Review of Zero-D and 1-D Models of Blood Flow in the Cardiovascular System,” *BioMed Eng OnLine*, vol. 10, no. 1, p. 33, Dec. 2011, doi: 10.1186/1475-925X-10-33.

[10] J. A. Goodwin, W. L. van Meurs, C. D. Sá Couto, J. E. W. Beneken, and S. A. Graves, “A Model for Educational Simulation of Infant Cardiovascular Physiology,” *Anesthesia & Analgesia*, pp. 1655–1664, Dec. 2004, doi: 10.1213/01.ANE.0000134797.52793.AF.

[11] M. W. Ni, R. O. Prather, G. Rodriguez, R. Quinn, E. Divo, M. Fogel, A. J. Kassab, and W. M. DeCampli, “Computational Investigation of a Self-Powered Fontan Circulation,” *Cardiovasc Eng Tech*, vol. 9, no. 2, pp. 202–216, Jun. 2018, doi: 10.1007/s13239-018-0342-5.

[12] W. Yang, F. P. Chan, V. M. Reddy, A. L. Marsden, and J. A. Feinstein, “Flow simulations and validation for the first cohort of patients undergoing the Y-graft Fontan procedure,” *The Journal of Thoracic and Cardiovascular Surgery*, vol. 149, no. 1, pp. 247–255, Jan. 2015, doi: 10.1016/j.jtcvs.2014.08.069.

[13] P. Frieberg, P. Sjöberg, J. Revstedt, E. Heiberg, P. Liuba, and M. Carlsson, “Simulation of aortopulmonary collateral flow in Fontan patients for use in prediction of interventional outcomes,” *Clin Physio Funct Imaging*, vol. 38, no. 4, pp. 622–629, Jul. 2018, doi: 10.1111/cpf.12457.

[14] F. Marcinno, A. Zingaro, I. Fumagalli, L. Dede, and C. Vergara, “A Computational Study of Blood Flow Dynamics in the Pulmonary Arteries,” *Vietnam J. Math.*, vol. 51, no. 1, pp. 127–149, Jan. 2023, doi: 10.1007/s10013-022-00595-y.

[15] R. D. Knight, *Physics for Scientists and Engineers*, 4th ed. Boston, MA, USA: Pearson, 2017, chs. 26–28, 32.

[16] “RC Parallel Circuit (Impedance, Phasor Diagram)” Electrical-Information.com. [Online]. Available: https://electrical-information.com/rc-parallel-circuit-impedance/ [Accessed: Dec. 15, 2024]

[17] K.-H. Hsu, T.-W. Wu, Y.-C. Wang, W.-H. Lim, C.-C. Lee, and R. Lien, “Hemodynamic reference for neonates of different age and weight: A pilot study with electrical cardiometry,” *Journal of Perinatology*, vol. 36, no. 5, pp. 481–485, Feb. 2016, doi: 10.1038/jp.2016.2.

[18] M. Koestenberger, G. Grangl, A. Avian, A. Gamillscheg, M. Grillitsch, G. Cvirn, A. Burmas, and G. Hansmann, “Normal reference values and Z-scores of the pulmonary artery

acceleration time in children and its importance for the assessment of pulmonary hypertension," *Circulation: Cardiovascular Imaging*, vol. 9, no. 8, Aug. 2016, doi: 10.1161/circimaging.116.005336.

[19] N. B. Basnet, S. Awa, T. Hishi, and M. Yanagisawa, "Pulmonary arterial compliance in children with atrial and ventricular septal defect," *Heart Vessels*, vol. 15, no. 2, pp. 61–69, Jan. 2000, doi: 10.1007/s003800050214.

[20] F. R. Menter, "Two-equation eddy-viscosity turbulence models for engineering applications," *AIAA Journal*, vol. 32, no. 8, pp. 1598–1605, Aug. 1994, doi: 10.2514/3.12149.

Appendix A: Python Script

A.1 Python Simulation

The following Python code was written to mimic and provide validation for the iCircuit model by showing the actual equations used by the software. It consists of three main functions to calculate the blood flow and pressure changes in the systemic and pulmonary circulations. Matplotlib was then used to generate the figures.

```
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt
from typing import Tuple

# constants
heart_rate           = 2.483333                # beats per second
cardiac_output       = 0.0038                  # L/s
systemic_resistance  = 10317                   # mmHg s/L
pulmonary_resistance = 2 * 60                  # WU * 60 = mmHg s/L
compliance           = 0.0002601               # L/mmHg
angular_freq         = 2 * np.pi * heart_rate  # radians

def blood_flow(t: float) -> float:
    # calculates the total blood flow at time t
    # for systemic, this function is sufficient
    # for pulmonary, needs to be split between resistor and capacitor in
parallel
    return cardiac_output * np.sin(angular_freq * t)

def systemic_circulation(t: float) -> Tuple[float, float]:
    # calculates blood flow and pressure change through the SVR at time t
    blood_flow_total  = blood_flow(t)
    pressure_change   = blood_flow_total * systemic_resistance
    return blood_flow_total, pressure_change

def pulmonary_circulation(t: float) -> Tuple[float, float, float]:
    # calculates blood flow through the parallel PVR and compliance and
pulmonary pressure change at time t
    pressure_change   = -blood_flow(t) / ((1/pulmonary_resistance) +
(angular_freq * compliance))
    peak_pressure     = cardiac_output / ((1/pulmonary_resistance) +
(angular_freq * compliance))
```

```
    peak_blood_flow_R = peak_pressure / pulmonary_resistance
    blood_flow_R      = -peak_blood_flow_R * np.sin(angular_freq * t)
    peak_blood_flow_C = peak_pressure * angular_freq * compliance
    blood_flow_C      = -peak_blood_flow_C * np.sin(angular_freq * t + np.pi/
2)
    return blood_flow_R, blood_flow_C, pressure_change

# simple tests to make sure blood flow calculations are correct
# total pulmonary should equal -systemic
blood_flow_systemic, P_systemic         = systemic_circulation(0.05)
blood_flow_R, blood_flow_C, P_pulmonary = pulmonary_circulation(0.05)
print(f"Systemic blood flow: {blood_flow_systemic}")
print(f"Pulmonary blood flow through Resistor: {blood_flow_R}; Capacitor:
{blood_flow_C}")
print(f"Total pulmonary blood flow: {blood_flow_R + blood_flow_C}")

# SIMULATION (for one value of PVR)
time                                    = np.arange(0, 3, 0.01)  # 3 seconds
at 100 Hz
pulmonary_resistance                    = 2 * 60 # WU * 60 = mmHg s/L
blood_flow_systemic, P_systemic         = zip(*[systemic_circulation(t) for t
in time])
blood_flow_R, blood_flow_C, P_pulmonary = zip(*[pulmonary_circulation(t) for
t in time])

# convert blood flow to L/min
blood_flow_systemic = [blood_flow_systemic[i] * 60 for i in range(len(time))]
blood_flow_C        = [blood_flow_C[i] * 60 for i in range(len(time))]
blood_flow_R        = [blood_flow_R[i] * 60 for i in range(len(time))]

# Blood Flow Plot
fig, ax1 = plt.subplots(1, 1, sharex=True, figsize=(6, 4))
ax1.plot(time, blood_flow_systemic, label="Systemic")
ax1.plot(time, blood_flow_R, label="Pulmonary (Resistance)")
ax1.plot(time, blood_flow_C, label="Pulmonary (Compliance)")
ax1.set_xlabel("Time (seconds)")
ax1.set_ylabel("Blood Flow (L/min)")
ax1.set_title("Blood Flow (PVR = 2 WU)")
ax1.legend()
plt.grid(axis='y', linewidth = 0.5)
plt.show()

# calculate pressure changes for different values of PVR
test_values      = [0.2, 2, 5, 20]
pressure_changes = []

for val in test_values:
    pulmonary_resistance                    = val * 60 # WU * 60 = mmHg s/L
    blood_flow_R, blood_flow_C, P_pulmonary = zip(*[pulmonary_circulation(t)
for t in time])
    pressure_changes.append(P_pulmonary)

# Pressure Change Plot
fig, (ax1, ax2) = plt.subplots(1, 2, sharex=True, figsize=(12, 4))
```

```
ax1.plot(time, P_systemic, label="Systemic Pressure Change")
ax1.set_title("Systemic Pressure Change")
ax1.set_xlabel("Time (seconds)")
ax1.set_ylabel("Pressure Change (mmHg)")
ax1.grid(axis='y', linewidth = 0.5)
ax2.plot(time, pressure_changes[0], label="PVR = 0.2")
ax2.plot(time, pressure_changes[1], label="PVR = 2")
ax2.plot(time, pressure_changes[2], label="PVR = 5")
ax2.plot(time, pressure_changes[3], label="PVR = 20", color="purple")
ax2.set_title("Pulmonary Pressure Change")
ax2.set_xlabel("Time (seconds)")
ax2.set_ylabel("Pressure Change (mmHg)")
ax2.legend()
ax2.grid(axis='y', linewidth = 0.5)
plt.show()

# peak blood flow and pressure based on PVR (range: 1-20 WU)
def peak_values_systemic() -> Tuple[float, float]:
    peak_blood_flow   = cardiac_output
    peak_pressure     = peak_blood_flow * systemic_resistance
    return peak_blood_flow, peak_pressure

def peak_values_pulmonary(R: float) -> Tuple[float, float, float]:
    peak_pressure     = cardiac_output / ((1/R) + (angular_freq *
compliance))
    peak_blood_flow_R = peak_pressure / R
    peak_blood_flow_C = peak_pressure * angular_freq * compliance
    return peak_blood_flow_R, peak_blood_flow_C, peak_pressure

PVR_range = range(1, 21)
peak_blood_flow_systemic, peak_pressure_systemic              =
zip(*[peak_values_systemic() for R in PVR_range])
peak_blood_flow_R, peak_blood_flow_C, peak_pressure_pulmonary =
zip(*[peak_values_pulmonary(R*60) for R in PVR_range])

# convert blood flow to L/min
peak_blood_flow_systemic = [peak_blood_flow_systemic[i] * 60 for i in
range(len(PVR_range))]
peak_blood_flow_C        = [peak_blood_flow_C[i] * 60 for i in
range(len(PVR_range))]
peak_blood_flow_R        = [peak_blood_flow_R[i] * 60 for i in
range(len(PVR_range))]

fig, (ax1, ax2) = plt.subplots(1, 2, sharex=True, figsize=(12, 4))
ax1.plot(PVR_range, peak_blood_flow_systemic, label="Systemic")
ax1.plot(PVR_range, peak_blood_flow_R, label="Pulmonary (Resistance)")
ax1.plot(PVR_range, peak_blood_flow_C, label="Pulmonary (Compliance)")
ax1.set_title("Peak Blood Flow")
ax1.set_xlabel("PVR (Wood Units)")
ax1.set_ylabel("Blood Flow (L/min)")
ax1.legend()
ax1.grid(linewidth = 0.5)
ax2.plot(PVR_range, peak_pressure_pulmonary, label="Peak Pressure Change")
ax2.set_title("Peak Pressure Change")
```

```
ax2.set_xlabel("PVR (Wood Units)")
ax2.set_ylabel("Pressure Change (mmHg)")
ax2.grid(linewidth = 0.5)
plt.show()

for i in range(len(peak_blood_flow_R)):
    if peak_blood_flow_C[i] > peak_blood_flow_R[i]:
        print(f"Blood flow through compliance is higher when PVR is > {i}
WU.")
        break
```

A.2 iCircuit Data Analysis

The following is the code used to analyze the raw data exported from the iCircuit simulations. Matplotlib was again used to generate the figures.

```
# calculate input amplitude based on PVR
R   = 0.2 * 60
amp = cardiac_output / ((1/R) + (angular_freq * compliance))
print(amp)

df = pd.read_csv('data_2WU.csv')[:257]

# simple tests to make sure blood flow calculations are correct
# total pulmonary should equal -systemic
print(f"Systemic blood flow: {df['Systemic Resistance.I'][4]}")
print(f"Pulmonary blood flow through Resistor: {df['PVR.I'][4]}; Capacitor:
{df['Compliance.I'][4]}")
print(f"Total pulmonary blood flow: {df['PVR.I'][4] + df['Compliance.I']
[4]}")

# convert blood flow to L/min
df['Systemic Resistance.I'] = df['Systemic Resistance.I'] * 60
df['PVR.I']                 = df['PVR.I'] * 60
df['Compliance.I']          = df['Compliance.I'] * 60

# Blood Flow Plot
fig, ax1 = plt.subplots(1, 1, sharex=True, figsize=(6, 4))
ax1.plot(df['Time'], df['Systemic Resistance.I'], label="Systemic")
ax1.plot(df['Time'], df['PVR.I'], label="Pulmonary (Resistance)")
ax1.plot(df['Time'], df['Compliance.I'], label="Pulmonary (Compliance)")
ax1.set_xlabel("Time (seconds)")
ax1.set_ylabel("Blood Flow (L/min)")
ax1.set_title("Blood Flow (PVR = 2 WU)")
ax1.legend()
plt.grid(axis='y', linewidth = 0.5)
plt.show()
```

```
# import pressure changes for different values of PVR
test_values          = [0.2, 2, 5, 20]
pressure_changes     = []
pressure_changes_sys = []

for val in test_values:
    filename = 'data_' + str(val) + 'WU.csv'
    df = pd.read_csv(filename)[:257]
    pressure_changes.append(df['PVR.Vd'])
    pressure_changes_sys.append(df['Systemic Resistance.Vd'])

# Pressure Change Plot
fig, (ax1, ax2) = plt.subplots(1, 2, sharex=True, figsize=(12, 4))
ax1.plot(df['Time'], pressure_changes_sys[0], label="PVR = 0.2")
ax1.plot(df['Time'], pressure_changes_sys[1], label="PVR = 2")
ax1.plot(df['Time'], pressure_changes_sys[2], label="PVR = 5")
ax1.plot(df['Time'], pressure_changes_sys[3], label="PVR = 20",
color="purple")
ax1.set_title("Systemic Pressure Change")
ax1.set_xlabel("Time (seconds)")
ax1.set_ylabel("Pressure Change (mmHg)")
ax1.grid(axis='y', linewidth = 0.5)
ax2.plot(df['Time'], pressure_changes[0], label="PVR = 0.2")
ax2.plot(df['Time'], pressure_changes[1], label="PVR = 2")
ax2.plot(df['Time'], pressure_changes[2], label="PVR = 5")
ax2.plot(df['Time'], pressure_changes[3], label="PVR = 20", color="purple")
ax2.set_title("Pulmonary Pressure Change")
ax2.set_xlabel("Time (seconds)")
ax2.set_ylabel("Pressure Change (mmHg)")
ax2.legend()
ax2.grid(axis='y', linewidth = 0.5)
plt.show()

# peak blood flow and pressure based on PVR (range: 1-20 WU)
PVR_range               = range(1, 21)
peak_blood_flow_systemic = []
peak_blood_flow_R        = []
peak_blood_flow_C        = []
peak_pressure_pulmonary  = []

for val in PVR_range:
    filename = 'data_' + str(val) + 'WU.csv'
    df = pd.read_csv(filename)[:257]
    peak_blood_flow_systemic.append(max(df['Systemic Resistance.I'])*60)
    peak_blood_flow_R.append(max(df['PVR.I'])*60)
    peak_blood_flow_C.append(max(df['Compliance.I'])*60)
    peak_pressure_pulmonary.append(max(df['PVR.Vd']))

fig, (ax1, ax2) = plt.subplots(1, 2, sharex=True, figsize=(12, 4))
ax1.plot(PVR_range, peak_blood_flow_systemic, label="Systemic")
ax1.plot(PVR_range, peak_blood_flow_R, label="Pulmonary (Resistance)")
ax1.plot(PVR_range, peak_blood_flow_C, label="Pulmonary (Compliance)")
ax1.set_title("Peak Blood Flow")
```

```
ax1.set_xlabel("PVR (Wood Units)")
ax1.set_ylabel("Blood Flow (L/min)")
ax1.legend()
ax1.grid(linewidth = 0.5)
ax2.plot(PVR_range, peak_pressure_pulmonary, label="Peak Pressure Change")
ax2.set_title("Peak Pressure Change")
ax2.set_xlabel("PVR (Wood Units)")
ax2.set_ylabel("Pressure Change (mmHg)")
ax2.grid(linewidth = 0.5)
plt.show()

# phase difference based on PVR
PVR_range             = range(1, 21)
phase_diff_PVR        = []
phase_diff_compliance = []

def first_peak(time, data) -> float:
    for i in range(1, len(data)):
        if data[i] >= data[i-1] and data[i] >= data[i+1]:
            return time[i]
    return -1.0

for val in PVR_range:
    filename = 'data_' + str(val) + 'WU.csv'
    df = pd.read_csv(filename)[:257]
    # find t for the first peak for each of SVR, PVR, and compliance
    t_svr  = first_peak(df['Time'], df['Systemic Resistance.I'])
    t_pvr  = first_peak(df['Time'], df['PVR.I'])
    t_comp = first_peak(df['Time'], df['Compliance.I'])
    phase_diff_PVR.append(abs(t_pvr - t_svr))
    phase_diff_compliance.append(abs(t_comp - t_pvr))

print(phase_diff_PVR)
print(phase_diff_compliance)
print(f"Average phase difference between Systemic and Pulmonary Resistance:
{np.mean(phase_diff_PVR)} seconds.")
print(f"Average phase difference between Pulmonary Resistance and Compliance:
{np.mean(phase_diff_compliance)} seconds.")

# Phase difference plot
fig, ax1 = plt.subplots(1, 1, sharex=True, figsize=(6, 4))
ax1.plot(PVR_range, phase_diff_PVR, label="Pulmonary - Systemic Resistance")
ax1.plot(PVR_range, phase_diff_compliance, label="Pulmonary Resistance -
Compliance")
ax1.set_xlabel("PVR (Wood Units)")
ax1.set_ylabel("Phase Difference (seconds)")
ax1.set_title("Phase Difference")
ax1.legend()
plt.grid(axis='y', linewidth = 0.5)
plt.show()

# Circuit with pressure fixed
df = pd.read_csv('data_fixedpressure_2WU.csv')[:257]
```

```
# simple tests to make sure blood flow calculations are correct
# total pulmonary should equal -systemic
print(f"Systemic blood flow: {df['Systemic Resistance.I'][4]}")
print(f"Pulmonary blood flow through Resistor: {df['PVR.I'][4]}; Capacitor:
{df['Compliance.I'][4]}")
print(f"Total pulmonary blood flow: {df['PVR.I'][4] + df['Compliance.I']
[4]}")

# convert blood flow to L/min
df['Systemic Resistance.I'] = df['Systemic Resistance.I'] * 60
df['PVR.I']                 = df['PVR.I'] * 60
df['Compliance.I']          = df['Compliance.I'] * 60

# Blood Flow Plot
fig, ax1 = plt.subplots(1, 1, sharex=True, figsize=(6, 4))
ax1.plot(df['Time'], df['Systemic Resistance.I'], label="Systemic")
ax1.plot(df['Time'], df['PVR.I'], label="Pulmonary (Resistance)")
ax1.plot(df['Time'], df['Compliance.I'], label="Pulmonary (Compliance)")
ax1.set_xlabel("Time (seconds)")
ax1.set_ylabel("Blood Flow (L/min)")
ax1.set_title("Blood Flow (PVR = 2 WU)")
ax1.legend()
plt.grid(axis='y', linewidth = 0.5)
plt.show()

# import pressure changes for different values of PVR
test_values      = [0.2, 2, 5, 20]
pressure_changes = []

for val in test_values:
    filename = 'data_fixedpressure_' + str(val) + 'WU.csv'
    df = pd.read_csv(filename)[:257]
    pressure_changes.append(df['PVR.Vd'])

# Pressure Change Plot
fig, (ax1, ax2) = plt.subplots(1, 2, sharex=True, figsize=(12, 4))
ax1.plot(df['Time'], df['Systemic Resistance.Vd'], label="Systemic Pressure
Change")
ax1.set_title("Systemic Pressure Change")
ax1.set_xlabel("Time (seconds)")
ax1.set_ylabel("Pressure Change (mmHg)")
ax1.grid(axis='y', linewidth = 0.5)
ax2.plot(df['Time'], pressure_changes[0], label="PVR = 0.2")
ax2.plot(df['Time'], pressure_changes[1], label="PVR = 2")
ax2.plot(df['Time'], pressure_changes[2], label="PVR = 5")
ax2.plot(df['Time'], pressure_changes[3], label="PVR = 20", color="purple")
ax2.set_title("Pulmonary Pressure Change")
ax2.set_xlabel("Time (seconds)")
ax2.set_ylabel("Pressure Change (mmHg)")
ax2.legend()
ax2.grid(axis='y', linewidth = 0.5)
plt.show()
```