ABSTRACT

CLIPP, RACHEL BETANY. Computational Models of the Pulmonary Vasculature Including the Dynamic Effects of Respiration. (Under the direction of Dr. Brooke N. Steele).

Recent computational modeling efforts have sought to predict the hemodynamic changes associated with cardiovascular disease progression and treatment options. Accurate hemodynamic predictions can only be achieved by creating a model with both a region of interest and the downstream network of vessels that are an accurate reflection of the organ system in question. An often-neglected aspect of modeling is the effect of regulatory mechanisms on the distal network of vessels. For the pulmonary vasculature in particular, respiratory effects have been shown to have a pronounced effect on pulmonary resistance, and therefore pulmonary pressure. However, little work has been done to include these effects in computational models of the pulmonary vasculature. This work identifies methods by which to dynamically include regulatory or feedback mechanisms on the distal network in computational models, quantifies the effects of respiration on the pulmonary physiology through experimental data collection and analysis, creates a dynamic boundary condition specifically for the pulmonary vasculature of the lamb and uses the dynamic boundary condition to evaluate the effects of pulmonary arterial stenosis on pulmonary hemodynamics.

A dynamic boundary condition was developed and implemented using structured-tree based impedance with a time-varying resistance component. By applying this boundary condition at the outlet of a region of interest, it was possible to simulate a regulatory or feedback mechanism. The boundary condition was tested using a lamb lung geometry and hemodynamic and respiratory data collected during positive-pressure ventilation (PPV) or mechanical ventilator assisted breathing. Experimental data was collected using excised lungs and a negative-pressure chamber to simulate the effects of respiration during both PPV and normal breathing, also known as negative-pressure ventilation (NPV). This allowed for the comparison of both types of ventilation for further development of a pulmonary model. The pulmonary outlet boundary conditions were then applied to a healthy pulmonary vasculature under NPV conditions and a pulmonary physiology with a pulmonary arterial stenosis located on the left pulmonary artery to determine the effects of the stenosis on hemodynamics, as well as the effects of respiration in the presence of stenosis.
Computational Models of the Pulmonary Vasculature Including the Dynamic Effects of Respiration

by
Rachel Betany Clipp

A dissertation submitted to the Graduate Faculty of North Carolina State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomedical Engineering, Raleigh, North Carolina, 2010.

APPROVED BY:

___________________________
Brooke N. Steele
Chair of Advisory Committee

___________________________  ___________________________
Carol Lucas                  Mette Olufsen

___________________________  ___________________________
Glenn Walker                 Mohammed Zikry
DEDICATION

I would like to dedicate this work to my husband, Brian, for all his support and his never-ending ability to give a pep talk.
BIOGRAPHY

I grew up in Northwest Ohio until moving to Daphne, Alabama, to finish high school. After graduating from Bayside Academy in 1999, I attended Clemson University in Clemson, South Carolina. While, I worked towards my degree I participated in the cooperative education program, working for Milliken’s Pendleton Finishing Plant for one semester and Cryovac: Sealed Air Corporation for five semesters. I studied in Bristol, England, for 4 weeks in the summer of 2003 as part of a study abroad program. In May 2004, I obtained a Bachelors of Science degree in Mechanical Engineering from Clemson. I married Brian Clipp in July of 2004 and began working as a Navy civilian employee in Dahlgren, VA. After a year, I began graduate school to pursue a doctorate in Biomedical Engineering. I began working with Dr. Brooke Steele to improve the capabilities of predictive modeling for the use with the cardiovascular physiology. In 2010, I have obtained a Masters degree in Biomedical Engineering and am completing my work on improved boundary conditions that are capable of including changes in the distal vascular network for computational models of the pulmonary vasculature.
I would like to thank my advisor for all of her hard work in helping me through the process of obtaining my doctorate. Without her guidance and assistance, it would have been a much more difficult prospect and much less enjoyable. I would like to thank my committee for their guidance and advice throughout the process. I would like to thank Dr. Egan, Dr. Boming Dong, Dr. Yueh Lee and Lucy Perkins for all their assistance in data collection.

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Chapter One

Introduction

1.1 Motivation

Predictive computational models can be used to increase the understanding of hemodynamics. However, different organ systems have different structures and functions providing different hemodynamic profiles. It is important to tailor the computational model to the organ, including differences in geometry, blood flow distribution, regulatory mechanisms and vessel wall properties. The pulmonary physiology has a unique structure and function within the body, which leads to a need for a unique computational model. By creating a computational model specific to the pulmonary vasculature it is possible to analyze the effects of disease and surgical intervention on the pulmonary circulation.

The majority of previous models of the pulmonary system have not included the effects of respiration as a dynamic regulatory mechanism [1-4]. By excluding the effects of respiration, an accurate picture of the blood flow and pressure cannot be achieved. A recent model by Marsden, et al [5] made an effort to include the effects of respiration; this inclusion was limited in its implementation to specific disease states. Published models have also failed to take into account the organ specific flow distribution present within the lung. This prompted the author to develop a pulmonary model that takes into account the specific structure and function of the lung that may more accurately predict
the hemodynamics of the pulmonary vasculature including the changes due to disease caused by geometric changes, as well as downstream vascular network changes.

1.2 Pulmonary Physiology

1.2.1 Pulmonary Specific Physiology

![Pulmonary and Systemic Circulations](image)

**Figure 1.1: Pulmonary and Systemic Circulations.** The pulmonary circulation begins with the right ventricle pumping oxygen poor blood out of the heart through the Main Pulmonary Artery to the lungs and returning oxygen rich blood to the left atrium. The oxygen rich blood then flows through the systemic circulation via the left ventricle and aorta. The oxygen poor blood returns to the heart via the Superior and Inferior Vena Cava.

As previously discussed, the lung has a specific structure and function that combines to create a unique physiologic system. The pulmonary circulation is a separate and distinct circulation from the systemic circulation. Oxygen poor blood leaves the right ventricle of the heart via the pulmonary arteries and moves into the lungs. Gas exchange occurs in the vascular arterioles creating oxygen rich blood. This blood then returns via the pulmonary veins to the left atrium of the heart. The oxygen rich blood then enters the
systemic circulation providing oxygen to the rest of the body. This is shown in Figure 1.1.

The pulmonary circulation differs from the systemic circulation in several ways. The pressure in the pulmonary circulation is significantly lower than that present in the systemic circulation. The arterial pressure in the pulmonary system is approximately 15 mmHg, while the systemic circulation has a substantially higher pressure of approximately 120 mmHg. The lower pressure present in the pulmonary arteries may be related to the large difference in compliance that is present between the pulmonary arteries and the arteries in the systemic circulation [6-8], the lower pressure generated by the right ventricle as compared to the left ventricle and the unique branching structure of the pulmonary arterial network [9].

Several studies have investigated the compliance of the pulmonary arteries, the common conclusion being that the pulmonary arteries are significantly more compliant than those in the systemic circulation. However, there was no consensus on how much they differed, with results showing that the pulmonary arteries were anywhere from two to ten times as compliant as the arteries in the systemic system [6-8].

Another major difference in the pulmonary circulation is the flow distribution within the lung. The impedance, the opposition to flow through a network, in the downstream network of vessels governs the flow of blood within the network of vessels. The impedance is not constant throughout the lung due to the relationship between arteriole and venous blood pressure and alveoli air pressure. Some authors [10-13] specify three zones of blood flow in the lung, described by the above relationships. In the first zone of the lung the alveoli pressure is larger than the arteriole and venous pressure, collapsing the blood vessels, increasing the impedance of the network and preventing flow through the network. In the second zone, the arteriole pressure exceeds that in the alveoli during systole, however the alveoli pressure still exceeds that of the pulmonary veins. In this scenario, the blood circulates through these blood vessels only during systole. In the final zone, the arteriole pressure and venous pressure both exceed the alveoli pressure. The arteriole pressure is substantially greater than the alveoli pressure, causing a slight
ballooning effect of the artery. This scenario provides the largest amount of blood flow through the arteries of the lung.

These relationships vary throughout the lung and the organization of these zones has been the topic of great debate in the literature [9-22]. West and colleagues specify three zones vertically in the lung, with zone one at the apex, zone two in the middle and zone three at the base of the lung [18, 23]. West, et al [11] goes further and states that zone one does not exist in the healthy lung breathing under normal conditions (negative-pressure ventilation, NPV), leaving a two-zone model in existence. In cases of disease and patients on a ventilator (positive-pressure ventilation, PPV), zone one is present [11]. The vertical lung model suggested by West and colleagues is based on the assumption that gravity is the primary cause of the pressure gradients that determine the zone distribution. Glenny, et al [20] completed a study investigating the role of gravity within the lung. Using baboons, flow distribution throughout the lung was measured in both upright and inverted animals. These results showed that while gravity was a factor in the flow distribution within the lung (approximately 25%), it was not the predominant cause of heterogeneous flow. Burrowes, et al [9] put forth the suggestion that asymmetric branching may have a strong impact on the flow distribution. The counterpoint to vertical zones influenced primarily or exclusively by gravity is horizontal zones with heterogeneous flow. The zone definitions (quantity of flow) are similar to the vertical zones, however the horizontal zones have each zone one-three occurring throughout the entire lung with varying frequency [9, 20, 21]. This results in a similar overall flow distribution, but with a different mechanism causing the distribution. While this is an ongoing topic of debate it is important to consider the unique flow distribution present in the lung when studying the pulmonary circulation.

1.2.2 Effects of Respiration

Another important characteristic of the pulmonary system is the negative feedback mechanism generated by respiration. As briefly mentioned above, respiration can occur in two forms: negative-pressure ventilation (NPV) and positive-pressure ventilation (PPV). During NPV, the negative pressure in the thoracic cavity causes the lung to
expand and air is pulled inside. The increase in thoracic pressure caused by lung inflation and the natural elastic recoil of the chest wall causes deflation, pushing air out of the lung. This process is associated with free, natural and normal breathing. During PPV, the patient is ventilated through intubation and a ventilator or by placing a mask over the face and using an ambu-bag. Both of these methods force air into the lung during inspiration and during expiration the lung naturally collapses forcing air out of the lungs.

The two methods of ventilation not only have different mechanisms for inflating the lung, but also result in a different relationship between the alveoli and arterioles. The relative pressure between alveoli and arterioles, as previously discussed, causes the arterioles to dilate or constrict. As the arterioles are constricted the resistance to flow is increased. This change in resistance during respiration has been studied for both PPV and NPV [24-28].

Burton and Patel [26] compare the effects of respiration during both PPV and NPV. Their results show that with constant perfusion pressure, the flow decreases, demonstrating an increase in pulmonary vascular resistance as the lung is inflated during PPV. The opposite effect was shown during NPV; as the lung was inflated with negative pressure the flow increases, demonstrating a decrease in pulmonary vascular resistance. Murgo and Westerhof [29] completed a study in human patients evaluating differences in impedance between expiration and inspiration. This study was completed for NPV, while patient pressure and velocity measurements were captured via sensors inserted during catheterization. The findings of this study were that there are no changes in pulmonary impedance or pulmonary vascular resistance during the respiratory cycle, indicating the lung volume (inflation) has no effect on the hemodynamics of the lung. A study completed by Petak, et al [28] compares the effects of NPV and PPV on pulmonary impedance and disagrees with the results by Murgo and Westerhof [29]. As with Burton and Patel [26], the lungs were excised to complete the study. They found a large increase in pulmonary impedance when moving from expiration to inspiration during PPV and a slight but significant decrease in pulmonary impedance during NPV when moving from expiration to inspiration. The disagreement present in the literature [18, 26, 29-32] may
be attributed to the variety of experimental techniques used to evaluate pulmonary hemodynamics. Few studies use the same method for data collection (i.e., excised versus intact lungs) and fewer still apply physiologic parameters (i.e., constant pressure and steady flow perfusion versus pulsatile flow perfusion) in order to quantify the effects of respiration.

While there is disagreement over the differences between PPV and NPV during respiration, the majority of studies agree that respiration has an important effect on pulmonary hemodynamics. A study using lambs quantified the effects of respiration on blood pressure and blood flow during PPV [27, 33]. This study is discussed in detail in Chapter 3. Figure 1.2 shows the effects of respiration as found in a representative data set from these studies.

Figure 1.2: The Effects of Respiration on Pulmonary Hemodynamics. Hemodynamic and respiration were collected in open-chest lambs during positive-pressure ventilation. This representative data set shows that while blood flow in the main pulmonary artery (MPA) is relatively insensitive to flow, blood pressure in the MPA is significantly impacted by respiration. As lung volume increases (inspiration), the blood pressure increases.

From the above figure, it is clear that the blood flow in the main pulmonary artery (MPA) is relatively insensitive to respiration, while the blood pressure experiences a sharp increase in average pressure with inspiration.
Figure 1.3: The Fontan Circulation. The Fontan circulation is used here to correct the mixing of oxygenated and non-oxygenated blood in the ventricles. The superior vena cava and inferior vena cava are disconnected from the right atrium and connected directly to the pulmonary artery. This provides oxygen poor blood from the body to the lungs to become oxygenated and then return to the heart for distribution throughout the body.

While, respiration has an effect on blood pressure in a healthy circulation, it is more important in a compromised circulation. An example of this is the Fontan circulation. Children born with a specific variety of congenital heart condition have only a single ventricle present at birth, which does not provide two distinct circulations (pulmonary and systemic) as described above. This prevents the appropriate quantity of oxygen-rich blood from entering the systemic circulation, causing a shortage of oxygen in the system. In order to address this situation a palliative procedure is used to create a circulation that takes the oxygen-poor venous flow from the systemic circulation and redirects it to the lungs. The pulmonary veins return the oxygen-rich blood to the heart to be pumped through the systemic circulation. This post surgical circulation has many variations [34-38], but is generally referred to as the Fontan circulation, named for the initial procedure by Fontan and Baudet [34]. An example of this circulation is shown in Figure 1.3. This
example of the Fontan circulation provides passive flow (venous) to the lungs, therefore increases in resistance due to respiration have a larger impact on pulmonary hemodynamics, as shown in Figure 1.4. The data shown in Figure 1.4 were collected during previous studies completed on open-chest lambs, the details can be found in Lucas, et al and Ketner [27, 33].

![Figure 1.4: The Effects of Respiration in the Fontan Circulation.](image)

The blood pressure and blood flow in the superior vena cava (SVC) are shown with the airway pressure in the normal circulation, as well as after the blood flow is redirected in a Fontan circulation. The Total-Cavo Pulmonary Connection (TCPC) is a Fontan circulation similar to the connection shown in Figure 1.3. In the normal circulation, the blood pressure and blood flow are only minimally affected by respiration, however in the Fontan circulation the effects of respiration are significant. Blood flow drops significantly during inspiration (increased airway pressure), while blood pressure increases and loses pulsatility.

The above figure shows that in the normal, healthy circulation the blood flow in the superior vena cava (a major vein that returns blood from the head to the heart) is relatively insensitive to respiration. There is also a slight increase in blood pressure when moving from expiration to inspiration. However, when looking at the compromised Fontan circulation, the effects of respiration are amplified. The blood flow is significantly depressed throughout the respiratory process, with a substantial drop (nearly to zero) in blood flow during inspiration. The blood pressure is also significantly impacted with the pulsatility of the blood pressure removed in the compromised
circulation. There was also an increase in blood pressure during inspiration. The increase in pressure and the decrease in flow result in a significant increase in pulmonary vascular resistance. Experimental studies have been conducted investigating the effects of respiration on the compromised Fontan circulation [39-42]. The study by Hjortdal, et al [41] that investigated the impact of respiration on the blood flow and blood pressure in both the inferior vena cava (a major vein that returns blood from the body to the heart) and superior vena cava concluded that respiration had critical effects on hemodynamics in the Fontan circulation.

1.3 Computational Modeling

Predictive computational models have the potential to assess the hemodynamics for both disease states and possible surgical solutions. However, a critical obstacle to their incorporation in clinical care lies in the inability to accurately describe specific organ systems including regulatory mechanisms, such as respiration. These computational models have different components that must all be tailored to the specific organ systems. The major components of computational models are the: large vessel geometry or region of interest, inlet boundary conditions, vessel wall properties and outlet boundary conditions. These components are shown in Figure 1.5.

1.3.1 Large Vessel Geometry

The large vessel geometry, or the region of interest, is comprised of the large vessels for which the simulation of computational models is predicting hemodynamics. This region can be described with an idealized or non-specific geometry, which is not specific to an individual, but is estimated from generalized data or multiple measurements. A second option is a patient specific region of interest, based directly on a specific patient or animal and is generally measured from medical imaging data, such as MRI or CT data.
Figure 1.5: Components of a Computational Model. Predictive computational models are composed of different components that are used to represent the physiologic parameters of an organ system. These components include the region of interest or geometry, outlet boundary conditions, inlet boundary conditions and the vessel wall properties. These topics are discussed in more detail in Section 1.3.

1.3.2 Vessel Wall Properties

The vessel wall properties, or constitutive model, are defined as the behavior of the large vessels that make up the region of interest. Three examples of models for vessel wall behavior are: rigid [3], elastic [43, 44] and visco-elastic [45, 46]. Rigid walls assume a vessel is unable to expand or contract with increasing flow. Elastic walls behave as a spring with both stretch and contraction behaving mechanically the same. Visco-elastic walls assume that stretch and contraction do not have the same behavior and include hysteresis between stretch and contraction.

1.3.3 Inlet Boundary Conditions

The inlet boundary condition is specified for each model at any inlet to the region of interest. This is generally described as either a pressure or flow waveform (or steady...
conditions). The data to prescribe this boundary condition have come from experimental data, or a generalized data set, similar to an idealized data set or directly from patient data, e.g. obtained via PC-MRI, catheterization, etc.

1.3.4 Outlet Boundary Conditions

The outlet boundary conditions are used to describe the downstream network of vessels, meaning the vessels not described in the region of interest. These boundary conditions are applied at all of the outlets of the model. Incorrectly describing the interaction between the region of interest and the downstream network can cause errors in predicted flow distributions. The most common and accurate boundary conditions are applied directly from experimental/clinical data, such as blood flow, however these data are often not available due to limitations in the resolution and invasive nature of current imaging technologies. In the absence of these data idealized boundary conditions must be applied.

There are a variety of commonly used idealized outlet boundary conditions, including constant pressure, resistance, lumped parameter models (impedance) and geometry based impedance [47]. Constant pressure boundary conditions are commonly used in three-dimensional (3D) models of vessels with rigid walls [3]. This method is justified for limited applications, but does not represent physiologic conditions. The resistance boundary condition (the ratio of pressure and flow in the time domain) provides a reasonable approximation for steady flow applications [5]. However, with the introduction of pulsatile flow, the resistance boundary condition results in a scaled relationship between pressure and flow that does not incorporate the effects of damping or the wave propagation found in compliant vessels [47, 48]. Impedance boundary conditions include both a modulus and phase component and are therefore able to incorporate the damping and phase lag present in compliant vessels. Lumped parameter impedance models [1, 2, 49] are electrical analog circuits comprised of resistors, capacitors and/or inductors to represent the vascular network. The circuit components are generally fit to experimental data, but in the absence of data at the outlets it is difficult to determine reasonable parameters for individual models. Geometry-based impedance
methods calculate impedance using Womersley’s method for a given geometry [50]. Such geometries can be directly measured or based on a derived tree representing a specific vascular region [43, 51, 52], such as the pulmonary vasculature [4, 44].

Recent work by Kim, et al [53] has recognized the need for a dynamic boundary condition to include regulatory and feedback mechanisms present within different organ systems. The study [53] investigates the coronary arteries, noting that the coronary vascular beds experience a different intramyocardial pressure based on their location, as well as the changing coronary pressure. To incorporate this effect on the downstream vessels in this study, a lumped-parameter model was used with an added intramyocardial pressure component. This method incorporates the feedback of the system directly into the downstream boundary condition calculation by adjusting a single component of the lumped parameter model to represent the changing impedance.

1.3.5 Current Pulmonary Models and Limitations

To date, several attempts have been made to incorporate physiologic variations in pulmonary hemodynamic models, but few have included the effects of respiration. In investigations of the effects of exercise and respiration on Fontan circulations, Marsden, et al [5, 54] modified the resistance boundary condition for small pulmonary arteries to represent the static difference between the rest and exercise states and modulated the inlet flow with polynomials to incorporate the dynamic effects of respiration. The polynomials were defined based on a number of parameters, including respiratory rate and mean flow. While modification of the inlet flow waveform is an effective method for representing the effects of respiration in a compromised Fontan circulation, it does not consider the cause, i.e., impedance changes due to arteriole constriction in the lung. In cases where measured flow is used as the inlet boundary condition, the effects of downstream influences, such as impedance changes, cannot be distinguished from driving forces. Therefore, care must be taken when prescribing boundary conditions to ensure that their selection does not unnecessarily influence computational results; especially when modifications (i.e. treatment planning scenarios) made in one location will influence hemodynamics in another location.
1.4 Specific Aims

The effects of disease, respiration and treatment options on the pulmonary vasculature have generated much interest with the desire to predict disease progression and treatment outcomes. This has led to the desire to predict hemodynamic changes associated with disease and surgical intervention with the use of computational models. However, for computational models to be useful to clinicians in the determination of the best course of treatment, the models must accurately reflect the physiology of the organ, including the effects of respiration. But with few exceptions, these effects have been neglected from the computational modeling of the pulmonary system, providing results that do not completely and accurately describe the hemodynamics of the vasculature. These specific aims were designed to identify the effects of respiration on pulmonary hemodynamics, determine a method for applying dynamic boundary conditions to a computational model, to incorporate the effects of respiration into dynamic boundary conditions, specifically for the pulmonary vasculature and to use the dynamic pulmonary boundary conditions to explore the effects of pulmonary arterial stenosis on pulmonary hemodynamics.

Specific Aim 1: Identify and Implement Dynamic Boundary Conditions

1A) Identify parameters for a geometry-based impedance boundary condition specifically for the pulmonary vasculature during maximal expiration by implementing an optimization routine within the fluid dynamics solver
1B) Use a scaling factor (respiration factor) to adjust the geometry to represent the pulmonary vasculature during maximal inspiration.
1C) Implement a time-varying outlet boundary condition and tailor it to the pulmonary vasculature using the parameters found in 1A and 1B.

Specific Aim 2: Collect Experimental Data to Quantify the Effects of Respiration on the Pulmonary Vasculature During Negative Pressure Ventilation (NPV)

2A) Collect pulmonary artery pressure and flow, as well as respiration cycle during PPV and NPV for two lamb lungs.
2B) Cast the lungs using methyl-methacrylyte casting material.

Specific Aim 3: Model the Pulmonary Vasculature Including Respiration

3A) Use the data collected in Aim 2, the dynamic boundary condition(s) found in Aim 1 will be tailored specifically to the pulmonary vasculature and the NPV respiratory cycle.

3B) Use the boundary conditions found in 3A to analyze the effects of pulmonary arterial stenosis on pulmonary hemodynamics.

1.5 Organization

The dissertation is organized into eight chapters. The following chapter, Background Methods, introduces the specifics of the fluid dynamic computational model used in all of the simulations discussed in this work. The solver and static boundary conditions used were developed in previous work [43, 52, 55, 56] and are reviewed here. Chapters three through seven discuss the individual studies completed. Chapter three outlines the identification of static outlet boundary conditions describing the pulmonary vasculature at expiration (Aim 1A) and inspiration (1B), while chapter four discusses implementation of a dynamic outlet boundary condition to incorporate dynamic distal network changes (Aim 1C). Respiratory and hemodynamic data were collected on open-chest lambs during PPV in previous studies and chapter five discusses the processing and statistical analysis on these data sets comparing the effects of respiratory rate and tidal volume changes on pulmonary hemodynamics. Chapter six discusses preliminary experimental data collection for NPV and PPV scenarios using the Lung-in-a-Box design protocol (Aim 2). The final aim (Aim 3) implements a dynamic boundary condition to represent the healthy pulmonary vasculature during normal breathing scenarios and the effects of pulmonary arterial stenosis on pulmonary hemodynamics, this is discussed in chapter seven. The final chapter in this work consists of general conclusions, implications and future work.
1.6 References


Chapter Two

Background Methods

2.1 Introduction

A wide variety of mathematical models exist that could be used to model the cardiovascular hemodynamics, including compartment models and fluid dynamics models. Compartment models [1, 2] describe the cardiovascular system with a series of mathematical equations and components (compartments). These models neglect the geometry of the large blood vessels, making a computationally efficient model. Fluid dynamics models [3-8] are models that can incorporate a specific geometry, as well as a hyperbolic series of equations that require both inlet and outlet boundary conditions in order to solve. The ability to include a specific geometry is an important feature when investigating changes to the geometry, such as a stenosis or the Fontan circulation. While, it is possible to incorporate these changes into a compartment model, it is more difficult to identify the parameter changes due to changes in geometry than to change the actual geometry of a fluid dynamics model. An additional limitation to not including the geometry as part of the model is the inability to calculate wave reflections. Experimental data includes the wave reflections that occur when the pressure and flow profiles reach a branching point. Without the geometry, there is no method for these wave reflections to occur and are therefore neglected.
2.2 One-Dimensional Fluid Dynamics Solver

This work utilizes a previously developed one-dimensional (1D) fluid dynamics solver [9-12]. As previously stated, there are advantages and disadvantages to using a 1D solver. The advantages include the ability to include geometry, and therefore wave reflection and propagation, at a reduced computational expense over three-dimensional (3D) analyses. The disadvantage is an inability to investigate wall shear stress and energy losses in complex flow situations.

The 1D solver assumes axial flow is dominant; therefore the remaining flow components could be neglected. It was also assumed that blood is a Newtonian fluid, as well as incompressible. The pressure, flow and area are calculated for the large vessel geometry, where laminar flow was assumed to be present. The vessel walls were considered to be impermeable. A no slip condition exists at the vessel walls, meaning that zero velocity components exist at the wall due to friction, leading to maximum velocity components at the center of the vessel [10, 11, 13, 14]. This leads to a parabolic flow profile, as shown in Figure 2.1.

![Figure 2.1: One-Dimensional Flow Profile. The one-dimensional assumptions for blood flow through a tube lead to a parabolic flow profile in the axial direction (x) through the blood vessel.](image)

The existing 1D finite element analysis tool uses the above assumptions to derive appropriate forms of the conservation of mass, equation (2.1), and momentum equations, equation (2.2), to solve for pressure, flow and area.
\[
\frac{\partial a}{\partial t} + \frac{\partial q}{\partial t} = 0 \quad (2.1)
\]
\[
\frac{\partial q}{\partial t} + \frac{\partial}{\partial x} \left( (1 + \delta) \frac{q^2}{a} \right) + \frac{a}{\rho} \frac{\partial p}{\partial x} = N \frac{q}{a} + \nu \frac{\partial^2 q}{\partial x^2} \quad (2.2)
\]

The above equation variables are defined by: \(a\) cross-sectional area (cm\(^2\)), \(q\) volumetric flow rate (cm\(^3\) s\(^{-1}\)), \(p\) pressure (dynes cm\(^{-2}\)), \(x\) axial location in the vessel (cm) and \(t\) time (s). The fluid properties are density \(\rho = 1.05\) (grams cm\(^{-3}\)) and kinematic viscosity \(\nu = 4.67 \times 10^{-2}\) (cm\(^2\) s\(^{-1}\)). The assumptions for flow previously discussed, plus the assumption that flow is through a circular cross-section lead to the following flow descriptions, equations (2.3) and (2.4).

\[
\delta = \frac{1}{3} \quad (2.3)
\]
\[
N = -8\pi\nu \quad (2.4)
\]

The 1D flow theory assumptions are not valid for complex flow situations that may occur, such as downstream of stenosis. The pressure losses associated with this more complex flow are not adequately calculated, therefore a minor loss coefficient \([15]\) must be included to incorporate these pressure losses, equation (2.5).

\[
K = \frac{\Delta p}{\frac{1}{2} \rho \left( \frac{q}{a} \right)^2} \quad (2.5)
\]
The dimensionless, experimentally determined $K$ term can be incorporated into the 1D solver by inclusion into the viscous term, $N$. The details of this derivation can be found in Steele, et al [11], however the resulting viscous term including the minor losses is shown in equation (2.6), where $L$ is the length (cm).

$$N = \frac{qK}{2L} \quad (2.6)$$

The minor loss term implemented was developed by Seeley and Young [16] for the stenosis model. The minor loss is calculated based on the ration between the area in the stenosed segment and the segment distal to the stenosis. This is discussed in detail in Steele et al [11], however the minor loss term is shown in equation (2.7).

$$K = 2 \left( \frac{K_v}{Re_o} + \frac{K_t}{2} \left[ \frac{a_o}{a_1} - 1 \right]^2 \right) \left( \frac{a_1}{a_o} \right)^2 \quad (2.7)$$

In the above equation, $K_v$ represents the viscous losses that are present and dominant at low Reynolds numbers, $Re_o$. $K_t$ represents the losses associated with turbulence. The subscript $o$ denotes the location distal to the stenosis, while a subscript $l$ denotes a location inside the stenosis. $K_t$ has been experimentally defined with an average value of 1.52. The details for the derivation of $K_v$, equation (2.8) can be found in Steele et al [11].

$$K_v = 32 \left( \frac{0.83L + 1.64D}{D_o} \right) \left( \frac{a_o}{a_1} \right)^2 \quad (2.8)$$

In the above equation, $L$ is defined as the length of the stenosis.
A third equation is required complete the system of three equations and three unknowns: pressure, flow and area. A constitutive equation is used to describe the vessel relationship between fluid pressure and wall deformation. The constitutive equation (2.9) used for this work is a linear-elastic model [5, 9].

\[
a(p(x,t),x) = \frac{a_o(x)}{\left(1 - \frac{r_o(x)}{Eh} p(x,t)\right)^2}
\]  

(2.9)

The above equation variables are defined by: \(a\) cross-sectional area (cm\(^2\)), \(q\) volumetric flow rate (cm\(^3\) s\(^{-1}\)), \(p\) pressure (dynes cm\(^{-2}\)), \(x\) axial location in the vessel (cm) and \(t\) time (s), \(a_o(x)\) (cm\(^2\)) is the unstressed area and \(r_o(x)\) (cm) is the unstressed radius of the vessel with respect to the axial location. The unstressed radius was assumed to be 86% of the diastolic radius [9, 17]. The elastic modulus term, equation (2.10), is defined as a constant \(c\), where \(Eh\) defines the properties the elastic wall properties of the systemic arteries [5, 9].

\[
Eh = c
\]  

(2.10)

2.3 Impedance

As previously discussed, the solution to the series of equations requires inlet and outlet boundary conditions, a variety of which are discussed in Section 1.3.4. This work utilizes an impedance boundary condition to represent the downstream network of vessels (outlet boundary conditions). This allows the incorporation of wave reflection and phase lag present in a branching geometry with pulsatile flow. The geometry-based impedance boundary condition previously derived from fractal-like trees [18, 19] was utilized throughout this work. Impedance \(Z\) is the frequency (\(\omega\)) domain based relationship between pressure \(P\) and flow \(Q\), as shown in equation (2.11).
\[ P(x,\omega) = Z(x,\omega)Q(x,\omega) \] \hspace{1cm} (2.11)

The convolution theorem, equation (2.12), provides the transition from pressure or flow in the frequency domain to the time domain.

\[ p(x,t) = \frac{1}{T} \int_{-T/2}^{T/2} z(x,t - \tau)q(x,\tau)d\tau \] \hspace{1cm} (2.12)

Further relationships are needed to describe the pressure and flow relationships at junctions or branching points, as shown in Figure 2.2.

\textbf{Figure 2.2: Junction within the Large Vessel Geometry.} At each junction or branching point, a parent and daughter vessels are defined. Relationships relating the pressure and flow between the parent and daughter branches are required and shown in equations (2.9) and (2.10).

Continuity of pressure is assumed at the junction, this establishes a relationship between pressure at the outlet of the parent vessel and the inlet to the daughter vessels. This assumes minimal pressure losses are present, which is a valid assumption when flow
is laminar. This has been shown to be a valid approximation for large blood vessels in previous experimental studies [20-22]. In the presence of turbulence, pressure losses begin to occur and the continuity of pressure may no longer be valid. The continuity of pressure equation is shown in equation (2.9).

\[ p_{\text{parent}}(L,t) = p_{d1}(0,t) = p_{d2}(0,t) \]  

(2.9)

It was also assumed that the flow in the two daughter vessels was equal to that in the parent vessel, as shown by the conservation of flow, equation (2.10). This simple assumes that no blood leaks out at the junction point.

\[ q_{\text{parent}}(L,t) = q_{d1}(0,t) + q_{d2}(0,t) \]  

(2.10)

These relationships are used to solve for pressure, flow and area in the large vessels of the computational model. As previously stated, outlet boundary conditions are needed to define the distal vessels.

**2.4 Structured-Tree Geometry**

The impedance boundary condition implemented in the 1D solver is calculated based on a bifurcating structured-tree [18, 19], shown in Figure 2.3. The structured-tree is constructed using a variety of parameters including branching exponents, length-to-radius ratios and asymmetry ratios that are combined to derive the scaling factors alpha and beta, shown in Figure 2.3. The length-to-radius ratio \( lrr \) defines the relationship between the length \( L \) and the radius \( r \) of each vessel segment in the structured-tree, equation (2.11).
Figure 2.3: Bifurcating Structured-Tree. The bifurcating structured-tree is ordered for computational efficiency using the scaling factors $\alpha$ and $\beta$. These scaling factors are used to scale the root radius for the appropriate order of the tree to determine radius.

\[ lrr = \frac{L}{r} \]  

(2.11)

The power law is used to relate the radius of the parent branch to the radii of the daughter branches at each bifurcation, equation (2.12) [23-25]. This law is derived based on the principle of minimum work and the value of the branching exponent, $k$, is based on the type of flow present. This is discussed further in Section 2.5.

\[ r_{\text{parent}}^k = r_{d1}^k + r_{d2}^k \]  

(2.12)

In addition to the branching exponent, $k$, the area ratio, $\eta$, defines the relationship between radii of the parent and daughter segments with an area conservation measure, equation (2.13).

\[ \eta = \frac{r_{d1}^2 + r_{d2}^2}{r_{\text{parent}}^2} \]  

(2.13)
The final parameter specified to define the structured-tree is the asymmetry ratio ($\gamma$). This term relates the radii of the two daughter vessels, equation (2.14).

$$\gamma = \frac{r_{d1}}{r_{d2}} \quad (2.14)$$

By combining the power law (2.12), the area ratio (2.13) and the asymmetry ratio (2.14) the scaling factors can be put into the terms of $k$ and $\gamma$.

$$\alpha = (1 + \gamma^{k/2})^{-\sqrt[k]{\gamma}} \quad (2.15)$$

$$\beta = \alpha \sqrt[2]{\gamma} \quad (2.16)$$

As shown in Figure 2.3, the scaling factors $\alpha$ and $\beta$ are used to order the structured-tree. This order allows for a reduction in computational costs due to pre-computed branches. The use of the scaling factors is shown in equations (2.17-2.19).

$$r_{d1} = \alpha r_{\text{root}} \quad (2.17)$$

$$r_{d2} = \beta r_{\text{root}} \quad (2.18)$$

$$r_{i,j} = \alpha^i \beta^{j-1} r_{\text{root}} \quad (2.19)$$

The impedance is then calculated from the structured tree. Equation (2.20) is the equation for the impedance at the axial location, ($x=0$), and for the frequency, $\omega$. 

29
In the above equation, $L$ is the length of the vessel, $c$ is the wave propagation velocity, which is dependent on radius and compliance and $g$ is the product of wave propagation velocity and compliance [23, 24]. At bifurcations the impedance is calculated as in a parallel circuit using daughter input impedance to calculate parent terminal impedance, equation (2.21).

$$\frac{1}{Z_p(L,\omega)} = \frac{1}{Z_{d1}(0,\omega)} + \frac{1}{Z_{d2}(0,\omega)}$$

(2.21)

### 2.5 Physiology of the Structured-Tree

The structured-tree parameters must have physiologic relevance in order to generate a physiologically relevant boundary condition. Experimental data has been previously collected and used to specify the parameters of the structured-tree. Length-to-radius ratio data has been collected from experimental data and estimated to be approximately $lrr = 50 \pm 10$ in the literature [26-28]. Zamir et al [25] also investigated this parameter and found that an appropriate range for the $lrr$ was $10 \leq lrr \leq 70$ depending on the location and size of the vascular bed/vessels. The power law exponent, $k$, is based on the type of flow in the tubes or vessels. For purely laminar flow $k = 2.33$ and for purely turbulent flow $k = 3.0$ [27, 29]. Olufsen et al [18, 19] chooses $k = 2.76$ for the flow through smaller arteries. Zamir et al [25] also provides a range of asymmetry ratios (between 0 and 1) [25].

The structured-tree was further refined for physiologic use by specifying three levels: capillaries ($r < 50\mu m$), resistance vessels ($50\mu m \leq r \leq 250\mu m$) and small arteries ($r > 250\mu m$) [6, 25]. This allowed for further specification of the tree based on location and function within the body. The levels of the tree are shown in Figure 2.4.
Figure 2.4: Structured-Tree with Three Levels. The three levels specify the three types of vessels present in the distal vascular beds. By designating the levels the trees can be given further organ specificity, as well as functional specificity.

This structured-tree implementation utilizes a power law exponent, $k$, and an asymmetry ratio, $\gamma$, for each level of the tree. Steele et al specified these parameters as shown in Table 2.1.

Table 2.1: Structure-Tree Parameters for a Three-Level Tree.

<table>
<thead>
<tr>
<th>Level</th>
<th>Power Exponent, $k$</th>
<th>Asymmetry Ratio, $\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Arteries</td>
<td>2.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Resistance Vessels</td>
<td>2.76</td>
<td>0.6</td>
</tr>
<tr>
<td>Capillaries</td>
<td>2.90</td>
<td>0.9</td>
</tr>
</tbody>
</table>

2.6 References


2007.


[16] B. D. Seeley and D. F. Young, "Effect of geometry on pressure losses across models


Chapter Three

Impedance Boundary Conditions for the Pulmonary Vasculature Including the Effects of Geometry, Compliance and Respiration

Rachel B. Clipp and Brooke N. Steele

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Abstract – With few exceptions, previous models of the pulmonary vascular system have neglected the effects of respiration. This practice is acceptable for normal cardiac function, however for compromised function respiration may be critical. Therefore, we have initiated the steps to develop boundary conditions that incorporate the effects of respiration through the use of an impedance boundary condition derived from a bifurcating structured tree geometry. The benefit to using the geometry based method lies in that strategic changes can be made to the geometry to mimic physiologic changes in vascular impedance. In this work, a scaling factor was used to modify the radius of resistance vessels of the structured tree to capture the maximum change in impedance caused by respiration. A large vessel geometry was established from a lung cast, the
structured trees were applied at the outlets and an experimental flow waveform was applied at the inlet. Finite element analysis was used to compute the resulting inlet pressure waveform. An optimization minimizing the difference between measured and computed pressure waveforms was performed for two respiratory states, maximal expiration and inspiration, to determine best-fit models for the pulmonary vasculature, resulting in pressure waveforms with an RMS error of 0.4224 and 0.7270 mmHg, respectively.

Index Terms—boundary conditions, computational modeling, pulmonary vasculature, respiration effects

3.1 Introduction

When modeling the vascular system it is important to consider the area of the body under investigation and ensure that enough organ-specific properties are applied to produce physiologically relevant solutions. Pulmonary physiology is subject to two different (pseudo) periodic inputs, the cardiac cycle and the respiratory cycle. In normal physiology, the respiratory cycle does not impact the cardiac cycle and is typically neglected when modeling the cardiopulmonary circulation. However, if the cardiopulmonary system is compromised, specifically if the right ventricle is not functioning properly, an increase in pulmonary resistance due to respiration may have a critical effect [1, 2]. This paper describes the first steps to create a model capable of representing alternate states of respiration. This was done by identifying geometric parameters for a fractal-like model that represents the functional impedance of a lung during the maximal expiration, followed by the determination of one additional parameter to scale the resistance vessels to represent maximal inspiration.

3.1.1 Pulmonary Physiology

Blood moves from regions of high to low pressure and the distribution of flow through a network is governed by relative impedance to flow. In the vascular system, impedance is modulated by variations in the radius of resistance vessels ($r \leq 250\mu m$). The impedance of the pulmonary vascular beds is governed by the relationship between
Airway and blood pressures. Airway, or alveoli, pressure is known to vary within the lung and is described by defining functional zones based on geometric location. The definition of zones, specifically the number of (2, 3 or 4) [3-5] and the role of gravity in the designation of lung function, is a topic currently being debated [6-9]. The first approach designates the zones of the lung by the vertical height citing the effects of gravity [3, 4, 10], while a second approach focuses on the horizontal flow planes where it is the large variations in branching patterns that delineate zones [11-13]. Upon further examination, it appears that both groups observe similar overall flow distributions, with little flow at the apex of the lung and more flow at the base. Based on this observation and because we are using a bifurcating structured tree we adopt the well-established vertical model by West and colleagues found in physiology texts [4, 14, 15].

West and colleagues [3, 4, 10] specify three zones that receive different amounts of blood flow based on the pressure relationship between alveoli $P_A$, pulmonary veins $P_v$ and pulmonary arterioles $P_a$. Zone 1, the upper third, receives little blood flow throughout the cardiac cycle due to the collapse of the arterioles that occurs when $P_A$ is greater than $P_a$. Zone 2, which typically consists of the center third of the lung, receives blood only during systole, when $P_a$ exceeds $P_A$, and $P_A$ exceeds $P_v$. Because blood flow is dictated by the relationship between $P_A$ and $P_a$, flow increases as $P_a$ exceeds $P_A$. In Zone 3, the lower third of the lung, $P_a$ and $P_v$ are greater than $P_A$, causing the arterioles to dilate and have unimpeded flow through the vessels [4, 10]. Zone 1 only occurs during disease or positive pressure ventilation and not in a normal healthy lung [4].

Vessel compliance is necessary to transition from pulsatile to steady flow. Because the pulmonary pressures are lower than those of the systemic circulation, the pulmonary arteries are similarly more compliant. There is disagreement in the studies conducted as to the degree of the compliance difference, suggesting that the pulmonary arteries are 2 to 10 times more compliant [16-18] as that of the vessels found in the systemic circulation. In this work, the pulmonary compliance is determined using experimental data.

Respiration modulates the impedance of the pulmonary vascular system. In normal respiration, changes in chest cavity volume change the pressure in the alveoli relative to
atmospheric pressure. This negative pressure ventilation (NPV), results in decreased alveoli pressure during inspiration and increased pressure during expiration. During ventilator assisted positive pressure ventilation (PPV) air is forced into the lungs creating the opposite effect, increasing alveoli pressure during inspiration and decreasing pressure during expiration. The effects of respiration on blood flow and pressure have been widely studied [19-23] for both PPV and NPV cases. Burton and Patel [21] found that in both cases the resistance to blood flow was not constant throughout the respiratory cycle, which is consistent with the premise that alveoli pressure variations alter the resistance of the vascular bed. In normal physiology, cardiac output is insensitive to respiration and consistent flow through the pulmonary system is achieved with an increase in pulmonary artery pressure comparable to the increase in alveoli pressure.

3.1.2 Computational Modeling

Clinical data collection focuses on the non-invasive capture of geometry and cardiac gaited flow. In a healthy cardio-pulmonary circulation, the right heart is able to generate pressure as needed to overcome any increase in pulmonary vascular resistance, which allows it to deliver a fairly consistent output that is insensitive to the effects respiration. Therefore, it is typical to neglect respiratory effects in cavo-pulmonary flow by using respiratory gaited or breath-held techniques to collect a periodic flow waveform. In computational modeling, it is common to impose such a periodic cardiac cycle as input to cardio-pulmonary models and impose outlet boundary conditions that are static or otherwise in phase with the cardiac cycle. Examples of this practice are seen in Pekkan’s use of a constant pressure boundary condition [24] and the use of static lumped parameter methods by de Leval, et al [25] and de Zelicourt, et al [26], and geometry based impedance boundary conditions by Spilker [27]. In the lumped parameter methods, pulmonary resistance was specified or mean pressure and flow rates were used to determine an average pulmonary resistance. While the effects of respiration on blood flow are minor in a healthy circulation, in a compromised cardio-pulmonary circulation, the effects of respiration are pronounced. Hjortdal, et al [28] shows how flow is impacted by variations in pulmonary vascular resistance in the absence of a functional right
ventricle. In this univentricular circulation, pulmonary flow is passive, driven by venous pressure that is at times insufficient to overcome the increase in pulmonary vascular resistance due to respiration. Marsden, et al [29] incorporates the effects of respiration by using a variable flow inlet boundary condition while maintaining static outlet boundary conditions. While this method was successful in modeling the impact of respiration on pulmonary blood flow, it overlooks the interaction between pulmonary vascular resistance and venous pressure that our proposed model will incorporate. A limitation of using the current lumped parameter model is that the pressure or resistance must be known a priori, either measured or assumed. While traditional lumped parameter methods use a small number of resistors, capacitors, and sometimes inductors to represent the behavior of a vascular bed, geometry based methods calculate the impedance directly from a geometry. Vascular impedance has been computed using random branching geometries [30], fractals [31], a variation of diameter-defined Strahler (DDS) geometry [27], and fractal-like structured trees [32-34].

The geometry of a human lung has been studied by Huang, et al [35], who noted that the branching pattern of the lung includes trifurcations and that much smaller branches originate from large branches. To organize this morphometry, Huang, et al used the DDS method. Spilker, et al [27] simplifies Huang, et al’s model by limiting the branching pattern to allow only bifurcations. While Spilker et al uses a geometry based impedance boundary condition to capture the phase shift between pressure and flow, he does not consider the effects of respiration.

The structured tree model [32] was proposed to increase the efficiency of impedance computation. With DDS and random trees, the computational algorithm must traverse every branch. The fractal like structured tree is organized to contain (N-1)! non-unique segment geometries, where N is the number of generations. Repeated segment geometries share a root impedance and need only be computed once. Therefore, for structured trees, impedance is computed for (N+1)! segments instead of 2^N segments for an unstructured bifurcating tree. This structured tree has been used to model specific organs and vessels within the systemic circulation [32, 33, 34]. Steele, et al introduced the use of a scaling
parameter $f_e$, to systematically modify the radii of resistance vessels within the tree to simulate the vascular response to exercise, $r_e = f_e r$ [34]. In this work, the small branches of each zone of the pulmonary vasculature at expiration are represented with structured trees, and a scaling parameter is used to modify the trees to simulate inspiration. The parameters defining the tree include a length-to-radius ratio $lrr$, branching exponent $k$, asymmetry ratios $\gamma$ and a scaling factor, $f_e$. The branching exponent and asymmetry ratios are combined to create scaling parameters $\alpha$ and $\beta$ for left and right branches so that a vessel radius is computed as $r_{i,j} = \alpha^i \beta^j r_{\text{root}}$, where $i$ and $j$ represent the number of left or right branching steps. The length-to-radius ratio, $lrr = L/r$, represents the relationship between the length $L$ and radius $r$ for each segment of the structured tree. The asymmetry ratio, $\gamma = r_1/r_2$, relates the radius of the two daughter vessels at each bifurcation [36]. The power law $r_p^k = r_{d_1}^k + r_{d_2}^k$ is used to describe the relationship between the parent vessel and the two daughter vessels. Studies show that the branching exponent $k$ varies between 2 and 3 [36-38], increasing as vessel diameter decreases. Steele, et al introduced diameter dependant levels representing small arteries, resistance vessels and capillaries [34], allowing the use of level specific parameters without impacting the efficiency of the structured tree.

The objective of this work was to use bifurcating structured trees to represent the small vessels of each zone to establish an impedance boundary condition specific to the pulmonary vasculature. An optimization routine was used to fit structured tree parameters based on the assigned zone for the expiration case. Maintaining the parameters found in the expiration optimization, an inspiration optimization was performed to find the scaling factors to represent the function of the altered geometry at maximal inspiration. This work differs from others by being the only work to establish impedance boundary conditions that consider zone specific behavior at specific states of the respiratory cycle.
3.2 Methods

3.2.1 Experimental Data

The experimental data used in this work was the control data collected in our lab from studies performed on open-chested lambs to investigate hemodynamics associated with Fontan repair [22, 23]. Lambs weighing between 10 and 25 kilograms are comparable in size and age to the patient population of interest. All animals were cared for in accordance with NIH Publication No. 86-23, revised 1985 and the standards of the Institutional Animal Care and Use Committee of the University of North Carolina at Chapel Hill. The animal was sedated, intubated, and ventilated at 10–15 ml/kg without any positive end expiratory pressure or adjusted accordingly to maintain optimal arterial blood gas tensions. A Validyne pneumotachometer (Validyne Engineering, Northridge, CA) was introduced into the air circuit in order to monitor and record airflow and a fluid filled polypropylene catheter was inserted and connected to a Statham P23Gb transducer (Statham Transducer P23Gb, Siemens) to measure airway pressure. A mid-sternotomy was performed that started at approximately the sixth interspace. A Millar Mikro-Tip Catheter (MPC-500, Millar Instruments, Houston, TX) pressure transducer was introduced and positioned in the main pulmonary artery (MPA), and Transonic T206 Small Animal Blood Flow probe (Transonic Systems Inc., Ithaca, NY) was positioned around the MPA. Data were recorded at a rate of 200 Hertz for individual episodes of 5.12 seconds or 1024 data points/episode (Figure 3.1).

This data shows the same PPV respiration effects that were found by Burton and Patel [21]. As expected, the blood flow in the MPA is relatively insensitive to the effects of respiration with only a slight depression at maximal inspiration. However, the increased pulmonary resistance coupled with a consistent cardiac output results in a significant increase in MPA blood pressure at maximal inspiration.
Figure 3.1: Experimental Data Showing the Effects of Respiration. The MPA blood flow (left, grey line) does not change significantly with changes in air pressure due to respiration (black line), because a normal heart will overcome any change in resistance to maintain blood flow. The blood pressure (right, grey line) is significantly impacted by the changes in air pressure and related resistance changes that occur with respiration (black line) [22].

3.2.2 1-D Finite Element Analysis

An existing finite element analysis (FEA) solver was used to determine the blood pressure and blood flow in the large pulmonary vessels. The one-dimensional (1D) FEA system developed by Steele, et al assumes incompressible, Newtonian, axially dominated flow with a parabolic profile [39-42]. Using these assumptions, 1D equations for the conservation of mass equation (3.1) and balance of momentum equation (3.2) can be appropriately derived and used to solve for blood pressure and flow.

\[
\frac{\partial a}{\partial t} + \frac{\partial q}{\partial x} = 0 \tag{3.1}
\]

\[
\frac{\partial q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{4}{3} \frac{q^2}{a} \right) + \frac{a}{\rho} \frac{\partial p}{\partial x} = -8\pi \nu \frac{q}{a} + \nu \frac{\partial^2 q}{\partial x^2} \tag{3.2}
\]

The variables in the equations are: \( a \) cross-sectional area (cm\(^2\)), \( q \) volumetric flow rate (cm\(^3\) s\(^{-1}\)), \( p \) pressure (dynes cm\(^{-2}\)), \( x \) axial location in the vessel (cm) and \( t \) time (s).
properties of the fluid are defined by the \( \rho \) density (g cm\(^{-3}\)) and the \( \nu \) kinematic viscosity (cm\(^2\) s\(^{-1}\)).

3.2.3 Lung Geometry

The large vessel geometry was created from a methyl methacrylate cast of lamb lungs created during work by Zhao [44]. Digital calipers were used to obtain measurements of the radius, length and position of vessels including the MPA and the subsequent three to four levels of pulmonary arteries (Figure 3.2). There are 34 vessel outlets in the geometry, which receive the impedance boundary condition as discussed in section 2.4. The radius at the outlets of these vessels range from approximately 0.35 cm to 0.1 cm, while the inlet of the main pulmonary artery has a radius of approximately 1.32 cm.

![Figure 3.2: Pulmonary Model](image)

*Figure 3.2: Pulmonary Model.* The large vessel geometry was defined from the measurements of a lung cast taken from a lamb. The one-dimensional solver calculates the flow, pressure and area in these large vessels. The bifurcating structured tree impedance boundary condition that represents the small arteries and microvasculature of the pulmonary arteries was applied at the outlets of the large vessel geometry. These structured trees were parameterized to represent the function in the different zones of the lung. The inlet boundary condition was specified as the experimental blood flow in the main pulmonary artery.
3.2.4 Boundary Conditions

Boundary conditions were specified for every inlet and outlet of the large vessel geometry. A representative expiration blood flow waveform was selected from the experimental data and applied as the inlet for the MPA. The outlet boundary conditions were specified as impedance computed from structured trees and prescribed at the outlet of each of the vessels shown in Figure 2.2. The structured tree parameters were specified to represent both the function of the zone and respiratory state. Although there is ongoing debate regarding the exact number and organization of the zones of the lung, the vertical West model [3, 4, 10] was adopted for this work. West suggested that two zones are present in a normal lung and three zones are present under PPV [4]. Both the two and three zone models were considered. The outlet zones were classified based on vertical position. Structured tree parameters were considered to be uniform within a zone so only one structured tree was found for each zone. Two different parameter combinations were used. The first method used a global \( lrr \) for all zones and zone specific scaling factors \((f_p)\), while the second method used zone specific \( lrrs \) to model the distribution of impedance in the lung. Both of these methods allowed each structured tree to be divided into three levels based on vessel radius. In each of the three levels, an asymmetry ratio and branching exponent were specified. From visual inspection of the lung casts we saw no significant change in the branching pattern in the different zones, leading to the assumption that the asymmetry ratios and branching exponents were uniform. Therefore, one set of asymmetry ratios (3) and branching exponents (3) were common to all structured trees.

To represent the change in impedance that occurs during the respiration cycle, a respiration factor \( f_R \) was introduced to mimic the effects inspiration and expiration have on the vascular bed. Two methods were used to mimic the effects of respiration. The first method assumed that the effects of respiration were uniform throughout zones, requiring a global \( f_R \), while the second method assumes zone specific \( f_R \).

Once the geometry of a structured tree has been established impedance is calculated.
based on the equations derived in detail by Olufsen, et al [32]. Briefly, the impedance at the inlet of the vessel ($x = 0$) is calculated based on vessel geometry and the terminal impedance at the outlet of the vessel ($x = L$) as shown in equation (3.3).

$$Z(0, \omega) = \frac{ig^{-1} \sin(\omega L / c) + Z(L, \omega) \cos(\omega L / c)}{\cos(\omega L / c) + igZ(L, \omega) \sin(\omega L / c)}$$  \hspace{1cm} (3.3)

In the above equation, $L$ is the length of the vessel, $c$ is the wave propagation velocity, which is dependent on radius and compliance and $g$ is the product of wave propagation velocity and compliance. The compliance of the pulmonary arteries is discussed further in section 3.5. At bifurcations the impedance is calculated as in a parallel circuit using daughter input impedance to calculate parent terminal impedance (equation 3.4).

$$\frac{1}{Z_p(L, \omega)} = \frac{1}{Z_{d1}(0, \omega)} + \frac{1}{Z_{d2}(0, \omega)}$$  \hspace{1cm} (3.4)

3.2.5 Compliance of the Pulmonary Arteries

In addition to the conservation of mass and balance of momentum equations, constitutive equations, equations (3.5-3.6) [32] characterizing the vessel properties, were used in the 1D solver.

$$p(a(x,t), x, t) = p_o + \frac{4}{3} \frac{Eh}{r_o(x)} \left(1 - \frac{a_o(x)}{a(x,t)} \right)$$  \hspace{1cm} (3.5)
\[ \frac{E h}{r_o(x)} = k_1 e^{k_2 r_o(x)} + k_3 \] (2.6)

\( P_o \) is the unstressed pressure that produces \( r_o(x) \), the unstressed radius of the vessel with respect to the axial location, \( a_o(x) \) is the unstressed area of the vessel with respect to the axial location, \( h \) is the arterial wall thickness, and \( E \) is Young’s Modulus. In equation (3.6), the radius dependent modulus is an exponential curve with coefficients based on experimental data from the systemic circulation [33].

**Table 3.1: Pressure Gradients and Compliance Parameters.** Pressure gradients were computed using a multiplier, \( m \), to scale the radius dependent modulus to find the value closest to the average experimental gradient, 8.73 mmHg. The pressure gradient for \( m = 0.3 \) was closest to that of the average experimental pressure, therefore was chosen to modify the radius dependent modulus.

<table>
<thead>
<tr>
<th>Multiplier, ( m )</th>
<th>Pressure gradient, ( \Delta P, \text{mmHg} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>4.1634</td>
</tr>
<tr>
<td>0.2</td>
<td>7.2919</td>
</tr>
<tr>
<td>0.3</td>
<td><strong>9.0646</strong></td>
</tr>
<tr>
<td>0.4</td>
<td>10.6518</td>
</tr>
<tr>
<td>0.6</td>
<td>12.3936</td>
</tr>
<tr>
<td>0.8</td>
<td>13.4563</td>
</tr>
<tr>
<td>1</td>
<td>14.0616</td>
</tr>
</tbody>
</table>

Pulmonary arterial pressure and vessel compliance are both lower than systemic values. The mean (unstressed) pressure value was reduced from 80 mmHg to 15.5 mmHg, as determined from experimental blood pressure data. To specify the modulus of the pulmonary arteries, we used the same radius dependent exponential curve, and reduced the overall modulus by scaling the \( k_3 \) term of equation (3.6) by a multiple, \( m \). Compliance dominates the pressure gradient, \( \Delta P \), the difference between systolic and diastolic pressure. Therefore, 1D analyses were performed using un-optimized
impedance boundary conditions for each \( m \) shown in Table (3.1) to compute the MPA \( \Delta P \). The \( \Delta P \) associated with \( m = 0.3 \) most closely matched that of the average experimental \( \Delta P \) and was used to modify the exponential curve.

3.2.6 Optimization Algorithm

The impedance parameters were optimized by comparing the computed inlet pressure waveform to experimental data using the Nelder-Mead optimization algorithm in the Gnu Scientific Library. An error vector was created by calculating the difference between the computed pressure and the experimental pressure at each time step. The least-squares error was calculated and minimized for the error vector. The analysis was run for four cardiac cycles to ensure a steady state solution was reached. Each cardiac cycle contained 50 time steps for a total of 200 time steps for each iteration. An optimization was performed for four model variations: zonal \( lrr \) with three zones (Z3) and two zones (Z2) and global \( lrr \) for three zones (G3) and two zones (G2). Because the majority of the respiratory cycle is in the expired state, this was considered to be the base state for the structured tree parameters. The inspired state was derived using the expired parameters and \( f_R \). The parameter initializations, shown in Table 3.2, are discussed in detail below.

3.2.6.1 Maximal Expiration

For the expired state, the \( \gamma \), \( k \), \( lrr \) and the \( f_P \) were initialized based on physiologic data found in the literature prior to optimization. Asymmetry ratios were found to be neither organ specific nor constant, with values ranging between 0 and 1 [36, 44]. The initial values were chosen as the median value, 0.5. The branching exponents were found to have values between 2 and 3 [36-38] and were initialized using the values in the previous 1D FEA found in Steele, et al [34]. These six parameters are consistent for all zones. Length-to radius ratios were found to be highly variable with a maximum value of 70 and a mean value of 20 [36]. Because the vessels in Zone 3 may bulge or “balloon” due to the relationship between arteriole and alveoli pressure, we assumed the \( lrr \) could have a minimum of 10. For model Z3, the range of \( lrr \) [10,70] was sub-divided into three
sub-ranges and a value within each sub-range was used to initialize the respective zonal $lrr$. For model Z2, it was assumed Zone 1 did not exist and the values for the zone dependent $lrr$s were raised slightly to account for the increased resistance that would have to exist in Zones 2 and 3. For models G3 and G2, the global $lrr$ was initialized at 25 as in Steele, et al [34] and the zonal pulmonary scaling factors were used to differentiate the zones. It was assumed that Zone 2 would be the baseline zone with a $f_P$ initialized at 1.0. To reduce the flow in Zone 1, the $f_P$ was initialized to 0.35. To represent the ballooning effect in Zone 3, the $f_P$ was initialized at 1.25. For model G3, Zone 1 was assumed to not exist, but no change was made to the initialization of parameters of Zones 2 and 3.

Table 3.2: Initialization for the Parameter Optimization at Maximal Expiration. The parameters were initialized as shown in the table for all of the models. The NA indicates that a parameter was not applicable to that model. Global parameters are applied to all structured trees within the lung, while the zone dependent parameters were applied based on lung zone geometry.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>3Z</th>
<th>2Z</th>
<th>3G</th>
<th>2G</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>$\gamma_3$</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>$k_1$</td>
<td>2.51</td>
<td>2.51</td>
<td>2.51</td>
<td>2.51</td>
</tr>
<tr>
<td>$k_2$</td>
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<tr>
<td>$k_3$</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>$lrr$</td>
<td>NA</td>
<td>NA</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td><strong>Zone Dependent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Local) Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$lrr_{1}$</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$lrr_{2}$</td>
<td>35</td>
<td>45</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$lrr_{3}$</td>
<td>55</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$f_{P1}$</td>
<td>NA</td>
<td>NA</td>
<td>0.35</td>
<td>NA</td>
</tr>
<tr>
<td>$f_{P2}$</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$f_{P3}$</td>
<td>NA</td>
<td>NA</td>
<td>1.25</td>
<td>1.25</td>
</tr>
</tbody>
</table>

3.2.6.2 Maximal Inspiration

After completing the optimization of the structured tree parameters for expiration, a
second optimization was performed to find the $f_R(s)$ required to model maximal inspiration. The previously optimized structured tree parameters were held constant during this optimization. For this analysis, two methods were used to mimic the effects of respiration. The first method assumed that the effects of respiration were uniform across the entire lung, creating a global $f_R$ that was initialized at 0.915 for all four models. The second method assumes that the effects of respiration are not uniform across the zones of the lung and zone dependent $f_R$ were used. These $f_R$ were initialized using the optimized global value found in method 1. The initialized values are shown in Table 3.3.

Table 3.3: Initialization for the Parameter Optimization at Maximal Inspiration. The parameters were initialized as shown in the table for all of the models. Each model was optimized twice, once with a global respiration factor ($rG$) and once with zone dependent respiration factors ($rZ$). The (NA) indicates that a parameter was not applicable to that model. Global parameters are applied to all structured trees within the lung, while the zone dependent parameters are applied based on lung zone geometry.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>3ZrG</th>
<th>3ZrZ</th>
<th>2ZrG</th>
<th>2ZrZ</th>
<th>3GrG</th>
<th>3GrZ</th>
<th>2GrG</th>
<th>2GrZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Parameters</td>
<td>$f_R$</td>
<td>0.915</td>
<td>NA</td>
<td>0.915</td>
<td>NA</td>
<td>0.915</td>
<td>NA</td>
<td>0.915</td>
</tr>
<tr>
<td>Zone Dependent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>(Local) Parameters</td>
<td>$f_{R1}$</td>
<td>NA</td>
<td>0.905</td>
<td>NA</td>
<td>0.905</td>
<td>NA</td>
<td>0.905</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>$f_{R2}$</td>
<td>NA</td>
<td>0.905</td>
<td>NA</td>
<td>0.905</td>
<td>NA</td>
<td>0.905</td>
<td>NA</td>
</tr>
</tbody>
</table>

3.3 Results

3.3.1 Maximal Expiration

The four models analyzed for this work were optimized for the expiration case and the pressure waveforms can be seen in Figure (3.3). For all cases, 2 zones were better than 3 zones and zonal lrr models were better than global lrr models. The optimized model that best fit the experimental data was model Z2, which had an RMS error of 0.4224 mmHg, which is less than 3% error when compared to the experimental mean pressure for the expiration.
Figure 3.3: Expiration Optimization Pressure Results. The four plots above show the blood pressure for expiration in the experimental data (light, grey line) and the computed model (black line). The root mean square (RMS) error is indicated on each plot. Model Z2 was the best-fit optimized model with an RMS error of 0.4244 mmHg or less than 3% error.

3.3.2 Maximal Inspiration

The optimization for maximal inspiration was performed twice, once with a global $f_R$ and once with zone dependent $f_R$. The pressure waveforms for the optimizations of the four models are shown in Figure (3.4). As in the expiration case the zonal $lrr$ models are a better prediction of the experimental data than the global $lrr$. As in the expiration case, the Z2 model is slightly better than the Z3 model for the zonal respiration factors, however the Z3 model is slightly better than the Z2 model for the global respiration case. Because the geometry was held constant except for the radii of the arterioles, the computed inspiration waveforms do not exhibit a significant change in shape, rather they primarily exhibit a mean offset. The Z2 model has a less than 4% error when compared to the experimental mean pressure for maximal inspiration, which is 0.7270 mmHg RMS error.
Figure 3.4: Inspiration Optimization Pressure Results. The four plots show the blood pressure at inspiration for the experimental (black dotted line), the zonal respiration factor model (light, grey line) and the global respiration factor model (black line). The root mean square (RMS) error for both computed models are indicated on each plot. The Z2 model with zonal respiration factors was found to be the best-fit optimized model with an RMS error of 0.7270 mmHg or less than 4% error.

3.3.3 Optimized Model

The Z2 model was found to best represent both expiration and inspiration. While, the Z3 models performed slightly better for the inspiration model with a global respiration factor, the best overall inspiration model was the Z2 zonal respiration factors model, therefore the Z2 model was chosen. The optimized parameters are shown in Table (3.4).
Table 3.4: Optimized Structured Tree Parameters. The best-fit optimized model was the 2ZrZ model, which has zonal length to radius ratios and zonal respiration factors. These parameters associated with the model are shown in the table.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>2ZrZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_1$</td>
<td>0.715</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>0.596</td>
</tr>
<tr>
<td>$\gamma_3$</td>
<td>0.459</td>
</tr>
<tr>
<td>$k_1$</td>
<td>2.938</td>
</tr>
<tr>
<td>$k_2$</td>
<td>2.845</td>
</tr>
<tr>
<td>$k_3$</td>
<td>2.973</td>
</tr>
<tr>
<td>$lrr_2$</td>
<td>41.365</td>
</tr>
<tr>
<td>$lrr_3$</td>
<td>23.047</td>
</tr>
<tr>
<td>$f_{r2}$</td>
<td>0.93</td>
</tr>
<tr>
<td>$f_{r3}$</td>
<td>0.915</td>
</tr>
</tbody>
</table>

The impedance for the Z2 model and the experimental data are shown in Figure (3.5). The percent error of the first harmonic, also known as the equivalent resistance, is approximately 1.03% for the expiration state and 2.01% for the inspiration state. The modulus for inspiration is unable to capture the content in the higher frequencies, displaying a more muted response. This is not as pronounced for the expiration case. The impedance phase for the Z2 model shows a response that is accurate for approximately the first 6 harmonics, but after that the computed data remains muted while the experimental data becomes more dynamic.
Figure 3.5: The Impedance Modulus and Phase. The impedance is shown for both the expiration and inspiration state for the optimized model (black line) and the experimental data (light, grey line). The equivalent resistance is indicated on the plot for both the experimental and optimized models. The percent error for the resistance is approximately 1.03% for the expiration state and approximately 2.01% for the inspiration state.

3.4 Discussion

The goal of this work was to identify the parameters for the structured tree based impedance boundary condition that approximates the function of the small vessels of the pulmonary vasculature. A 1D FEA was used to compute the pressure and flow distribution for a model of the large pulmonary vessels. Structured trees were used to calculate the outlet boundary conditions of the large vessels and a flow waveform extracted from experimental data was used as the inlet boundary condition. The structured tree parameters were optimized by comparing the computed inlet pressure waveform to experimental data. While there is a general trend for the computed amplitude to have fewer oscillations than the measured data, the optimized parameters for
both inspiration and expiration produced pressure waveforms that are reasonable approximations of the experimental waveforms. While this work demonstrates only the first steps, it is anticipated that such a morphometry based model of the small pulmonary arteries will translate between similar subjects eliminating the need for pulmonary pressure measurements that are not easily captured in vivo.

The 1D solver, using minor loss coefficients to include pressure loss associated with branching and stenoses, is validated for modeling flow through vascular networks [41]. While the 1D solver does not provide the same detailed map of hemodynamic phenomena as a 3D solver, these phenomena were not pertinent to the specification of a pulmonary boundary condition. Because the flow distribution through the lung is still a topic for debate, a detailed map of flow would lack validation. Additionally, the detailed features of the 3D model are dependent on wall properties, vessel motion, and boundary conditions, all of which are not easily quantified. Therefore, our method to create a representative boundary condition for the pulmonary system using impedance and a 1D model can provide the function of the lung without the expense of a 3D model. In future work, this simplified yet effective boundary condition can be coupled to a 3D solver of the larger pulmonary branches when detailed features are desired, as in the Fontan circulation where the hemodynamics of the reconstructed areas are important. It is anticipated that outlet flow from the 3D solver will be specified as the inlet to the 1D pulmonary model which will return an impedance based pressure. This pressure value will then be applied to every vertex on the outlet face of the 3D model.

The 1D solver was modified to reflect the more compliant pulmonary vessels. The pulmonary compliance was found by scaling an existing arterial compliance model [33] by comparing computed and experimental $\Delta P$. The resulting pressure strain elastic modulus used in this study was 230 gcm$^{-2}$, which is 3.33 times more compliant than the systemic model. This modulus falls within the range of published pulmonary data [16, 17]. Future work will include testing tissue samples from different anatomical locations in the lung to determine if the compliance is uniform or strain dependent, which may explain the differences in $\Delta P$ found between expiration and inspiration previously.
discussed.

The experimental data used in this study was collected in ventilated, open-chested lambs resulting in a PPV scenario. The $\Delta P$ due to inspiration in PPV is opposite to the $\Delta P$ found in free breathing or NPV. This difference will affect the structured tree parameters in one of two ways. In the first case, the expired state is similar in both PPV and NPV, with alveoli pressure equal to atmospheric pressure. This would result in the use of the same optimized PPV expiration parameters for the expired NPV case with new $frs$ to decrease inspired NPV pulmonary resistance. In the second case, the airway pressure in close-chested NPV is a mirror image of the PPV case. This could be modeled by simply reversing the current structured trees, allowing the current maximal inspiration structured tree to represent expiration and vice versa. Further experimental data is needed to validate a negative pressure model.

The boundary conditions for this model were based on a periodic cardiac cycle. While there are beat-to-beat variations in heart rate and stroke volume, the cardiac output is generally assumed to be periodic for computational models. Because the impedance boundary condition computes the relationship between periodic pressure and flow waveforms it is superior to pure resistance in that it can capture the phase lag that is present in visco-elastic arteries. In addition, with pulsatile flow and distensible arteries, negative flow occurs during diastole (Figure 2.1), which, unlike impedance, will result in negative pressure if a resistance boundary condition is used. During active ventilation, the pressure waveform is not periodic. However, this paper only sought to identify the limits of impedance during expiration and inspiration. The next step in this work is to implement a dynamic transition that will address the time varying changes in vascular resistance.

The optimization algorithm used in this study determines a local minimum for the error, therefore the optimized parameters found are not unique and a different combination of parameters may provide equally as accurate results. Because the algorithm did not use upper and lower bounds to constrain the parameters, it was necessary to carefully select the physiologic initial values, as discussed in section 2.6 and
compare the optimized values to the physiologic ranges found in literature [34, 36-38, 44]. While the results of the Z2 and Z3 models were very similar, the Z2 model has a slightly lower RMS error, and was therefore the best fit model. It should be noted that the Z2 model had fewer parameters than any other model. The Z2 RMS error was 0.4224 mmHg for the expiration state, which is an error of less than 3%. The main errors for the computed waveform lie in the $\Delta P$ and the absence of high frequency oscillations. The $\Delta P$ is dominated by vessel compliance, which was prescribed by scaling a radius dependent modulus by a factor $m$ to produce a $\Delta P$ representative of the experimental data. The representative experimental $\Delta P$ was found by averaging the dissimilar gradients measured for inspiration and expiration. Therefore, the vessel compliance is expected to result in under-estimation of expiration and over-estimation of inspiration pressure. The high frequency oscillations are produced by high frequency impedance components which are absent from the computed data. This error may be reduced by optimizing more parameters in the structured tree (i.e. using fewer global variables) or selecting an alternate branching strategy. For the inspiration state, the RMS error was 0.7270 mmHg or less than 4% error. This error was expected to be higher than expiration, because at most three parameters were used to optimize models with at best approximately 3% error. In future work, it is anticipated that inspiration errors will decrease as expiration models are improved as described above.

This first step in developing a pulmonary specific boundary condition provides a foundation upon which we will continue to work to improve our ability to model the function of the pulmonary vasculature. The limitations found in this study will be addressed in future work, such as implementation of a time varying resistance boundary condition, the compliance of the pulmonary arteries, parameter identification and branching strategies that will capture high frequency pressure oscillations and functional data collection using negative pressure ventilation. We will also investigate subject specific variations and the ability to use allometric scaling to modify the large vessels while maintaining a generic pulmonary boundary condition.
3.5 Acknowledgements

We would like to acknowledge the team that collected the experimental data used here: Dr. Carol Lucas, Dr. Warner Lucas, Dr. Mark Ketner, Dr. M.R. Mills and Dr. Brett Sheridan under a BRP grant from the National Heart, Lung, and Blood Institute, HL67622.

3.6 References


Chapter Four

An Evaluation of Dynamic Outlet Boundary Conditions in a 1D Fluid Dynamics Model

Abstract: When modeling the cardiovascular system, the use of boundary conditions that closely represent the interaction between the region of interest and the surrounding vessels and organs will result in more accurate predictions. An often-overlooked feature of outlet boundary conditions is the dynamics associated with regulation of the distribution of pressure and flow. This study implements a dynamic impedance outlet boundary condition in a one-dimensional fluid dynamics model using the pulmonary vasculature and respiration (feedback mechanism) as an example of a dynamic system. The dynamic boundary condition was successfully implemented and the pressure and flow were predicted through an entire respiration cycle. The cardiac cycles at maximal expiration and inspiration were predicted with a root mean square error of 0.61 mmHg and 0.59 mmHg respectively.

4.1 Introduction

Mathematical models can be used to improve our understanding of physical systems. Sufficiently accurate computer models of the cardiovascular system may be used to design improved treatment options by predicting blood flow distribution and pressure due
to disease [1,2] or as a result of surgical intervention [3-5]. While the potential of using computational modeling to improve patient care is tremendous, several challenges must be overcome before predictive models can be included in routine clinical use. In this work we describe how to incorporate downstream (i.e. distal) dynamic phenomena into a local hemodynamic model of blood flow and pressure. This method may be used to consider the effects caused by regulatory or feedback mechanisms in specific organ systems, such as respiration [6-9] or pressure regulation within the renal system [10,11]. These regulatory mechanisms can modulate flow, maintain pressure (i.e., renal nephrons) or cause pressure increases due to the interaction between two physiologic systems (i.e. pulmonary arterioles and alveoli). The inclusion of distal dynamics may improve the predictive ability of models that previously assumed static distal hemodynamic behavior.

4.1.1 Boundary Conditions

A variety of static boundary conditions have been used to model distal vascular beds, including constant pressure [12], resistance [13], lumped parameter models [14-16] and geometry-based impedance [1,17-19]. While trivial to implement, constant pressure representations are a poor choice in compliant walled models with pulsatile flow for all but a few circumstances where the pressure is steady. The specification of measured pressure or flow waveforms at both inlet and outlet vessels may be problematic if the vessel compliance is not known. Resistance boundary conditions provide an alternative in the form of a constant relationship between pressure and flow. As with pressure, this relationship is not always realistic, including in regions where retrograde flow is present that would lead to negative pressure. Additionally, the resistance boundary condition does not incorporate the effects of damping nor does it enable the model to account for wave propagation or the phase lag between pressure and flow waves found in compliant vessels [20,21]. These resistance limitations can be overcome by using an impedance boundary condition. Lumped parameter impedance models have typically been derived from electrical analog circuits comprised of resistors, capacitors and/or inductors fit to experimental data to represent a vascular network [15,22]. In the absence of data at the outlets, or in predictive models where the modeled region of interest impacts flow
distribution, it is difficult to determine reasonable lumped parameters for each outlet. This lumped parameter limitation is overcome by using geometry-based methods to calculate the impedance of a representative vascular geometry (i.e., fractal-like model) using Womersley’s method [20,23,24]. Such geometries can be directly measured or based on a derived structured tree representing a vascular region [18,19]. Previous work tailored impedance boundary conditions to specific vascular regions at specific physiologic states, such as the pulmonary vasculature at inspiration and expiration [1,17], or viscera, peripheral, and pulmonary vascular beds at rest and exercise [13,19,25]. Although impedance boundary conditions may be tuned to accurately represent the pulsatile relationship between pressure and flow over a cardiac cycle, these outlet boundary conditions are static in that they do not change over time to reflect physiologic changes outside of the cardiac cycle.

The representation of dynamic physiology has been presented previously by Marsden et al [13,25] and Kim et al [26]. In investigations of the effects of respiration on TCPC (total cavo-pulmonary connection) subjects, Marsden, et al [13,25] incorporated the effects of respiration into the inlet flow. TCPC patients lack a functioning right-heart, so pulmonary flow is dependent on venous return, respiratory and peripheral pumps [27,28]. Modifying the inlet flow waveform is an effective method for representing the effects of respiration in the compromised Fontan circulation, however it does not consider the cause, i.e., impedance changes due to arteriole constriction in the lung. In cases where measured flow is used as the inlet boundary condition, the effects of downstream influences, such as impedance changes, cannot be distinguished from driving forces. Therefore, care must be taken when prescribing boundary conditions to ensure that their selection does not unnecessarily influence computational results; especially when modifications (i.e., treatment planning scenarios) made in one location may influence hemodynamics in another location. Kim et al [26] incorporates a dynamic boundary condition in a model of the coronary arteries. The inlet boundary condition was specified as a contraction (i.e., pressure increase) in the cardiac tissue to pump blood. This contraction was coupled with the outlet boundary condition of the coronary arteries. This
coronary pressure provided feedback to the downstream vascular bed, altering the vascular impedance in the coronary artery beds based on location and cardiac output. This model effectively describes a dynamic boundary condition of the coronary arteries, but does not consider dynamics that are not coupled to the cardiac cycle or inlet boundary condition.

4.1.2 Respiration as a Feedback Mechanism

In this work, respiration is considered as an example of distal dynamics that is not coupled to the cardiac cycle. While the pulmonary system is not specifically performing a regulatory function with respiration, the arterioles in the pulmonary system are subject to systematic fluctuations in alveolar arteriolar pressure that result in the modulation of arteriole diameter and pulmonary vascular impedance. The effects of respiration on pulmonary pressure, flow and impedance have been studied for both the healthy [6-9] and the compromised cardio-pulmonary systems [29,30]. For the healthy lung, Burton and Patel [6] conducted animal studies for both positive pressure ventilation (PPV) and negative pressure ventilation (NPV) in which they concluded that pulmonary impedance is variable throughout the respiratory cycle for both ventilation methods. In normal circulation, this change in impedance does not impact the cardiac output due to the ability of the healthy heart to increase driving pressure as required to overcome any increase in impedance. In a compromised cardiopulmonary system, the fluctuations in pulmonary impedance may have a critical effect on both pulmonary pressure and flow, because without a healthy right ventricle to drive against the increased impedance, flow through the pulmonary arteries may halt or reverse. Therefore, the effects of respiration are critical to the computational analyses of compromised cardio-pulmonary systems and must be considered when using these analyses to assess treatment options.

Models of the pulmonary physiology have been used to investigate pulmonary stenosis and the potential surgical outcomes to resolve the stenosis [1], as well as possible repair options associated with congenital heart defects, such as a Fontan procedure, known as TCPC [12,13,15,31]. However, the majority of pulmonary models have ignored the effects of respiration when incorporating the downstream network. Marsden,
et al [13] found that including the effects of respiration produced results that led to a
different optimal surgical solution when considering the Fontan circulation.

The objective of this work was to extend the work of Kim et al [26], Marsden et al
[13,25] and Clipp and Steele [17] to develop a time-varying outlet boundary condition for
computational analyses that can be used to represent the effects of physiologic regulation
or feedback. The pulmonary vasculature was used as the test case for implementation of
the dynamic boundary condition.

4.2 Methods

4.2.1 Experimental Data Analysis

In previous work, pulmonary pressure and flow data were collected over multiple
cardiac cycles to capture hemodynamics associated with respiration during PPV in an
open-chest lamb. The details of the experimental data collection can be found in Clipp
and Steele [17]. Pressure and flow data extracted at maximal inspiration and maximal
expiration Figure 4.1 were used to compare the effects of respiration. The blood pressure
was filtered with a low-pass Butterworth filter with a cutoff frequency of 20 Hz to
remove noise. As seen in Figure 4.1a, blood flow is largely insensitive to respiration,
with only a slight change in cardiac cycle length (0.48 and 0.465 seconds for the expired
and inspired states, respectively) and no significant change in mean flow or waveform
shape. In Figure 4.1b, respiration is shown to have an impact on mean blood pressure
with a 21.5% increase from expiration (15.01 mmHg) to inspiration (18.24 mmHg).

A numerical study to investigate the effects of respiration was performed by the
authors [17] using pseudo-dynamic outlet boundary conditions to quantify the
relationship between pulmonary geometry, impedance and respiration. In the previous
study, several fractal-like geometries were created to represent smaller vessels as they
branched from the main pulmonary arteries. The impedance calculated for each of these
small artery structures was used as the outlet boundary condition for the large vessel
model. Experimental data of pressure and flow in the main pulmonary artery showed that
while the periodic flow delivered by the healthy right ventricle was relatively insensitive
to respiration, pressure increased with PPV induced inspiration. This data was used to
optimize geometric parameters of the fractal-like trees in the exhaled state and then to determine the geometric changes in the resistance vessels \( r \leq 250\mu m \) required to produce the pressure changes observed in the inhaled state. While the previous work quantified the geometric transition required to modulate impedance as observed during respiration, it did not attempt to dynamically model changes associated with respiration as presented by Marsden, et al [13,25].

Figure 4.1: Experimental Lamb Data Comparison Between Maximal Expiration and Maximal Inspiration. The blood flow, blood pressure and impedance modulus and phase for one cardiac cycle are shown for both the maximal expiration and maximal inspiration case in the main pulmonary artery (MPA).

Pulmonary impedance was computed using the experimental data for each respiratory state and the resulting modulus and phase are compared in Figures 4.1c and 4.1d. Upon examination, it was found that the most significant difference between the two spectra is the zero-frequency (or resistance) modulus component. At maximal expiration and
inspiration, the resistance is 609 and 775.5 dynes s cm\(^{-5}\) respectively, which corresponds to a 21.5\% increase. This is the same increase seen with the mean pressure and suggests that the pressure gain is due to the gain in pulmonary vascular impedance. While the higher frequency phase components show large fluctuations, these differences may be due to noise in the system model and geometry simplification (i.e., loss of reflection points).

4.2.2 Time-Varying Boundary Condition

The total resistance of a vascular network can be predicted from the relationship between the pressure gradient and flow, where the pressure gradient is required to drive the flow through the vascular network. The resistance of a tube can be directly computed and is inversely proportional to vessel diameter [32]. Therefore, if vessel diameter changes with time, so will its resistance. In the case of respiration, arteriole and alveoli dimensions fluctuate as air distends the alveoli. When alveoli are distended during inspiration, vascular resistance increases as shown by the increase in pressure required to drive the same flow through the pulmonary beds.

Because the primary difference between the impedance spectra was found in the resistance component, the dynamic boundary condition was focused on the variation of the resistance parameter. The hybrid (TVR-Z) boundary condition is a combination of the time-varying resistance and a static impedance spectrum. Impedance is the pulsatile analog to resistance and incorporates the phase lag and damping observed in compliant networks. The impedance was determined from structured geometric representations of networks of small arteries and capillaries as described in Olufsen et al [18,33] and Steele et al [19]. The parameters for the structured-tree geometry were optimized specifically for the pulmonary vasculature in Clipp and Steele [17]. The resistance, or zero-frequency component of impedance, was specified using a linear, time-varying equation to increment the resistance based on an initial and final resistance \((R_i, R_f)\) over a desired number of time steps \(n,\)
\[ R_k = R_{k-1} + \frac{1}{n} \left( R_f - R_i \right) \] (4.1)

where, \( R_k \) is the resistance at the current time step and \( R_{k-1} \) is the resistance at the previous time step.

4.2.3 Application

4.2.3.1 Fluids Solver

The TVR-Z boundary condition was implemented in a previously described one-dimensional (1D) finite-element fluids solver [3,5,19,34,35]. The 1D solver assumes incompressible, Newtonian, axially dominated flow with a parabolic flow profile. Based on the assumptions, appropriate derivations for the conservation of mass equation (4.2) and the conservation of momentum equation (4.3) were found. A third constitutive equation, equation (4.4) is required to solve for the three unknowns: pressure, flow and area. In this work, a linear elastic constitutive model was used with the Young's modulus \( E \) and wall thickness \( h \) specified to be constant.

\[
\frac{\partial a}{\partial t} + \frac{\partial q}{\partial x} = 0
\] (4.2)

\[
\frac{\partial q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{4}{3} \frac{q^3}{a} \right) + a \frac{\partial p}{\partial x} = -8\pi \nu \frac{q}{a} + \nu \frac{\partial^2 q}{\partial x^2}
\] (4.3)

\[
a(p(x,t),x) = \frac{a_o(x)}{\left(1 - \frac{r_o(x)}{Eh} p(x,t)\right)^2}
\] (4.4)

The above equation variables are defined by: \( a \) cross-sectional area (cm\(^2\)), \( q \) volumetric flow rate (cm\(^3\) s\(^{-1}\)), \( p \) pressure (dynes cm\(^2\)), \( x \) axial location in the vessel (cm) and \( t \) time (s), \( a_o(x) \) (cm\(^2\)) is the unstressed area and \( r_o(x) \) (cm) is the unstressed radius of
the vessel with respect to the axial location. The unstressed radius was assumed to be 86% of the diastolic radius. The $Eh$ term was specified to be 30% of approximate systemic wall properties, or $Eh=184$ (mmHg cm) as described in [17]. The fluid properties are density $\rho=1.05$ (grams cm$^{-3}$) and kinematic viscosity $\nu=4.67 \times 10^{-2}$ (cm$^2$ s$^{-1}$).

4.2.3.2 Pulmonary Model

![Figure 4.2: Large Vessel Geometry of Computational Models](image)

The pulmonary model consisted of a large-vessel geometry, an inlet boundary condition representing the flow from an entire respiration cycle (over 10 cardiac cycles) and the outlet boundary conditions. The outlet boundary condition was a structured-tree impedance boundary condition with parameters optimized for the pulmonary vasculature with a time-varying resistance component.

The pulmonary geometry (Figure 4.2) from the authors’ previous work [17] was analyzed using the pulsatile flow waveforms (experimental flow from [7]), and the dynamic boundary condition for an entire respiratory cycle. The respiratory cycle involves a transition from expiration to inspiration and then a return to the expiratory phase. Although a periodic waveform could have been used, the flow for an entire respiratory cycle was specified at the inlet to include the slight change in period during
inspiration. The first cardiac cycle was repeated six times to allow the solver to sufficiently settle before respiration was initialized. A total of 16 cardiac cycles were evaluated and only the cycles after initialization are shown.

The geometry-based impedance spectra were known from the structured-trees determined in the authors' previous work [17]. The impedance spectra were found using an optimization algorithm to determine the structured-tree parameters at each outlet for both expiration and inspiration, providing the zero-frequency or resistance values. The resistance at expiration and inspiration were defined as $R_e$ and $R_i$, respectively. The change from expiration to inspiration occurs between $t=0.92s$ and $t=1.22s$, while the return to expiration from inspiration occurs between $t=1.8s$ and $t=2.12s$. The pulmonary model was run with a static boundary condition, and with a dynamic step and linear transitions to investigate the changes in pressure due to varying blood flow, as well as to varying resistance. The analyses were completed using 200 time steps per cardiac cycle (for a period of 0.48 s) on a 2.4 GHz Intel Core 2 Duo MacBook.

4.3 Results

The dynamic boundary condition was successfully implemented for the pulmonary model and the inlet pressure was accurately predicted for an entire respiratory cycle. A comparison of the measured and predicted values for blood pressure and blood flow in the main pulmonary artery, as well as the respiratory cycle are shown in Figure 4.3. The dynamic boundary condition is able to accurately reflect the impedance calculated by the structured-tree and the increased vascular impedance caused by compression of the arterioles by the air-filled alveoli. The dynamic boundary condition is able to react quickly with little delay apparent in the resulting pressure calculation. The return to an expiration state is also completed quickly with little delay in the pressure calculation.
Figure 4.3: Pulmonary Model Results. The predicted linear dynamic and measured main pulmonary artery (MPA) flow and pressure are shown. The respiration curve is also shown, highlighting the increase in blood pressure for both the predicted dynamic and measured data. The dynamic boundary condition is able to represent the changes in vascular impedance caused by respiration.

The static boundary condition (parameters optimized to the expiratory phase) was compared to both the step and linear transition dynamic boundary condition, as shown in Figure 4.4. The results for the static boundary condition analysis demonstrate that the minute changes in flow that occur between cardiac cycles have an important effect on the pressure and area. This serves to emphasize the importance of including the dynamic changes present due to the cardiac output, as well as distal network regulation.

The step transition dynamic boundary condition analysis demonstrates the slight response time limitation of the numerical solution. The ability of the solver to incorporate a dynamic transition is limited by its ability to reach a stable solution. The initial solution (before transition) required the completion of multiple cardiac cycles to reach a stable solution. After the onset of transition the numerical solution begins to acquire instability that manifests as a delay in response time for the resulting pressure and area calculation. As evident by the results of the linear transition dynamic boundary
condition analysis, this slight instability does not limit the ability of the numerical solution to react physiologically.

![Graph showing predicted pulmonary model results]

**Figure 4.4: Predicted Pulmonary Model Results.** Comparison of linear and step change dynamics and a static model. The predicted static data demonstrates the variation in pressure simply as a result of varying blood flow, but notes the need for varying outlet boundary conditions. The step change shows that a faster response is possible, and that future work must determine the proper dynamic waveform required to model respiration.

To give a closer view, the predicted maximal expiration pressure waveforms (the first full cardiac cycle) and the predicted maximal inspiration pressure waveform (the fourth full cardiac cycle) are shown with the measured data in Figure 4.5. The root mean square error was calculated for each state, resulting in an RMS error of $RMS=0.61 \text{ mmHg}$ and $RMS=0.59 \text{ mmHg}$, for expiration and inspiration respectively.
Figure 4.5: Maximal Expiration and Inspiration Pressure Waveforms. Waveforms isolated from the measured and predicted data to demonstrate the ability of the boundary conditions to represent the downstream network of vessels during both states of respiration.

4.4 Discussion

4.4.1 Conclusions and Significance

The dynamic boundary condition was successfully implemented in a model of the pulmonary vasculature. The results of this work demonstrate that a time-varying boundary condition may be used to model pressure changes due to a distal mechanism. The dynamic boundary condition was able to react quickly to the changes in resistance applied to the model and the predicted pressure waveforms have a low error when compared to the measured pressure at each cardiac cycle throughout the respiratory cycle.

This work is significant in that it examines a dynamic boundary condition capable of incorporating organ specific features and demonstrates the importance of including both these dynamic distal effects and those dynamic effects present in the cardiac output. While this model can be extended to describe any organ, the pulmonary system was selected for the initial studies due to the regular, dynamic effects of respiration. This work demonstrates that it is possible to dynamically change the outlet boundary conditions to simulate distal changes in the vascular network and to accurately predict pressure and flow in an region of interest while considering regulatory or feedback
mechanisms. It is important to note that models of the Fontan circulation have been analyzed in previous work, but few have included the effects of respiration, most notably Marsden et al [13], which has been discussed previously. Both Marsden et al [13] and the authors believe that a more accurate model of the Fontan circulation can be achieved with the inclusion of respiratory effects.

Spilker et al [1] analyzes a pulmonary model with a pulmonary arterial stenosis and without to determine whether stenosis removal would present a favorable outcome or the patient. The study suggests that the decrease in pressure/increase in flow that would result from the procedure would not warrant the surgical risk. However, Spilker et al [1] does not consider the effects of respiration when considering the surgical outcome. As shown in the Experimental Data Analysis section, the pressure in the main pulmonary artery may increase by 20% during inspiration and these effects should be considered when evaluating surgical outcomes. This increase in pressure coupled with the stenosis, which would further increase pressure, may result in a different treatment recommendation.

While this study used dynamic outlet boundary conditions to analyze the pulmonary physiology, this method can be applied to all organ systems. Throughout the body, organ systems use feedback mechanisms to regulate blood flow through vessel constriction and/or dilation. The current dynamic boundary condition assumes a time-varying response, however the dynamic change could be modified to utilize a pressure- or flow-varying response. As the pressure in the organ increases or decreases, the resistance could be scaled to reflect a response in the resistance vessels, modulating the pressure as naturally occurs in the organ system.

4.4.2 Limitations and Future Work

One of the limitations of this work was the lack of consideration for any changes in the compliance of large vessels during the respiratory cycle. The large vessels maintained the same pulmonary compliance determined in previous work [17] throughout the entire respiratory cycle. It is clear that a change in compliance for the large vessels is present by the change in pressure gradient between maximal expiration and maximal inspiration,
approximately a 1.5 mmHg decrease or a 16% change. Altering the properties of the structured-tree does not provide a substantial change in the pressure gradient nor does changing the resistance of the downstream network. To incorporate this change would require a change in the large vessel properties based on the state of respiration. In the future, when tailoring a dynamic boundary condition to the pulmonary system and the respiratory cycle it will be important to consider the compliance changes in both large vessels described by the constitutive model and the small vessels described by the boundary condition.

A second limitation of this work was found in the experimental data used to develop the pulmonary model. The data was collected from lambs (to represent the pediatric model) intubated and on a ventilator during an open-chest procedure. The differences between positive-pressure ventilation (PPV) and negative-pressure ventilation (NPV) have been considered [6,8] and it is known that the effects on the hemodynamics of the pulmonary vasculature differ between the two ventilation mechanisms. In the future, NPV data should be assessed to determine normal, free-breathing changes in pulmonary vascular impedance due to respiration. With the addition of NPV hemodynamic and air pressure data, it will be possible to correlate the change in resistance and the change in pulmonary air pressure.

Future work will also use the dynamic boundary condition to assess the implications of surgical intervention to remove a stenosis. This will be compared to Spilker et al [1] to determine whether including respiration in the analysis of options would have impacted the surgical recommendation. In addition to pulmonary stenosis, the dynamic boundary condition will also be used to evaluate the Fontan circulation. This will require a more complex feedback loop that must include changes in passive flow entering the pulmonary circuit, as well as the dynamic changes to impedance caused by respiration.

4.5 References


Chapter Five

Effects of Tidal Volume and Respiration Rate on Pulmonary Vascular Pressure, Flow and Resistance


*My contributions to this chapter were the data processing and analysis, the statistical analysis, as well as the primary writing responsibility.

Abstract: Purpose: This study investigates the effects of tidal volume and respiratory rate changes on the hemodynamics of the pulmonary vasculature in open-chested lambs. Methods: Twelve lambs (16 ± 6 kg) had a main pulmonary artery pressure and flow measured during respiratory episodes. The data was collected for 8 difference respiratory protocols (4 tidal volume protocols and 4 respiratory rate protocols). The expiration and inspiration cardiac cycle data was compared within each protocol and the changes in hemodynamics were compared across the protocols. Results: As was expected, there were significant differences between expiration and inspiration pulmonary hemodynamics across all lambs and all protocols. Significant differences were found between the majorities of the tidal volume protocols, however few significant differences were found between the respiratory rate protocols. Conclusions: It was found that for the
data studied, respiration plays a critical role in pulmonary hemodynamic changes with tidal volume changes greatly affecting the blood pressure in particular. Respiratory rate was less important to the pulmonary vascular condition and had little effect of the hemodynamics.

Keywords: Pulmonary Hemodynamics, Respiration, Pulmonary Vascular Resistance

5.1 Introduction

The interaction between airway pressure, vascular resistance and compliance has long been investigated to determine the effects of respiration on pulmonary vascular mechanical behavior [1-3]. However, these studies have neglected the effects of changes in respiratory patterns, such as changes in tidal volume and respiratory rate, on vascular resistance. Instead they have focused on the differences between positive-pressure ventilation (PPV) (ventilation scenarios) and negative-pressure ventilation (NPV) (normal breathing scenarios) [4, 5], the flow pattern within the pulmonary vascular bed [6-8], and the effects of respiration on a compromised pulmonary vasculature [9, 10]. Additionally, many studies have excised the lungs to record pulmonary data [4, 5], and while this is necessary for collecting NPV data it can lead to experimental complications and data collection errors. Many studies comparing PPV and NPV use constant pressure perfusion or steady flow perfusion [4, 5], neither of which are physiologic conditions. The variety of experimental protocols used to collect data has led to conflicting results [1, 4, 5, 11, 12].

It is critical to investigate the relationship between respiration and pulmonary vascular resistance not only during PPV and NPV, but also during different respiration rates and tidal volumes. The changes in respiration rate and tidal volume that occur during exercise and disease are analogous to the changes that occur in cardiac rate and stroke volume during these states. It has long been accepted practice to attempt to collect and include this cardiac data in computational models [13-15], however little work has been done to include respiration in computational models. Recent improved models have begun to include this data [16-18], however there is a lack of published data comparing
the effects of tidal volume and respiratory rate on pulmonary vascular resistance. This study investigates lamb pulmonary vascular and airway mechanics during PPV over 8 different ventilation protocols. Vascular mechanics and airway dynamics collected from open-chested lambs were used to characterize the effects of changes in respiratory protocol on pulmonary vascular resistance.

5.2 Methods

All animals were cared for in accordance with the “Guide for the Care and Use of Laboratory Animals” (NIH Publication No. 86-23, revised 1985) and were in accordance with the standards of the Institutional Animal Care and Use Committee of the University of North Carolina at Chapel Hill.

5.2.1 Data Collection Procedure

Twelve lambs weighing 16 ± 6 kg [mean ± standard deviation] were sedated using ketamine (30 mg/kg) intramuscularly and intubated with an endotracheal tube. The animals were then ventilated with an appropriate mixture of isoflurane and oxygen at a rate of 10-15 ml/kg to maintain optimal arterial blood gas tensions. Measurements of respiration rate, carbon dioxide (CO₂) return, and pulse oximetry (placed on the tongue) were monitored. A Validyne pneumotachometer (Validyne Engineering, Northridge, CA) was used to measure airway flow and a fluid filled polypropylene catheter was inserted and connected to a Statham P23Gb transducer (Statham Transducer P23Gb, Siemens) to measure airway pressure.

An incision was made to the internal jugular and a double lumen catheter was inserted allowing for intravenous fluid and pharmaceutical administration throughout the procedure. Arterial blood gases were closely monitored throughout the procedure using an iSTAT analyzer (Abbott Laboratories, IL) and pharmaceutical adjustments were provided when needed. Parameters monitored included hematocrit, hemoglobin, sodium, potassium, pH, PCO₂, PO₂, Calcium, O₂ saturation, bicarbonate and base excess.

A mid-sternotomy was performed that started at approximately the sixth interspace. Exposure was from the superior azygous vein to the diaphragm. A Millar Mikro-Tip
Catheter (MPC-500, Millar Instruments, Houston, TX) pressure transducer was placed in the main pulmonary artery (MPA). To record blood flow, a Transonic T206 Small Animal Blood Flow probe (Transonic Systems Inc., Ithaca, NY) was positioned around the MPA slightly distal to the pressure transducer. Conductive gel was placed between the vessel and transducer in order to improve the signal quality.

5.2.2 Respiration Protocol

The tidal volume and respiratory rate were set on the ventilator. To determine the effects of different tidal volumes on pulmonary vascular mechanics, a constant respiratory rate of 13 breaths per minute was used in combination with tidal volumes of 300 ml, 400 ml, 500 ml and 600 ml. To analyze the effects of respiration rate, a constant tidal volume of 400 ml was used in combination with respiratory rates of 8, 13, 18 and 23 breaths per minute. The protocols are shown in Table 5.1. After each respiratory protocol was established, five to ten episodes of data were recorded. Data episodes were recorded at a rate of 200 Hertz for individual episodes of 5.12 seconds. After data collection was completed, the lambs were euthanized using a lethal dose of concentrated potassium.

Table 5.1: Respiration Protocols. For each tidal volume protocol the respiratory rate is shown in parenthesis and for each respiratory rate protocol the tidal volume is shown in parenthesis.

<table>
<thead>
<tr>
<th>Tidal Volume Protocols (Respiratory Rate)</th>
<th>Respiratory Rate Protocols (Tidal Volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mL (13 breaths/min)</td>
<td>8 breaths/min (400 mL)</td>
</tr>
<tr>
<td>400 mL (13 breaths/min)</td>
<td>13 breaths/min (400 mL)</td>
</tr>
<tr>
<td>500 mL (13 breaths/min)</td>
<td>18 breaths/min (400 mL)</td>
</tr>
<tr>
<td>600 mL (13 breaths/min)</td>
<td>23 breaths/min (400 mL)</td>
</tr>
</tbody>
</table>

5.2.3 Data Processing and Statistical Analysis

For each of the respiration protocols tested, multiple data episodes were collected. The airway pressure was used to determine the state of expiration and inspiration within each episode. Pressure and flow waveforms were isolated for both expiration and
inspiration in each episode. These waveforms were used to calculate an average pressure and flow waveform for expiration and inspiration in each protocol for each lamb.

The pulmonary vascular resistance ($R_v$) was calculated for the expiration and inspiration state using Equation (5.1).

$$R_v = \frac{P_{MPA}}{Q_{MPA}}$$  \hspace{1cm} (5.1)

The average pressure ($P$) and flow ($Q$) were calculated from the averaged waveforms and these values were used to determine the average pressure, flow and resistance differences between the respiratory states of each animal. These three values were compared for each of the 8 respiratory protocols across each lamb individually, as well as across all lambs for statistical differences using ANOVA analysis and multiple mean comparisons in the Matlab toolbox.

5.3 Results

The average pressure and flow waveforms in the MPA for a representative lamb are shown in Figure 5.1 for both the expiration and inspiration state in the four tidal volume protocols. Figure 5.2 displays the same data for the four respiratory rate protocols.
Figure 5.1: Blood Pressure and Flow at the Maximum Inspiration and Maximum Expiration Cardiac Cycle for One Lamb Across the Four Tidal Volume Protocols. Expiration (dashed line) and inspiration (solid line) waveforms for a representative lamb are shown for the four tidal volume protocols. As the tidal volume increases the inspiration blood pressure increases and the inspiration blood flow decreases.

Figure 5.3 shows the mean pressure and flow waveforms with a standard deviation in either direction for one tidal volume protocol and one respiratory rate protocol. This demonstrates the low variability exhibited within each lamb for the different protocols. The average pressure, flow and pulmonary vascular resistance for both inspiration and expiration for the same representative lamb are compared in Figure 5.4 and Figure 5.5.
Figure 5.2: Blood Pressure and Flow at the Maximum Inspiration and Maximum Expiration Cardiac Cycle for One Lamb Across the Four Respiratory Rate Protocols. Expiration (dashed line) and inspiration (solid line) waveforms for a representative lamb are shown for the four respiratory rate protocols. Unlike with the tidal volume protocols, increasing the respiratory rate has only a minor effect on the blood pressure and blood flow.
Figure 5.3: Average and Standard Deviation for Blood Pressure and Blood Flow Waveforms. For each animal there was a low standard deviation for the pressure and flow waveforms. The solid lines of either side of the markers note one standard deviation above and below the mean waveform.

Statistically significant differences were found between expiration and inspiration in all of the respiration protocols. As the tidal volume increases, so does the difference between the expired and inspired state, moving from an 11% increase in pressure at a tidal volume of 300 mL to a 30% increase at a tidal volume of 600 mL. A decrease in MPA flow is seen from expiration to inspiration, with a similar trend apparent with the change in tidal volume (11% decrease in flow at 300 mL to a 30% decrease in flow at 600 mL). The combined changes in pressure and flow result in an increases in pulmonary
vascular resistance, $R_v$, from expiration to inspiration of 25% at 300 mL to an 80% increase at 600 mL.

Figure 5.4: Comparison of Pressure and Flow Values for a Representative Lamb Across the Respiration Protocols. The average pressure and flow are shown for both inspiration and expiration for each of the tidal volume protocols, as well as the respiratory rate protocols. A standard deviation is shown for each average pressure and flow. There is a significant difference between expiration and inspiration average pressure for all of the protocols. The blood pressure and flow differences become larger as the tidal volume increases.

Figure 5.5: Comparison of Resistance Values for a Representative Lamb Across the Respiration Protocols. The average resistance is shown for both inspiration and expiration for each the tidal volume protocols, as well as the respiratory rate protocols. The difference in resistance between expiration and inspiration increases as the tidal volume increases. As the respiratory rate increases the difference between expiration and inspiration loses significance.
The differences between the respiratory rate protocols were less clear. While there was a minimum of a 15% increase in pressure and a 12% decrease in flow from expiration to inspiration, there was no trend associated with the four protocols. There was little difference between inspiration and expiration between the four respiratory rate protocols, with a statistically significant difference present for the pressure only between the 8 and 23 breaths/min protocols. The percentage $R_v$ difference also had a much smaller range for the respiratory rate protocols, with a 43% increase from expiration and inspiration at 8 breaths/min and a 31% increase at 23 breaths/min.

The variation in subject size and weight caused a large difference in cardiac output preventing a direct comparison of average flow and pressure values between animals. However, the pressure and flow differences between expiration and inspiration did not present a significant difference between animals, allowing for comparisons to be made. Figure 4.6 shows the differences between expiration and inspiration for pressure and flow in the MPA averaged across all of the lamb subjects. The pressure difference between the two respiratory states increase with tidal volume, with significant differences between all tidal volume protocols except between 400 and 500 mL. The flow difference also showed a trend of increasing between expiration and inspiration as tidal volume increased. However, the variation across the lambs was too great to observe any significant differences between the tidal volume protocols.

The respiratory rate protocols were also compared across the lambs to determine the effects of rate on pressure and flow. Respiration rate was found to have a less pronounced effect than tidal volume. As the rate increased, the pressure difference decreased slightly. The only significant difference found was between the 8 and 23 breaths/min protocols. As with the tidal volume protocols, there was a large variation between the lambs when comparing the flow difference between expiration and inspiration, and no statistical significance was found. Unlike the tidal volume protocols, there is no clear trend of increasing or decreasing flow differences for the rate protocols.
Figure 5.6: Comparison of Respiratory Protocols Across All Animals. The average pressure and flow differences in the main pulmonary artery between expiration and inspiration are shown for each of the eight respiratory protocols. There were significant differences between the four tidal volume protocols for pressure and a clear trend present for both pressure and flow, however the results of the respiratory rate protocols was less clear with large variations between the lambs.

5.4 Conclusion

5.2.1 Significance

As previously stated, the variety of experimental protocols used to study the effects of respiration has led to conflicting results in the literature. However, the majority of studies agree that respiration has a significant effect on the hemodynamics of the pulmonary vasculature. This study attempts to determine the effects of respiration on the pulmonary vasculature during PPV, including investigating the effects of tidal volume changes and respiratory rates on the pulmonary vasculature. The results of this study agree with previous findings that demonstrate that respiration has a significant effect on pulmonary hemodynamics [4, 5, 9]. This is exhibited here by a significant increase in the
average pressure from expiration to inspiration, irrespective of either tidal volume or respiratory rate. Also evident is a significant decrease in average flow rates from expiration to inspiration. However, the average flow rate has more variation than the average pressure value within each lamb, as well as from lamb to lamb. Both of these observations lead to a pulmonary vascular resistance that significantly increases from expiration to inspiration. The increase in $R_v$ agrees with Burton and Patel [5] who also studied the effects of PPV on pulmonary hemodynamics.

An increase in the tidal volume causes an increase in the pressure in the MPA. This is shown by the increase in the pressure difference and the decrease in the flow difference shown in the figures. As the tidal volume increases, the amount of air inside the lungs increases causing the alveoli to increase in volume putting external pressure on the vasculature. The external pressure on the vasculature causes an increase in resistance that manifests itself as a restriction in flow and an increase in pressure. As expected the more air forced into the lungs, the more the resistance increases. This trend is clearly shown in the data collected here. As expected, the tidal volume plays a significant role in the hemodynamics of the pulmonary vasculature.

In contrast, how the respiratory rate affects pulmonary hemodynamics was less clear. By increasing the respiratory rate but not the tidal volume, the amount of air inside the lungs should have remained the same. Therefore, an increase in $R_v$ would be expected between expiration and inspiration, as with all PPV scenarios, and no changes would be expected between respiratory rate protocols. The pressure data (shown in Figures 5.4 and 5.6) supports this assumption with less variation between the rate protocols than the tidal volume protocols. The pressure difference was small, between 3.5 and 4.5 mmHg for all four protocols, with a significant difference present only between the 8 and the 23 breaths/min protocols. The pressure differences associated with the respiratory protocols are centered around the pressure difference associated with a tidal volume of 400 mL. This leads to the conclusion that the tidal volume has more effect on pulmonary hemodynamics than the respiratory rate. It is more likely that the increase in respiratory rate causes the tidal volume to subtly decrease, causing the changes in $R_v$.  

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Based on these results and those found in other studies, it is clear that respiration plays an important role in pulmonary hemodynamics. While this effect is important in healthy subjects, it is even more critical for an unhealthy patient [9, 19]. The extension of this study is that the effects of tidal volume should be taken into account when considering the effects of respiration for both patients that are healthy and those suffering from diseases, specifically those effecting the pulmonary system. Computational models have begun to include the effects of respiration on pulmonary hemodynamics [16-18] and it should be concluded from this paper that just as the effects of increased cardiac output from exercise are included in computational models [13] it is important to include the increased respiratory tidal volume associated with exercise.

5.2.2 Limitations and Future Work

A limitation of this work was that it was unable to consider the effects of tidal volume or respiratory rate during NPV. Current experimental methods require the lungs be excised to investigate the effects of respiration on pulmonary hemodynamics and this was not undertaken in this work. Future work should include removing the lungs from healthy animals and using a negative pressure chamber to inflate and deflate the lungs. This will provide the data necessary to investigate the effects of respiration on pulmonary hemodynamics. Included in this analysis should be the investigation of the effects of changing the tidal volume and respiratory rate on $R_v$ and pulmonary blood pressure and flow. It is expected that similar results will be present, with the tidal volume playing a more important role than the respiratory rate.

5.5 Acknowledgements

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5.6 References


Chapter Six

Effects of Respiration on Pulmonary Vascular Function During Negative-Pressure and Positive-Pressure Ventilation

Abstract: The effects of respiration on pulmonary vascular mechanics vary with ventilation mechanism. Positive-pressure ventilation (PPV) causes non-uniform expansion of the alveoli, compressing the arterioles and increasing resistance more dramatically than the uniform distribution of air and alveoli expansion that occurs with negative-pressure ventilation (NPV). Using excised lamb lungs, a negative-pressure chamber and steady flow perfusion, the changes due to respiration in blood flow and pressure and pulmonary vascular resistance were measured across a range of tidal volumes (300-450 mL). It was found that there were no significant differences in the flow change between the two ventilation mechanisms or the tidal volume protocols. The pressure drop was found to differ significantly between ventilation protocols and have a trend of increasing pressure change with increasing tidal volume for PPV and a trend of
decreasing pressure change with increasing tidal volume for NPV. The pressure drop was significantly larger during PPV than during NPV. These results confirm that there is a difference in pulmonary vascular mechanics and hemodynamics between the ventilation mechanisms. They also confirm that respiration has an important effect on both hemodynamics and mechanics and should not be ignored when considering the pulmonary vasculature and treatment options.

Keywords: Pulmonary Hemodynamics, Respiration, Pulmonary Vascular Resistance, Negative-Pressure Ventilation, Positive-Pressure Ventilation

6.1 Introduction

Respiration causes changes in the pulmonary vasculature that directly effect the blood pressure and vascular resistance in the lung. There are two mechanisms for ventilation: positive-pressure ventilation (PPV) and negative-pressure ventilation (NPV). During PPV, a patient or animal is connected to a ventilator, which pushes air into the lungs to achieve inflation. In contrast, NPV is natural, normal breathing during which the negative pressure in the thoracic cavity combined with the muscular efforts of the abdominal region and the chest cause the lung to expand, pulling air into the pulmonary airways, while the natural elastic recoil of the lung and ribcage then cause exhalation [1]. It is widely accepted in literature that both ventilation mechanisms cause changes in vascular resistance, however there is disagreement in the literature as to the exact changes that occur [2-7].

Much of the disagreement in the literature can be attributed to the differences in experimental procedure. This is especially true in the case of NPV, which requires that the patient/animal chest be closed throughout respiration in order to achieve negative pressure in the thoracic cavity. This requirement means that most experimental protocols for testing NPV involve extracting the lungs and using a negative pressure chamber to simulate the thoracic cavity [2-4]. Murgo and Westerhof [5] collected blood pressure and velocity measurements in vivo during NPV by inserting a velocity flow probe and pressure sensor during catheterization. However, the results of this study, that respiration
causes no changes in the pulmonary vasculature disagree with the studies completed by Burton and Patel [2] and Petak, et al [3]. Both of these studies found that there were significant differences in pulmonary vascular resistance between the expiration state and the inspiration state of respiration for both NPV and PPV, however they were completed ex vivo. These studies removed the lungs and placed them in a negative pressure chamber, then applied constant pressure perfusion to assess the changes in pulmonary vascular resistance during different states of lung inflation (inspiration and expiration). Burton and Patel [2] measured the blood flow and the blood pressure was known from the constant pressure perfusion protocol, allowing for the calculation of pulmonary vascular resistance. Petak, et al [3] used a modified forced oscillation technique to measure the impedance of the lung in the negative pressure chamber. These different data collection techniques along with others [4] have led to conflicting results and conclusions.

The goal of this study was to investigate the changes in vascular resistance due to respiration in both PPV and NPV. Previous studies have not always presented the blood pressure and blood flow data, as well as the vascular resistance, leaving this data unavailable for use in computational models or for comparison to other measured data. Additionally, previous studies have not investigated the effects of changing tidal volume on pulmonary vascular resistance. This work measured the blood pressure, blood flow and respiratory cycle of lamb lungs during both NPV and PPV. Through the use of a custom built box that allows the excised lung to be exposed to NPV and PPV, using steady blood flow and varying the tidal volume used to inflate the lungs, a more accurate representation of the effects of respiration can be achieved.

6.2 Methods
6.2.1 Lung Removal and Preparation

Lungs were harvested from lambs (2) at market age (< one year old) and weight (10-20 kg) from VealCo (Madison, NC). These animals were intended for slaughter, then consumption, therefore IACUC approval was not required. The heart-lung block was excised from the animal at the time of death. The heart was then removed, leaving the
back of the left atrial wall attached to the lung. The lung was intubated and inflated for examination, ensuring no air or blood leaks and/or damage were present. After clamping the trachea to maintain lung inflation, the endotracheal tube was removed and the lungs were perfused, both antegrade and retrograde, with chilled Perfadex (Vitrolife, Inc., Englewood, CO), an organ preservative, buffered with 3.3 mL/L of THAM (tromethamine; tris-hydroxymethyl aminomethane). The lungs were then stored in clean, chilled Perfadex and placed on ice for transport. Excess tissue was then dissected free of the lungs and the main pulmonary artery (MPA) was cannulated with a 3/8” to ¼” barbed connector. A piece of ¼” Tygon tubing was attached on the connector to be used for de-airing. The lungs were de-aired by retrograde perfusion with clean Perfadex through the each of the pulmonary veins until all air was removed from the lung vasculature.

6.2.2 Perfusion and Ventilation Circuit

The schematic of the experimental set up is shown in Figure 6.1. The perfusion circuit was controlled by a Cole Parmer microprocessor–based digitally controlled pump driver and pump head (MicroPump, IDEX Corp., Northbrook, IL). This precision pump was computer controlled to deliver user-defined flow waveforms up to 3.25 L/min at physiologic pressures. The pump was controlled with a data acquisition (DAQ) system (NI 6036E) using a custom user-interface and the Matlab DAQ Toolbox. A heat exchanger composed of a hot plate and water bath was used to heat the perfusate to 37 C. A custom built air tight acrylic box was used to simulate both NPV and PPV with airtight ports for passing tubes and wires into the box. Also inside the box was the perfusate reservoir. A manually controlled bellows was attached to a side port on the box for NPV and an ambu-bag was attached to the endotracheal tube to simulate PPV. The composition of the perfusate is shown in Table 6.1. The glucose level of the perfusate was monitored and maintained at 100-200 mg/dL through the use of an i-STAT analyzer (Abbot Lab, Abbot Park, IL) with G cartridges and dextrose. The pH was monitored and maintained between 7.2 and 7.3 through the use of pH strips and bicarbonate.
Figure 6.1: Experimental Set Up for Perfusion and Ventilation of an Excised Lung. The perfusion circuit is controlled by a programmable pump that applies steady flow to the lungs. The perfusate is heated to 37 °C by a heat exchanger. The respiration circuit is controlled by either a bellows system (NPV) or an ambu-bag (PPV). The data was collected with a custom data acquisition interface using the Matlab DAQ toolbox.

A Transonic (Ithaca, NY) PAX flow probe was placed around the MPA distal to the connector to measure the blood flow. A Millar™ MikroTip pressure catheter was inserted into the MPA slightly proximal to the flow probe to measure the blood pressure. The lungs were suspended from a force/weight transducer (Grass Technologies, Warwick, RI) in the chamber in order to measure the weight and monitor for pulmonary edema. A thermocouple (Omega Engineering, Inc, Stamford, CT) was placed in the perfusate
reservoir to ensure temperatures of 37 C. The tubing used for perfusion, 1/4” Tygon tubing, was connected to the MPA tubing used for de-airing by a 1/4” to 1/4” barbed connector and passed through an airtight port in the side of the box. As perfusion took place, the perfusate returned to the reservoir through the pulmonary veins and was transported out of the box via suction tubing passed through an airtight port in the side of the box. This protocol is modified from that used in Inokawa, et al [8] and Egan, et al [9, 10].

Table 6.1: Composition of the Perfusate. Components and quantities for the blood simulant perfusate used in this work.

<table>
<thead>
<tr>
<th>Perfusion Components</th>
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<tbody>
<tr>
<td>1.25 L Ringer’s Lactate</td>
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<tr>
<td>7.0 g/dL Low EndoToxin Bovine Albumin</td>
</tr>
<tr>
<td>50% Dextrose (glucose level of 300-250 mg/dL)</td>
</tr>
<tr>
<td>Bicarbonate (pH level between 7.0-7.2)</td>
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Perfusion began at a steady flow rate of 0.2 L/min until the perfusate and tissue had reached a temperature of 37 C. The trachea was then unclamped and the lungs were intubated. The lid was placed on the box with the endotracheal tube passing through an airtight port in the top of the box. A pneumotachometer (Validyne Engineering Corp., Northridge, CA) was placed on the endotracheal tube to measure tidal volume. The pressure in the negative-pressure chamber was monitored with a Millar™ MikroTip pressure catheter inserted into the box via an airtight port.

6.2.3 Data Collection Protocol

The weight of the lungs was measured at the beginning and end of data collection to check for edema development. A metronome was used to insure a respiration rate of
approximately 15 breaths per minute. Data was recorded at 200 Hz for seven second episodes.

6.2.3.1 NPV

The lungs were ventilated with NPV through the use of a bellows system that was connected to the box via an airtight port in the side of the box. The bellows were manually moved to remove air from the box or push air into the box. This caused the more natural inflation (negative thoracic cavity pressure) and deflation of the lungs associated with NPV. Steady flow was applied to the system beginning at the initial warming flow rate of 0.2 L/min and then increased by 0.1 L/min until a physiologic pressure was reached in the MPA (between 15 and 20 mm Hg). Data collection then began for multiple episodes. NPV ventilation was maintained throughout the perfusion protocol with the tidal volume varying between approximately 300 mL and 450 mL.

6.2.3.2 PPV

The second ventilation protocol involved positive-pressure ventilation. The ambu-bag was connected to the top of the endotrachial tube and air was forced into the lungs by squeezing the bag and allowed to escape by releasing the pressure on the bag. The perfusion protocol used for NPV was repeated for the PPV scenario and data was recorded. PPV ventilation was maintained throughout the perfusion protocol with the tidal volume varying between approximately 300 and 450 mL. A port on the side of the box was opened to allow the pressure in the box to remain at approximately 0 mmHg (atmospheric pressure).

6.2.4 Analysis of Pulmonary Behavior During Respiration

Data was extracted from each episode for both maximal expiration and maximal inspiration for comparison. The data was organized by tidal volume for each lung. The resistance ($R_v$) was calculated using equation (6.1).

\[ R_v = \frac{P_{MPA}}{Q_{MPA}} \quad (6.1) \]
Average blood pressure, flow and vascular resistance were calculated for each tidal volume and each lung. The blood pressure, blood flow and resistance changes from expiration to inspiration were compared during NPV and PPV across tidal volumes and lungs using ANOVA and multiple mean comparison tests in Matlab’s statistical toolbox.

### 6.3 Results

No edema development was observed during the perfusion scenarios for each lung as no weight change was observed from the start of the experiment until completion. A representative data set or episode for both NPV and PPV is shown in Figure 6.2. The blood pressure and flow, as well as the respiration cycle are shown for both scenarios. In both respiration scenarios, the blood pressure increases as lung volume increases (inspiration), however, the blood flow required to reach physiologic pressure levels was significantly lower during PPV than during NPV.

![Figure 6.2: A Representative Respiration Cycle shown with Corresponding Hemodynamic Data for Both PPV and NPV](image)

The blood flow was significantly lower during the PPV protocols than during the NPV protocols (1.1 L/min versus 2.3 L/min). This demonstrates that while the shape of the respiration cycle is slightly different, the overall tidal volume is similar (approximately 400 mL). The blood pressure increases as lung inflation occurs and then decreases with lung deflation for both protocols.
Variation in lamb size and therefore lung size meant that the blood flow used to perfuse the lung and reach physiologic blood pressure differed across the lungs studied. However, the same-subject pressure, flow and resistance gradients observed for NPV and PPV were comparable. The blood pressure gradients for both respiration scenarios are shown in Figure 6.3. For all respiration protocols, the blood pressure increases from expiration to inspiration. During NPV, the blood pressure gradient was smaller than during PPV, with the exception of the 300 mL tidal volume. The differences in blood pressure gradient between NPV and PPV were statistically significant for all tidal volumes. However, the blood pressure gradients were only significantly different across tidal volumes when comparing the 300 mL tidal volume with the remaining tidal volumes within either PPV or NPV. It should be noted that despite a lack a statistical significance, which is not surprising considering the small changes in tidal volume of 50 mL and the small sample size, there was a trend present in the data. For the PPV respiration protocol, a trend of increasing pressure gradients was present with the increasing tidal volumes. However, for the NPV respiration protocols, the trend was that of a decreasing pressure gradient with the increasing tidal volumes.

Not shown in are the blood flow gradients due to respiration. The blood flow did not change significantly between expiration and inspiration in any of the respiration protocols tested. The largest change present was less than 0.5% of the average steady flow rate applied during the testing protocols. There were neither any significant difference between the protocols nor were there any trends present in the blood flow gradient data. As the pump supplied the specified flow throughout the respiratory cycle this was expected.

The pulmonary vascular resistance \( (R_v) \) was calculated, equation (6.1), and the difference between \( R_v \) at expiration and \( R_v \) at inspiration is shown in Figure 6.4 for all of the tested respiratory protocols. The overall resistance was higher during the PPV protocol than during the NPV protocol. Additionally, the resistance change from expiration to inspiration was significantly greater during the NPV protocols than during the PPV protocols. The first three tidal volume protocols (300mL, 350mL and 400mL)
also show a trend of increasing resistance gradients as the tidal volume increases during PPV, while the opposite trend (decreasing resistance gradient as tidal volume increases) is present during NPV. The fourth tidal volume protocol (450 mL) did not follow this trend.

Figure 6.3: Blood Pressure Gradients Between Expiration and Inspiration For Different Tidal Volumes During NPV and PPV. There were significant differences between the pressure gradients during NPV and PPV in all tidal volumes except the 300 mL tidal volume. There was a significant different between the pressure gradient at 300 mL and the remaining tidal volumes during PPV.

6.4 Discussion

6.4.1 Conclusions

The pressure and resistance gradients due to respiration were higher during PPV than during NPV. It has been shown that the increase in lung volume is achieved by the recruitment of additional alveoli with studies suggesting that the number of alveoli recruited plays a larger role in lung inflation than the size of the alveoli [11-13]. However, it has also been observed that during ventilator assisted breathing there is a greater risk for lung damage at similar tidal volumes to that of normal breathing [11, 14, 15]. This may be explained by the difference in PPV alveoli recruitment. During ventilator assisted breathing it has been shown that alveoli recruitment is non-uniform,
causing some alveoli to expand further while others remain inactive [11, 15]. This non-uniform recruitment could result in regions of hypoxia, and vasoconstriction [16] and may serve to explain the increased pressure/resistance present during PPV as compared to NPV. The more natural NPV protocol is thought to result in a more uniform recruitment of alveoli results in a slight compression evenly across arterioles, which raises blood pressure and resistance, but substantially less than that that occurs during PPV.

Figure 6.4: Pulmonary Vascular Resistance Difference Between Expiration and Inspiration. The change in resistance from expired to inspired state was larger during all of the PPV respiration protocols than during the NPV protocols. This difference was significant for all of the tidal volume protocols.

While the data here suggests that NPV does not completely eliminate the increase in vascular resistance and pulmonary pressure, it certainly reduces this effect. It should be noted that NPV in an ex-vivo setting, such as the one in this study, cannot completely replicate the normal breathing scenario seen in vivo. This is due to the lack of connective tissue attaching the lungs to the surround organs and securing its position within the thoracic cavity, as well as a lack of muscular activity from the chest wall (normally assisting during expiration) and from the diaphragm (normally playing a role in inspiration). Both of these components could play a role in further reducing pulmonary vascular resistance by increasing the volume of the lung as air is pulled into the lungs, decreasing the compression of arterioles.
The results of this study show that there is a clear difference in the effects of PPV and NPV on the hemodynamics of the pulmonary vasculature. This disagrees with the study completed by Murgo and Westerhof [5], which states that there were no effects on hemodynamics by respiration. It is possible that this is due to the *ex vivo* nature of this study as compared with *in vivo* nature of the work completed by Murgo and Westerhof [5], however since studies have found that there are effects of respiration during NPV [2-4] it is more likely this is due to the complications inherit with collecting data in patients.

These results show an increase in pulmonary resistance and pressure caused by an increase in alveoli pressure and hypoxia-induced vasoconstriction due to respiration during PPV. These results agree with the study by Petak, et al [3], which shows a similar increase in resistance as the lung inflates. The effects of increasing tidal volume on the increasing pulmonary pressure and resistance agree with a recent study by the authors [16]. However, the effects of respiration during NPV on pressure and resistance are less clear in their agreement with previous work. This work suggests that while the effects of respiration are dampened by the more natural ventilation mechanism, there is still an increase in vascular resistance and pressure. Petak, et al [3] observed a very slight decrease in vascular resistance during NPV, which disagrees with this work. It is unclear why conflicting results are present, but it is possible that it is related to the data collection methods. As previously stated, a variety of techniques have been used in previous studies [2-7], not all of which collect pressure and flow data. Petak, et al [3] used constant pressure perfusion and collected only pulmonary impedance using an acoustic method, whereas this study used steady flow perfusion to collect both MPA pressure and flow in order to calculate pulmonary vascular resistance.

This study also investigates the effects of increasing tidal volume on the hemodynamics of the lung during NPV, as well as during PPV. The effects of increasing tidal volume during NPV show the opposite trend as those apparent during PPV, as tidal volume increases the pulmonary vascular resistance and pressure decrease. This is an interesting and novel finding as little research has been done on the effects of tidal volume changes on pulmonary hemodynamics.
6.4.2 Limitations and Future Work

While this study is novel and provides insight into the effects of respiration including the changes causes by differing tidal volumes, there are three significant limitations to this study. The first limitation is that steady flow was used. While, the steady flow protocol use here is similar to the studies that used constant pressure perfusion [2, 3], it does provide the ability for changes in both pressure and flow in the pulmonary arteries as exhibited by the results through the use of a large perfusion circuit. However, a more physiologic experiment would make use of pulsatile flow to more closely replicate the cardiac cycle.

A second limitation to this study was that the lungs were removed from the animal and studies were completed ex vivo. It is known that the properties of the lung differ from ex vivo to in vivo, however collecting the data in patients or intact animals is invasive at best and endangers the health of the animal at worst. This could compromise any data collected making it difficult to assess the effects of respiration. However, while the actual values for pressure, flow and resistance may not be physiologic, the authors believe the pressure and resistance gradients found in this study do reflect the general behavior of the lungs for both in vivo and ex vivo conditions.

The final limitation lies in the manual ventilation methods: the ambu-bag and the bellows. The manual control allows for limited specification of the tidal volume by the user. The two different methods for ventilating the lungs also caused the shape of the respiration curve to vary between NPV and PPV.

Future work should include addressing the first and third limitations discussed above, as well as collecting data for additional tidal volumes. This study includes data for tidal volumes from 300mL to 450mL; the average tidal volume for a lamb or healthy human is approximately 400mL. This range of tidal volumes should be expanded to test for not only normal, healthy tidal volumes, but also those tidal volumes associated with exercise or disease.
6.5 Acknowledgements

The authors would like to thank Lucy Perkins for her assistance. We would also like to thank Dr. Thomas Egan and Dr. Boming Dong.

6.6 References


Chapter Seven

1D Fluid Dynamics Evaluation Pulmonary Artery Stenosis Including Respiration

Abstract: Pulmonary arterial stenosis is a common complication of congenital heart defects, leading to children with compromised pulmonary flow even after repair of the primary defect. A dynamic boundary condition tailored to the pulmonary vasculature to include the effects of respiration was applied to both a healthy pulmonary model and a model with a left pulmonary artery stenosis. The stenosis caused a redistribution of blood flow, resulting in a 28% increase in blood pressure in the main and right pulmonary artery and a 23% decrease in blood pressure in vessels below the stenosis. In addition to the rise in blood pressure due to the stenosis, respiration caused an additional 11% rise in blood pressure. These results demonstrate the importance of including the effects of respiration in a model of the cardiovascular, especially in compromised physiologies.
Keywords: Pulmonary Hemodynamics, Respiration, Pulmonary Vascular Resistance, Negative-Pressure Ventilation, Pulmonary Arterial Stenosis

7.1 Introduction

The pulmonary physiology is susceptible to a number of diseases and conditions that compromise blood flow resulting in compromised blood oxygenation. Arterial pulmonary stenosis, the narrowing of a pulmonary artery, is an example of such a condition and is common in children with repaired congenital heart defects [1]. As with all treatment of cardiovascular disease, the decision to repair or avoid the risk of surgery is based on patient data (hemodynamic and geometric) and the judgment of the surgeon. Recent work has investigated using computational modeling to evaluate pre- and post-operative scenarios to determine a patient-specific solution with a favorable outcome [2-6].

Spilker et al [4] investigated the case of applying this patient-specific approach to cases of arterial pulmonary stenosis. However, a limitation to the work by Spilker et al [4] was the lack of consideration for effects of respiration on pulmonary hemodynamics. Studies have shown that respiration has an important effect on pulmonary hemodynamics [7, 8] and recent models of the pulmonary vasculature have included these effects and concluded that in evaluating treatment options these effects can be critical [2, 3].

The interaction between the alveoli and arterioles in the pulmonary vasculature causes changes in impedance to the distal vessels. These changes must be included in the distal beds of any computational model of a pulmonary region of interest. Several idealized boundary conditions have been used to model the downstream vessels of the pulmonary arterial network, including constant pressure [9], resistance [2, 3], lumped parameters models [10-12] and fractal-like trees [4, 13]. Constant pressure has been implemented in three-dimensional computational models as a simple outlet boundary condition, however this is not a physiologic representation for large vessels. Resistance models have been applied to the downstream network, particularly when modeling disease or compromised physiologies [3]. Resistance is the scaled relationship between pressure and flow and must be applied to outlets carefully, especially in cases of disease when blood flow may drop to zero or negative flow (retrograde). This will result in zero
or negative pressure, which is not physiologic. Lumped–parameter models represent the impedance of the downstream network through electrical analog components, such as resistors, capacitors and inductors. Impedance as a boundary condition is able to capture the effects of wave reflection and phase shift that occur in a compliant model that resistance is not able to represent. However, these analog component values are generally fit to experimental data that may be difficult to collect and are considered to have limited physiologic meaning. The fractal-like trees or structured-trees are branching networks that represent the downstream vascular bed. Impedance may be calculated from the geometry of the trees and is a good choice when experimental flow or pressure data is not available.

Of these, the most physiologic and morphometric are the fractal-like trees or structured-trees. They are defined by a variety of parameters that can be tailored to the organ or system under consideration [14, 15]. Further, they have been tailored to the size of the vessels and their function to make them more anatomic, addressing some concerns that structured-trees are too generic to model networks that vary with size and function [13, 16].

As previously stated, a limitation to previous pulmonary analyses has been the lack of consideration for the effects of respiration. While respiration effects may be trivial for the normal, healthy patient, it becomes critical when considering disease and compromised physiologies [17, 18]. Spilker et al [4] uses fractal-like models to represent the pulmonary vascular beds, but includes no respiration data when evaluating the effects of the pulmonary arterial stenosis. Without including respiration in the model it is difficult to assess the effects of the stenosis and the surgical outcome if the stenosis is removed. Marsden et al [2, 3] includes the effects of respiration when evaluating the repaired geometry from a single ventricle compromised physiology. This was accomplished by altering the inlet flow rather than the outlet boundary conditions. Although, this is a critical inclusion of respiration effects, this method is only effective when passive flow is present and in actuality ignores the effects of respiration at the outlets. However,
Marsden et al [3] does note that without including respiration, the results of the evaluation are incomplete.

The authors have completed previous work developing outlet boundary conditions for the pulmonary vasculature using structured trees to represent both the expiration and inspiration case [13], as well as develop a dynamic outlet boundary condition to vary the resistance of pulmonary beds over the respiration cycle [19]. Additionally, Kim et al [20] have developed and implemented a dynamic boundary condition that includes a feedback component in a lumped-parameter model to alter the impedance of coronary vessels over the cardiac cycle.

This work proposes to extend the dynamic boundary condition previously developed and implemented by the authors to evaluate both a healthy pulmonary circulation, as well as a pulmonary circulation effected by a pulmonary arterial stenosis. These results will be compared to those found in Spilker et al [4] to determine whether respiration effects are critical in the evaluation of treatment options when considering pulmonary arterial stenosis.

7.2 Methods

7.2.1 Measured Data

Experimental data was collected in open-chest lambs during ventilation protocols in a previous study [21]. This data provides blood pressure and blood flow in the main pulmonary artery (MPA), as well as respiratory cycle data. These data have been used in previous work to model the pulmonary vasculature [13, 19], however, these data were collected during ventilation protocols with positive-pressure ventilation. Negative-pressure ventilation is the process of natural, normal respiration, where the lungs expand due to negative pressure in the thoracic cavity pulling air into the lungs. Positive-pressure ventilation forces air into the lungs and forcing lung expansion. These two methods have been comparatively studied and it is known that the effects of the two methods on pulmonary hemodynamics differ [7, 8].

An unpublished study by the authors collected both PPV and NPV data for excised lungs. The pressure and flow gradient due to respiration were compared for PPV and
NPV. The change in flow was found to be statistically insignificant for both cases, while the change in pressure was found to be 47.5% lower for NPV. Because the in vivo data [21] was collected at physiologic flow rates, the 47.5% difference in pressure change was applied to the PPV pressure to create an NPV pressure waveform, as shown in Figure 7.1.

7.2.2 Region of Interest

The region of interest was measured from a methyl-methacrylate cast of a lamb lung created during the work of Zhao [22]. The cast was measured using digital calipers and the radius, length and position of the main, right and left pulmonary arteries, as well as the subsequent two to three branches were recorded. This resulted in a pulmonary region of interest with 34 outlets, as shown in Figure 7.2.

![Figure 7.1: Measured Pressure and Flow for Positive-Pressure and Estimated Pressure for Negative-Pressure.](image)

The measured data was collected in lambs during positive-pressure ventilation. The effects of respiration vary with ventilation mechanism, so the blood pressure was adjusted to represent negative-pressure or normal ventilation. The mean pressure is shown with a horizontal line, demonstrating the difference between mean pressure at inspiration for the two respiration phases.
7.2.3 One-Dimensional Finite Element Analysis

Existing one-dimensional (1D) finite element analysis (FEA) software was used to calculate the pressure, flow and area in the pulmonary arteries [23-26]. The solver assumes blood is an incompressible, Newtonian fluid and that flow in the arteries is axially dominant with a parabolic flow profile. Based on these assumptions, the blood pressure and flow were solved for using 1D equations derived from the conservation of mass (7.1) and conservation of momentum (7.2).

\[
\frac{\partial a}{\partial t} + \frac{\partial q}{\partial x} = 0 \quad (7.1)
\]

\[
\frac{\partial q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{4q^2}{3a} \right) + \frac{a}{\rho} \frac{\partial p}{\partial x} = N \frac{q}{a} + \nu \frac{\partial^2 q}{\partial x^2} \quad (7.2)
\]

The above equation variables are defined by: \( a \) cross-sectional area (cm\(^2\)), \( q \) volumetric flow rate (cm\(^3\) s\(^{-1}\)), \( p \) pressure (dynes cm\(^{-2}\)), \( x \) axial location in the vessel (cm) and \( t \) time (s), \( a_o(x) \) (cm\(^2\)) is the unstressed area. The fluid properties are density \( \rho = 1.05 \) (grams cm\(^{-3}\)) and kinematic viscosity \( \nu = 4.67 \times 10^{-2} \) (cm\(^2\) s\(^{-1}\)). The term \( N \) represents viscous energy losses and is used to incorporate minor losses [26]. The minor loss term includes energy losses associated with junctions (branching points) or sharp changes in radius (i.e., stenosis) that are otherwise neglected by a 1D method.

A linear elastic model developed previously [14, 25] was used as the constitutive model (7.3) to represent the behavior of the vessel walls. The Young’s modulus \( E \) and the thickness of the vessel wall \( h \) were specified as a constant.
\[ a(p,(x,t),x) = \frac{a_o(x)}{\left(1 - \frac{r_o(x)}{Eh(p(x,t))}\right)^2} \]  

(7.3)

The \( a_o(x) \) (cm\(^2\)) is the unstressed area and \( r_o(x) \) (cm) is the unstressed radius of the vessel with respect to the axial location. The unstressed radius was assumed to be 86\% of the diastolic radius. This value was found by comparing the computed distal area to the measured distal area at the measured pressure.

The literature modulus data used to fit the \( Eh \) term did not include pulmonary data. However, it is known that the pulmonary arteries are 2-10 times as compliant as the systemic arteries [27-29], which is partially responsible for the lower pressure present in the pulmonary circulation. Previously, the authors specified the modulus term as 30\% of approximate systemic wall properties, or \( Eh=184 \) (mmHg cm) [13, 19]. Here, the \( Eh \) term was optimized to a best-fit value during optimization of the outlet boundary conditions, which is further discussed in the Optimization section 7.2.5.

7.2.4 Outlet Boundary Conditions

Impedance boundary conditions were calculated using structured-tree geometries. Structure-trees were generated based on the outlet radii of each pulmonary branch and a set of parameters that define the trees. These parameters include a length-to-radius ratio, asymmetry ratios and branching exponents were defined to represent the structure and function of the pulmonary vascular bed. Three asymmetry ratios and branching exponents were defined based on the varying size of the vessels in the microvasculature, as described in Steele et al [16]. To develop a pulmonary specific model, the length-to-radius ratio was defined based on the location of the structured-tree within the lung. This was done to represent the different zones of the lung [30-33], as is discussed in detail in Clipp and Steele [13]. A two-zone model was found to be the best-fit model in previous work [13] and was used in this work, resulting in two length-to-radius ratios. The selection of these parameters is further discussed in the Optimization section 7.2.5.
The impedance was calculated from the structured-tree representation, as is discussed in detail in Olufsen et al [14, 15]. Briefly, the inlet impedance \((x=0)\) is calculated based on the vessel segment geometry, while the impedance \((Z)\) at the outlet of a vessel is given by equation (7.4).

\[
Z(0, \omega) = \frac{ig^{-1} \sin(\omega L / c) + Z(L, \omega) \cos(\omega L / c)}{\cos(\omega L / c) + igZ(L, \omega) \sin(\omega L / c)}
\] (7.4)

In equation (7.4), \(\omega\) is the frequency, \(L\) is the length of the vessel, \(c\) is the wave propagation velocity, which is related to the radius and compliance of the vessel and \(g\) is the product of \(c\) and the compliance.

At each bifurcation, the impedance is calculated based on parallel circuit theory, as shown in equation (7.5).

\[
\frac{1}{Z_p(L, \omega)} = \frac{1}{Z_{d1}(0, \omega)} + \frac{1}{Z_{d2}(0, \omega)}
\] (7.5)

In equation (7.5), the subscript \(p\) refers to the parent vessel and \(d1\) and \(d2\) refer to the two daughter vessels resulting from a bifurcation.

The impedance represents a static boundary condition. A dynamic boundary condition was incorporated into the solver to implement the effects of respiration. The resistances at expiration and inspiration were known from experimental data [13]. The resistance (zero-frequency component) of the structured-tree impedance was modified to transition from the expiration value to the inspiration value and back to the expiration value as the respiration cycle progressed. The dynamic boundary condition is discussed in detail in Clipp and Steele [19].
7.2.5 Optimization

The measured blood flow waveform for maximal expiration (one cardiac cycle) was applied as the inlet boundary condition to the region of interest and the structured-trees were applied at all of the outlets. The structured-tree parameters and the constitutive model parameter were optimized using the Nelder-Mead optimization algorithm in the GNU Scientific Library. The least-squares error was calculated between the measured MPA pressure and the predicted MPA pressure for the expiration cardiac cycle. The optimization algorithm attempted to minimize the least-squares error (between the measured and predicted MPA pressure) for the expiration cardiac cycle until a local minimum was determined. The resulting pulmonary model parameters were then considered to be the best-fit parameters. The simulation was completed with 200 time steps per cardiac cycle and 5 cardiac cycles to ensure a steady state solution was achieved. A total of 9 parameters were optimized: a length-to-radius ratio for each of the two zones of the lung, an asymmetry ratio and branching exponent for each of the three levels of the tree, and the $Eh$ constitutive model term.

A second optimization was performed for the inspiration case, providing the impedance spectrum at all of the outlets for both expiration and inspiration. The radii of the arterioles were scaled to represent the effect of expanding alveoli constricting the arterioles. The measured blood flow at maximal inspiration (one cardiac cycle) was applied at the inlet and the best-fit structured-trees were applied at the outlets. The simulation was completed with 200 time steps per cardiac cycle and 5 cardiac cycles to ensure a steady state solution was achieved. A total of 2 parameters were optimized: a respiration scaling factor for each of the two zones of the lung.

7.2.6 Healthy Pulmonary Physiology

The optimized model was considered the best-fit healthy model. The resistance at each outlet for expiration and inspiration were known from the optimized structured-trees. The impedance spectrum from expiration was used and the zero-frequency/resistance component was scaled from the expiration to the inspiration value and then back to expiration as the respiratory cycled progressed. The measured flow was
used as the inlet for the entire respiration cycle (approximately 10 cardiac cycles). The healthy pulmonary physiology model is shown in Figure 7.2. The simulation was completed with 200 time steps per cycle and 5 cardiac cycles were used to establish a stable solution before the respiration cycle (approximately 10 cardiac cycles) began.

![Graph](image)

**Figure 7.2: Healthy Pulmonary Physiology and Pulmonary Arterial Stenosis.** The healthy physiology (left) and the pulmonary physiology with a stenosis (right) were both specified as a region of interest. The structured-trees were used to establish the impedance spectra at the outlets and the resistance component was varied with the respiratory cycle. The blood flow for an entire respiratory cycle was specified as the inlet boundary condition.

### 7.2.7 Pulmonary Arterial Stenosis

A pulmonary arterial stenosis was created on the left pulmonary artery (LPA) reducing the area in the stenosed section by approximately 50%, as shown in Figure 7.2.
The measured flow waveform for the entire respiratory cycle was applied at the inlet and the dynamic boundary conditions found for the healthy physiology were applied at the outlets. The simulation was completed with 200 time steps per cycle and 5 cardiac cycle were used to establish a stable solution before the respiration cycle (approximately 10 cardiac cycles) began.

7.2.8 Disease Recruitment

An important consideration for pulmonary arterial stenosis models is the effect disease has on vessel recruitment. It has been suggested that in the case of disease, additional vessels will be recruited in the diseased (stenosed) lung, decreasing resistance. The current lung model assumes two zones, zone 2 with restricted flow and zone 3 with unimpeded flow. To simulate the effect of recruitment due to disease, the left lung was altered to a single zone lung, with only zone 3 present. The simulation for the pulmonary arterial stenosis model was repeated using the modified recruitment zones.

7.2.9 Exercise

The effects of exercise on patients with stenosis have been examined. The patients experience shortness of breath and increased blood pressure during light exercise, when healthy patients would normally see no change. The effects of exercise were incorporated into both the healthy and stenosis simulations, by increasing the blood flow based on experimental data [34, 35]. The healthy patient would experience no increase in blood pressure due to this increase flow due to vessel recruitment and the dilation of resistance vessels. To include these effects, the lungs were transitioned to a single zone model with only zone 3 present and an exercise factor [16] was used to scale the diameter of the resistance vessels. The exercise factor was chosen by dilating the vessels until the blood pressure level did not increase in the healthy patient. These changes were also applied to the pulmonary arterial stenosis model and both the healthy and stenosis simulations were completed for the exercise scenario.
7.3 Results

7.3.1 Healthy Pulmonary Physiology

The optimization resulted in a set of nine parameters that represent the pulmonary distal network for the expiration state that produced a predicted pressure waveform with a root mean square (RMS) error of 0.42 mmHg. The inspiration optimization resulted in two parameters that scaled the arterioles of the optimized structured-trees, resulting in an RMS error of 0.57 mmHg for the inspiration cardiac cycle.

![Graph showing pressure and flow comparison](image)

**Figure 7.3: Healthy Pulmonary Physiology Results.** The healthy pulmonary model resulted in a pressure waveform that accurately represents the dynamic behavior of the respiratory cycle. The dashed vertical lines represent the timeframe the transitions from expiration to inspiration and from inspiration to expiration were applied.

The predicted blood pressure and flow are shown compared to the measured blood pressure and flow data in Figure 7.3. The cardiac cycle at maximal inspiration (fourth full cardiac cycle) and maximal expiration (eighth full cardiac cycle) are shown in Figure 7.4 to demonstrate the accuracy of the predicted individual cardiac cycles when using the
dynamic outlet boundary condition. The expiration waveform produces a slightly better fit than the inspiration, because the expiration optimization uses nine parameters to fit the pressure waveform, where as the inspiration optimization only uses two parameters to fit the pressure waveform. Additionally, the inlet flow waveform was the same for both optimizations; however, the cardiac cycle has a slightly shorter period during inspiration. This may lead to further error in the inspiration optimization.

![Figure 7.4: Blood Pressure Results for Maximal Expiration and Inspiration.](image)

Main pulmonary artery pressure waveforms for the measured and predicted data have a low error.

### 7.3.2 Pulmonary Arterial Stenosis

The results of the healthy pulmonary physiology provide a branching structure for the pulmonary distal network. These boundary conditions applied at the outlets of the stenosis model allowed for a prediction of the effects of a pulmonary arterial stenosis including the effects of respiration. The stenosis caused a redistribution of flow, the limited flow through the stenosis on the LPA increased the flow though the RPA. The pressure, flow and area in the LPA below the stenosis were compared to the same region of the LPA in the healthy physiology, shown in Figure 7.5. As expected, the flow was significantly lower below the stenosis, resulting in lower pressure and area. The pressure in this region experiences a 27% drop due to the stenosis. The increased flow in the RPA
causes increased pressure and area in the healthy vessels on the right side of the pulmonary vasculature, as shown in Figure 7.5. The resulting 17% increase in flow causes an 18% increase in pressure and a less than 1% increase in area.

Figure 7.5: Pulmonary Artery Hemodynamics in the Presence of a Stenosis. The stenosis causes a reduction in flow, resulting in decreased pressure and area below the stenosis. The predicted pressure decreases by 27%, the flow decreases by 23% and the area changes by less than 1% compared to the healthy physiology. The redistribution of flow caused by the stenosis, resulted in increase pressure and area in the RPA. The predicted pressure increases by 18%, the flow increases by 17% and the area changes by less than 1% compared to the healthy physiology. The pressure in the MPA increases by 20% and the area increases by 5% in the presence of the stenosis.

The respiratory effects are clear in both the LPA and the RPA for the healthy model, as well as, the arterial stenosis model. As inspiration occurs, the pressure rises as expected in both models, however the increase in pressure is approximately the same for
the healthy and stenosis models. This was unexpected, as the authors believed the stenosis would cause a more sharp increase in pressure as inspiration occurred. To further investigate the effects of respiration in the stenosis model, the pressure, flow and area for the MPA are shown in Figure 7.5. The pressure in the MPA had an overall increase of 20% and the area increased by approximately 5% in the stenosis model. This clearly shows the increased pressure due to the stenosis, as well as the increased pressure due to respiration. While the authors expected the stenosis to further increase the pressure change due to respiration, this was not the case. Instead the pressure increase was slightly dampened by the presence of the stenosis. While it is clear that the stenosis causes a rise in pressure and that respiration causes a further increase in pressure, it is not clear that the pressure reaches a level that would require surgical intervention in this scenario.

7.3.3 Disease Recruitment

Additional vessel recruitment on the diseased side of the lung alters the resistance and therefore the distribution of flow. By changing the left lung to a zone 3 only lung, the lower resistance below the stenosis helps to balance the flow between the two lungs that was redistributed by the stenosis. The blood flow, pressure and area in the RPA and LPA are shown for the healthy, stenosis and disease recruitment stenosis models in Figure 7.6. The vessel recruitment results in a pressure increase in the RPA of approximately 10% instead of the original predicted pressure increase of 18% due to the stenosis. This is due to the slightly altered redistribution of flow, the flow to the left side is slightly increased by the reduced resistance inherent in a completely zone 3 lung. The peak inspiratory blood pressure is reduced from approximately 25 mmHg in the stenosis model to approximately 23 mmHg in the vessel recruitment model.
Figure 7.6: Effects of Additional Vessel Recruitment in the Presence of a Stenosis. The stenosis causes a reduction in flow, resulting in decreased pressure and area below the stenosis. Additional vessel recruitment to a fully zone 3 lung on the left side reduces the pressure caused by flow redistribution. The predicted pressure in the RPA increases by 10% instead of 18%. However, little change was seen in the predicted pressure in the LPA with additional vessel recruitment.

7.3.4 Exercise

In order to simulate exercise the heart rate and cardiac output were increased, the lung was transitioned to a single zone (zone 3) model and the resistance vessels were dilated with an exercise factor. The exercise factor was chosen to prevent an increase in blood pressure due to light exercise in the healthy model. This same exercise factor was applied to the stenosis model. The stenosis causes a redistribution of flow just as in the previous simulations. The LPA pressure was largely unaffected by exercise, due to the dominant characteristics of the stenosis. The stenosis limits flow through the stenosis and the effects of exercise are not seen below the stenosis. However, the RPA blood pressure was further increased by exercise, with a peak inspiratory blood pressure of over 30 mmHg.
Figure 7.7: Exercise Effects for the Healthy and Stenosis Pulmonary Models. The blood pressure in the RPA increases with exercise in the presence of a stenosis. This rise in pressure brings the peak inspiratory blood pressure to over 30 mmHg in the RPA. There is little change in the blood pressure in the LPA due to expiration. The redistribution of flow due to the stenosis is the dominant determinant in blood flow distribution and

7.4 Discussion

The development of models and simulation techniques that can further the understanding of cardiovascular disease and treatment outcomes is of paramount importance. Critical to the accuracy of these models is the inclusion of regulatory/feedback mechanisms that alter pressure and/or flow within a region of interest. This work demonstrates that the dynamic behavior of distal networks can be included in the prediction of pressure and flow in a cardiovascular model and this behavior can be used to assess the effects of disease, such as pulmonary arterial stenosis.
This work quantified the effects of a stenosis that reduced the area through the stenosis by 50% and included the additional effects of respiration.

While, the results of this occlusion demonstrate that the pressure was not elevated to a dangerous level during any phase of the respiratory cycle, it clearly shows elevated pressure due to both the stenosis and respiration. These results do not agree with Spilker et al [4], which concluded that the pulmonary arterial stenosis located on the LPA of a 16 year old has no significant effect on pressure or flow within the pulmonary vascular network. This lack of change is explained with the possibility of vascular remodeling or additional recruitment of vessels on the right side to compensate for the increased resistance on the left side. However, no changes to the boundary conditions are made to represent this effect and no experimental data was available for comparison to validate the results, making it more likely that an error occurred when designing the model. Spilker et al [4] does not perform an analysis for different phases of the respiratory cycle ignoring the possibility of increased pressure during the inspiratory phase.

The results shown here do show agreement with the animal model also studied in Spilker et al [4]. The porcine model applied a stenosis on the LPA and compared measured and predicted hemodynamic values revealing a significant increase in pressure and flow on the non–stenosed pulmonary artery and a significant decrease in pressure and flow below the stenosis. As the predicted data was compared to measured data for the animal model, the authors find this to be a more reasonable result than the human model.

In cases of pulmonary arterial stenosis as a complication of a congenital heart defect, lung development may be unbalanced favoring the side free of stenosis. This effect was addressed by simulating additional vessel recruitment by altering the zone distribution in the lungs. The original pulmonary model in this work assumes a two zone lung model, as supported by previous modeling efforts [13] and experimental data [30]. Additional vessel recruitment is simulating by transitioning to a single zone pulmonary model, decreasing the resistance of the lung to mimic the use of additional vessels. This reduces the impact of the stenosis, lowering the pressure above the stenosis by nearly 50%. It should be noted that the recruitment of additional blood vessels (decreasing the
resistance) to moderate the effects of disease might limit the ability of the lung to respond to exercise. The normal response to exercise is vessel recruitment and dilation, which has been partially completed to address the effects of disease.

It is known that a compromised pulmonary physiology can limit the ability of a patient to participate in physical activity [36, 37]. This work has shown an increase in the blood pressure within the pulmonary arteries of nearly 30% due to stenosis. Increased cardiac output and heart rate due to exercise caused an additional rise in pressure. In the healthy scenario, the blood pressure did not increase in the pulmonary arteries as is supported in the literature. The exercise effects in the stenosis model are considerably larger; the pressure above the stenosis increases, resulting in a peak inspiratory pressure over 30 mmHg.

This work demonstrates the importance of including the effects of respiration in a model of a compromised physiology, in this case, pulmonary arterial stenosis. The blood pressure varies throughout the respiratory cycle and without the inclusion of impedance changes to the distal network it is likely that the blood pressure risks can be underestimated. These respiratory effects become more important as disease and exercise are investigated to determine the proper course of treatment.

7.5 References


8.1 General Conclusions

Chapters Three and Four of this work demonstrated the need for dynamic boundary conditions to represent the regulatory or feedback mechanisms of distal vascular networks. Using the pulmonary vasculature as an example of an organ system with a dynamic distal network, dynamic boundary conditions were implemented to represent the relationship between arterioles and alveoli throughout the respiratory cycle. As the alveoli fill with air during inspiration, the surrounding arterioles are compressed, increasing the impedance to blood flow. This relationship was simulated in Chapter Three through the use of two separate pulmonary models with structured-tree impedance boundary conditions. The first model was optimized to the expiration phase, while the second was optimized to the inspiration phase. This demonstrated the ability of the
structured-trees to be tailored to not only the pulmonary vasculature, but also the changes in the distal network due to respiration.

This was taken a step further in Chapter Four, where the observation was made that the major difference between the impedance spectra at expiration and inspiration was in the zero-frequency component or resistance. In order to simulate the pulmonary vasculature including the dynamic nature of the arterioles, a dynamic boundary condition was developed. This boundary condition combined the structured-tree impedance with a time-varying resistance boundary condition by utilizing the impedance calculated from the tree and varying the resistance (TVR-Z) with the respiration cycle. This work demonstrated the ability of a TVR-Z boundary condition to simulate the changes in the pulmonary vasculature and accurately portray the effects of respiration in a simulation of the healthy physiology.

The above boundary conditions were tested and the pulmonary physiology was simulated using experimental data collected in open-chest lambs during mechanical, positive-pressure ventilation. This is the process of a ventilator forcing air into the lungs, as compared to normal, quiet breathing, which uses negative-thoracic cavity pressure and abdominal muscle activity to inflate the lungs and the natural, recoil of the chest to exhale. Chapter Five discussed the data collection methods associated with PPV experimental data collection and shows that increased tidal volume (the amount of air drawn into the lungs during a single breath) affects the pressure in the large pulmonary arteries. As the tidal volume increased, the pulmonary blood pressure difference (between expiration and inspiration) increased, as well. However, the respiratory rate (number of breaths per minute) had little affect on pulmonary pressure. These observations made it clear that just as the cardiac output is considered when developing models of specific regions of interest, for the pulmonary physiology it is important to consider how the tidal volume will impact the distal network.

While the information in Chapter Five revealed important information about respiration effects, it is important to note that these effects are valid for PPV scenarios only. It is known that PPV and NPV have different effects on the pulmonary vasculature,
however those exact differences vary from study to study. Chapter Five discussed the study conducted to collect pulmonary hemodynamic data for both the NPV and PPV scenarios. This work revealed that the pulmonary pressure change from expiration to inspiration is greater during PPV than during NPV scenarios. It was also concluded that the blood pressure difference increased for increasing tidal volumes during PPV and decreased for increasing tidal volumes during NPV. However, this data was all collected ex-vivo, which causes increased stiffness in the lungs raising the pressure in the pulmonary arteries and reducing the cardiac output or blood flow that the lungs can handle without sustaining damage.

Chapter Seven combined the dynamic outlet boundary condition developed in Chapters Three and Four with the experimental data processed and collected in Chapters Five and Six. This work altered the in vivo blood pressure data collected in Chapter Five to represent NPV data rather than PPV data using the relationships established in Chapter Six. The dynamic boundary condition was then optimized for the healthy pulmonary physiology experiencing normal, quiet breathing. After establishing dynamic outlet boundary conditions for the healthy pulmonary physiology including the effects of respiration, these boundary conditions could now be applied to a compromised geometry to investigate the effects of disease.

A common cardio-pulmonary condition that accompanies many forms of congenital heart disease is pulmonary arterial stenosis. Previous models neglected to incorporate the effects of respiration in the models of pulmonary stenosis, so to conclude this body of work a pulmonary arterial stenosis (located on the left pulmonary artery) model was investigated including the effects of respiration. The pulmonary blood flow was redistributed due to the blockage of flow in left pulmonary artery, which caused increased blood pressure in the main pulmonary artery and the right pulmonary artery. The blood pressure was also significantly lower below the stenosis on the left pulmonary artery. The pressure increase due to the stenosis was approximately 30%, while the pressure increase due to respiration was approximately 10%. Both pressure increases were found to be critical in determining a course of treatment.
This body of work developed a dynamic boundary condition that can be used to incorporate the effects of regulation and feedback on the downstream network of vessels, tailored the boundary conditions to a specific organ system and its feedback relationship between alveoli and arterioles and used the collected data and optimized boundary conditions to evaluate a specific disease state and explore the importance of the respiration mechanism on the disease state.

8.2 Future Directions

While this work represents a novel approach to addressing dynamic changes in vascular models and its specific relevance to the pulmonary vasculature, the future implications are also of importance. The dynamic boundary conditions can be used to investigate not only the effects of respiration on the pulmonary vasculature, but also the effects of auto-regulation on the renal distal arteries and exercise on the distal vascular beds of a variety of regions of interest. Additionally, the experimental data collected in Chapter Four was collected over a small sample size (two lungs) and should be expanded to confirm the relationship between PPV and NPV, as well as the effects of changing tidal volume on pressure changes during respiration. With the development of pulmonary specific boundary conditions that include the effects of respiration, more complicated geometries can be studied to determine the best course of treatment and to gain further understanding of surgical outcomes.