Tools for the Investigation of Reduced Exercise Capacity in Fontan Patients

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TOOLS FOR THE INVESTIGATION OF REDUCED EXERCISE CAPACITY
IN FONTAN PATIENTS

A Thesis
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Master of Science
Mechanical Engineering

by
Akash Gupta
December 2018

Accepted by:
Dr. Ethan Kung, Committee Chair
Dr. Richard Figliola
Dr. Phanindra Tallapragada
ABSTRACT

Univentricular heart defects represent one of the most complex forms of congenital heart defects, which left untreated, is fatal. Univentricular patients typically undergo three highly invasive surgeries that culminate in the Fontan procedure. The Fontan physiology is associated with several long-term complications, one of which is reduced exercise capacity. Previous studies have found an empirical correlation between the fluid power losses in the Fontan junction (indexed to body size and flow rate), and reduced exercise capacity. There is evidence suggesting that the narrowing of vessels in the Fontan junction results in increased indexed power loss and lowered exercise capacity. Several alternate configurations of the Fontan junction geometry have been proposed with the objective of mitigating the power loss. However, the significance of the power loss in the context of global haemodynamics remains unclear. The power loss characteristics of the alternate surgical configurations and their impact on global haemodynamics at various levels of exercise are also unknown.

In this thesis, we detail the development of competencies and techniques that allow us to characterize the power loss and its effects on the global haemodynamics using patient specific Fontan geometries and considering different levels of exercise physiologies. Starting from a dataset consisting of three surgical configurations for six patients developed under the guidance of a surgeon, we derive a pulmonary artery growth model from literature data to scale these geometries to an adult size. Next, we describe the process of realistically scaling these geometric models. Further, we describe an adaptive meshing protocol that we have developed leveraging an existing adaptive meshing algorithm for the automated optimal meshing of the scaled patient specific geometry. Multi-scale simulations provide closed-loop feedback between a finite element model and a lumped parameter model of the Fontan physiology, providing detailed local haemodynamic information and its impact on global haemodynamics. The succeeding portion of this document demonstrates the progress in performing multi-scale simulations and extracting results of local haemodynamic parameters such as power loss and global haemodynamic parameters such as the cardiac output, using an inferior vena cava stenosis in a Fontan patient as an example case scenario.
DEDICATION

This thesis is dedicated to all diagnosed with congenital heart defects. They teach us the meaning of courage by virtue of their very existence.
ACKNOWLEDGMENTS

I would like to thank Dr. Ethan Kung and my committee members for their guidance without which this thesis would not be possible. I would like to thank my family whose constant support propelled me through this process. Special thanks should be given to Adam Updegrove and Aeekansh Verma for their help with the technical aspects of SimVascular. I am grateful to the faculty and staff of the Department of Mechanical Engineering at Clemson University, who always do their utmost to support and encourage graduate students. Finally, I would like to acknowledge the immense contribution of my colleagues in the lab and my friends. Their constructive feedback, constant encouragement and support made this body of work possible.
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CHAPTER ONE: INTRODUCTION

1.1 An Introduction to the Fontan physiology:

A double circuit, i.e. the systemic and pulmonary, is a characteristic of a normal human post-natal cardiac circulation connected in series, driven by the “left” and “right” heart respectively (Figure 1.1 left). However, certain complex cardiac malformations effectively reduce the heart to a single ventricle system (Figure 1.1 right). This single ventricle then drives both the systemic and the pulmonary circulations, which connect in parallel. It has been over 40 years since Fontan and Baudet[1] first described a method by which the entire systemic venous return was routed to the pulmonary arteries bypassing the right ventricle as palliative measure for tricuspid atresia. Norwood in the 1980s developed the novel concept of having the right ventricle serve as the pumping source for the systemic circulation[2]. This development significantly increased the population of patients eligible for the Fontan palliation, making it one of the most widely performed surgical procedures for complex congenital heart defects. Patients exhibiting univentricular physiology are principally managed using a staged surgical palliative approach, with the ultimate objective of undergoing the Fontan procedure[3].

1.2 Indications for the Fontan palliation and patient selection criteria:

Patients exhibiting complex cardiac malformations with a functionally single ventricle, either due to the absence of an adequate atrioventricular valve or a pumping chamber, qualify as candidates for the Fontan palliation. Examples of such malformations include pulmonary atresia with an intact ventricular septum, tricuspid atresia, double inlet ventricle, hypoplastic left heart syndrome, and complete atrioventricular septal defects[4,5].

The criteria for the optimal selection of patients for the Fontan operation has undergone significant revision since Choussat and Fontan detailed their recommendations for a successful Fontan operation as being adequate cardiac output (CO) at an acceptable systemic venous pressure[5]. These revised criteria now aim for low left atrial pressure and low trans-pulmonary gradient after repair. Cardiac requirements include unobstructed ventricular inflow, i.e. no coarctation, no subaortic stenosis, and no arterial hypertension. Pulmonary requirements include (1) an unobstructed connection from the systemic veins to the pulmonary arteries, (2) adequate size of pulmonary arteries without distortions, (3) well-developed distal pulmonary vasculature, (4) near normal pulmonary vascular resistance (< 2.5 U/m²), and (5) unobstructed pulmonary venous return. Deviations from these criteria may lead to increased operative mortality, late morbidity, and late mortality[5].
Figure 1.1 – A normal heart vs. a univentricular heart. Normal human heart (left); Hypoplastic left heart syndrome (right), an example of one type of complex cardiac malformations palliated by the Fontan procedure.[6]

1.3 The three stages of surgery:

The Fontan procedure is the third and final stage in the surgical palliation of univentricular physiology. At birth, the high pulmonary vascular resistance and the small size of the caval vessels and pulmonary arteries make it impossible to create a Fontan circulation. The staged approach also allows the body to progressively adapt to the non-standard haemodynamics, thus reducing the overall operative morbidity and mortality[5]. Additionally, the staged approach allows for better patient selection and intermediate preparatory procedures.

1.3.1 Stage 1 – The systemic to pulmonary shunt:

This procedure is generally performed immediately after birth. The primary objective of this procedure is the removal of systemic obstructions and to allow pulmonary flow, which is adequate for oxygen delivery to the tissues and pulmonary arterial growth. In order to ensure that the pulmonary vascular resistance (PVR) is kept low and that the ventricle does not suffer from an excessive volume load, pulmonary blood flow is minimized by placing a restrictive synthetic conduit between a major systemic vessel and a proximal pulmonary artery (Figure 1.2 – A).
Figure 1.2 – Stages of the Fontan palliation: (A) Stage 1: Artificial shunt placed between right subclavian artery and the right pulmonary artery; (B) Stage 2: Superior vena cava anastomosed to the right pulmonary artery; (C) Stage 3: The Fontan procedure – Extracardiac conduit establishes a connection between the inferior vena cava and the right pulmonary artery (portion in the dotted outline is commonly referred to as the “Fontan Junction”)[4]

1.3.2 Stage 2 – The superior cavopulmonary connection:

This is the second palliative procedure, which is generally performed between 2-6 months of age, once the pulmonary arteries have grown sufficiently such that the PVR is low. The procedure employed in this stage is either the bi-directional Glenn shunt or a hemi-Fontan operation. Both methods achieve cardiopulmonary bypass by the anastomosis of the superior vena cava (SVC) to the proximal right pulmonary artery (Figure 1.2 – B). The systemic to pulmonary conduit placed in the previous procedure is
ligated. This step reduces the significant volume overload of the single ventricle induced in stage 1 to slightly below normal levels for body surface area (BSA). At this stage, the patient remains cyanotic with peripheral oxygen saturation of about 80-85%.

1.3.3 Stage 3 – The Fontan procedure:

The Fontan operation is performed between 1-5 years of age, depending on the particular center’s criteria for growth of the pulmonary vasculature and cyanosis at rest and during exercise. Two techniques are currently used: the lateral tunnel technique and the extracardiac conduit technique. Regardless of the techniques, the inferior vena caval (IVC) flow is re-directed into the pulmonary circuit either through an intra atrial baffle in case of the lateral tunnel technique or through a synthetic conduit external to the heart in the case of the extracardiac conduit technique (Figure 1.2 – C). A fenestration may be created between the conduit and the atrium for “high-risk” patients with sub-optimal PVR. The fenestration produces a right-to-left shunt, which limits caval pressure and congestion, increases the preload of the systemic ventricle; this improves cardiac output at the expense of slight desaturation. The artificially created confluence of the inferior and superior vena cava with the pulmonary arteries is commonly referred to as the Fontan junction and is depicted in the dashed box of Figure 1.2-C.

1.4 Long-term sequelae associated with the Fontan palliation:

Fontan patients suffer from a whole host of long-term complications, which include arrhythmias, progressive decline in exercise capacity, thromboembolic events, liver dysfunction, protein losing enteropathy, and eventual heart failure. The focus of this thesis is the complication of reduced exercise capacity, which we describe in detail subsequently.

The numerous cardiovascular, psychological, and prognostic benefits of exercise are well documented, and the ability to exercise is a vital indicator of overall health[7,8]. Patients with a Fontan circulation lead a normal life and engage in mild to moderate sports activities despite their abnormal circuit. A majority of all hospital survivors fall within the New York Heart Association (NYHA) functional class I or II[5]. Exercise tolerance is, however, significantly reduced in Fontan patients and progressive decline in exercise capacity has been reported[9]. The cardiac output at rest in a Fontan circulation is reduced to 70% (range 50-80%) of normal with an increased peripheral oxygen utilization to compensate for the reduced oxygen delivery[10]. During exercise, the maximal CO is half that of normal, with a normal or supra-normal oxygen utilization[11].

1.5 Clinical significance of reduced exercise capacity in Fontan patients:

The exercise capacity of an individual provides important information regarding the functioning of the cardiovascular, muscular, and ventilatory systems[12]. The utility
of the exercise capacity as a predictor for the outcome and survivability of patients with cardiovascular disease and healthy subjects has led to its widespread adoption in clinical practice[13,14]. Guidelines have been published by several professional organizations regarding the interpretation of maximal exercise tests in adults[15–17] and children[18].

Univentricular patients have been reported to suffer from a significant reduction in exercise tolerance, the reasons for which are not fully understood. It has been hypothesized that the size and geometry of the Fontan junction and pulmonary arteries have a major effect on the patients’ cardiovascular performance. A proposed parameter called the “indexed power loss” has been reported to display a significant negative linear correlation with the Ventilatory Anaerobic Threshold (VAT) [19], which is a noninvasive measure of cardiorespiratory endurance performance. The authors negatively correlate haemodynamic energy loss in the Fontan junction to the exercise capacity of Fontan patients. There is evidence that narrowing of the vessels of the Fontan junction leads to elevated indexed power loss and detriment of exercise capacity[20], but this study does not provide global haemodynamic information and is constrained by the use of inflexible time-averaged boundary conditions. In addition, modeling studies such as the one conducted by Kung et al. [21] report the power loss being one order of magnitude smaller than the pulmonary power loss and two orders of magnitude smaller than total ventricular output during resting conditions. During exercise, an increase in flow rate through the Fontan junction occurs in tandem with a decrease in vascular resistance, which may elevate the significance of the junction power loss in the context of the systemic physiology. The impact of the junction power loss during exercise on the systemic physiology remains poorly understood.

In order to mitigate the power loss, proposals have been made to alter the design of the Fontan junction (Figure 1.3). Therefore, clinically relevant questions remain unanswered regarding the power loss characteristics of these proposed designs for the Fontan junction and its consequent impact on the systemic physiology in adults during exercise.

![Figure 1.3 – Proposed surgical geometries for the Fontan junction.](image-url)
1.6 Unanswered questions and the thesis goal:

Despite significant study of the Fontan physiology, the following questions remain unanswered:

1. “How does the Fontan junction geometry change with patient growth?”
2. “Can we find out how the local power loss affects the rest of the body?”
3. “How do we obtain an efficient mesh for the finite element component of multiscale simulations?”

1.7 Organization of the thesis document:

In this thesis we intend to answer the questions stated in the previous section in the following chapters:

2. “Can we find out how the local power loss affects the rest of the body?” – Chapter 5
CHAPTER TWO: PULMONARY ARTERY AND SOMATIC GROWTH IN FONTAN PATIENTS

2.1 Introduction and Literature Review:

Univentricular physiology represents one of the most severe forms of congenital heart disease. Patients exhibiting functionally univentricular physiology undergo staged surgical palliations ultimately culminating in the Fontan procedure. This involves the routing of the entire systemic venous return to the pulmonary arteries, bypassing the right ventricle. Consequently, the flow to the pulmonary arteries lacks a pumping source and is driven by the central venous pressure.

Exercise intolerance is one of many long-term sequelae associated with the Fontan circulation (others include protein-losing enteropathy, atrial arrhythmias, ventricular dysfunction, thrombotic complications, arteriovenous malformations, etc. [1]). It has been hypothesized that the size and geometry of the Fontan junction and pulmonary arteries have a significant impact on the patient’s cardiovascular performance[2]. Improving our understanding of pulmonary artery growth in Fontan patients is a critical step toward enhancing our insight into exercise-induced stresses on the Fontan physiology.

While the survival of Fontan patients in the short and medium term has improved dramatically over the last 20 years, it is uncertain that these patients can reach their third or fourth decade without developing severe complications or needing cardiac transplantation[3]; therefore, it is imperative that we improve our understanding of the adult Fontan physiology. Attempts have been made to model the Fontan circulation using patient-specific, closed-loop models[4–6]. For multiscale modeling, a necessary step in developing 3D patient-specific models is the acquisition of patient imaging data. However, standard practice in most clinical centers involves angiographic imaging shortly before and after the Fontan procedure [7]. Acquiring post-procedure imaging data at regular intervals through to adulthood is impractical, thus limiting the utility of these patient-specific multi-scale models in simulating the adult Fontan physiology. A predictive model of pulmonary artery growth patterns in Fontan patients would allow for the formulation of evolving anatomic models without requiring patient imaging data at multiple time points.

Scattered attempts have been made to study pulmonary artery size in single ventricle patients. A majority of the relevant literature focuses either on changes in the size of the pulmonary arteries between the various stages of the surgical palliation [8–10], or on linking the pre-operative pulmonary artery size to functional outcomes post-surgery [11–14]. Studies that constitute the former category of literature lack comprehensive data tracking pulmonary artery growth through to adulthood. The majority of the investigations that constitute the latter category of literature present normalized metrics of pulmonary artery size, such as the PAI and their utility in the optimal selection of
patients for the Fontan procedure. No mathematical model has been published that describes the temporal evolution of pulmonary artery growth in Fontan patients from infancy to adulthood. This chapter addresses this gap by consolidating existing literature through weighted regression analysis.

2.2 Methods:

An extensive literature review revealed several studies that have measured the Left Pulmonary Artery (LPA) and Right Pulmonary Artery (RPA) diameters in Fontan patients (Table 2.1). Several studies also provided valuable information regarding somatic growth in Fontan patients (Table 2.2). The BSA data corresponding to the report by Kansy et al.[27] was obtained by personal communication with the authors.

Due to the diversity of measurement metrics employed in previous literature, we constructed a procedure as outlined in Figure 2.1 to extract the necessary data. The relevant literature was classified into three categories based on their utility in deriving the relationship between pulmonary artery diameter and age. The studies that fall into the first category (Table 2.1: Section A) reported mean LPA and RPA diameters directly, whereas the studies that comprise the second category (Table 2.1: Section B) reported findings in normalized metrics from which the mean pulmonary artery diameter data needed to be derived. The third category (Table 2.1: Section C) comprises those studies that were used for preliminary assessment of the fitted pulmonary artery diameter versus age relationship.

The PAI is a normalized metric originally proposed by Nakata et al.[28] to serve as a prognostic indicator in the optimal selection of single ventricle patients for the Fontan palliation and is defined as:

\[
PAI = \frac{r - PA area + l - PA area}{BSA}
\]  

An analysis of the studies reporting both LPA and RPA diameters (Table 2.3) reveals a negligible difference between the mean LPA and mean RPA diameters. Based on this data, we assume that the LPA and the RPA sizes are equal. Applying this assumption, we extract the pulmonary artery size using the following equation:

\[
PAI = \frac{\pi d^2}{2 BSA}
\]

Where \(d\) is the mean of the systolic and diastolic diameter of the LPA or the RPA.

Buheitel et al.[29] presented pulmonary artery size measurements as z-scores, which are normalized against the mean pulmonary artery size expected in healthy children. The CDC growth charts[30] were utilized to calculate the mean normal BSA at a specific age. The resulting BSA was then combined with the normal pulmonary artery growth curves reported by Rammos et al.[31] to obtain the mean normal pulmonary
artery size at the specific age. The mean normal pulmonary artery size was used to de-normalize the z-scores and obtain the mean measured LPA and RPA diameters.

**Table 2.1**

A summary of previous publications reporting pulmonary artery size information in Fontan patients

<table>
<thead>
<tr>
<th>Ref No.</th>
<th>Authors</th>
<th>Sample Size</th>
<th>Initial Measuremnt age (years)</th>
<th>Follow-up Measuremnt age (years)</th>
<th>Measuremnt Metric (Units)</th>
<th>Initial PA diameter (LPA/RPA/combined)</th>
<th>Follow-up PA diameter (LPA/RPA/combined)</th>
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<tr>
<td>Section A: Publications reporting direct measurements of pulmonary artery diameters</td>
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<tr>
<td>15</td>
<td>Baek et al.(2011)</td>
<td>120</td>
<td>19.3</td>
<td>-</td>
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<td>13.9/13.8/215.2</td>
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<td>16</td>
<td>Wagner et al.(2012)</td>
<td>28</td>
<td>26.7</td>
<td>-</td>
<td>Direct measurement (mm)</td>
<td>17 / 17.35 / -</td>
<td>- / - / -</td>
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<tr>
<td>17</td>
<td>Restrepo et al.(2015)</td>
<td>48</td>
<td>11.8</td>
<td>17.4</td>
<td>Direct measurement (mm)</td>
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<td>15 / 15 / -</td>
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<td>9</td>
<td>Buheitel et al.(1997)</td>
<td>16</td>
<td>3.46</td>
<td>6.97</td>
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<td>61</td>
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<td>8.32</td>
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<td>- / - / 206.6</td>
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<td>- / - / 120</td>
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<td>20</td>
<td>Bossers et al.(2016)</td>
<td>23</td>
<td>11.1</td>
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<td>Mean indexed area (mm²/m²)</td>
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<td>- / - / 113</td>
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PA, Pulmonary Artery; LPA, Left Pulmonary Artery; RPA, Right Pulmonary Artery; PAI, Pulmonary Artery Index; **Bold, italicized values represent median data reported by the authors.**

All other parameter values represent mean data reported by the authors.
Figure 2.1 - Literature data extraction and compilation workflow.
Table 2.2
A summary of publications reporting somatic growth in Fontan patients

<table>
<thead>
<tr>
<th>Ref No.</th>
<th>Authors</th>
<th>Sample Size</th>
<th>Initial Measurement Age (years)</th>
<th>Follow-up measurement Age (years)</th>
<th>Initial mean BSA (m²)</th>
<th>Follow-up mean BSA (m²)</th>
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<td>Kansy et al. (2013)</td>
<td>24</td>
<td>7.1</td>
<td>14.5</td>
<td>0.81</td>
<td>1.4</td>
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</table>

BSA, Body Surface Area;

Table 2.3
A comparison of reported mean left and right pulmonary artery diameters in Fontan patients

<table>
<thead>
<tr>
<th>Ref No.</th>
<th>Authors</th>
<th>Sample Size</th>
<th>Mean LPA Diameter (mm)</th>
<th>Mean RPA Diameter (mm)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Robbers-Visser et al. (2008)</td>
<td>14</td>
<td>16.35</td>
<td>16.07</td>
<td>1.75</td>
</tr>
<tr>
<td>15</td>
<td>Baek et al. (2011)</td>
<td>120</td>
<td>13.9</td>
<td>13.8</td>
<td>0.72</td>
</tr>
<tr>
<td>16</td>
<td>Wagner et al. (2012)</td>
<td>28</td>
<td>17</td>
<td>17.35</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>Restrepo et al. (2015)</td>
<td>48</td>
<td>15</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

LPA, Left Pulmonary Artery; RPA, Right Pulmonary Artery;

Some investigators have measured and reported systolic pulmonary artery diameters rather than the mean diameter. The definition of distensibility was employed to determine the diastolic and subsequently the mean diameter (Equation 3). Of the investigations that have examined pulmonary artery distensibility in Fontan patients (Table 2.4), the study conducted by Bossers et al. reported the highest patient sample size. Therefore, we have used a numerical value of 0.15 for distensibility in our calculations according to their report.

\[
\text{Distensibility} = \frac{A_{\text{max}} - A_{\text{min}}}{A_{\text{max}}} \tag{3}
\]

Where \(A_{\text{max}}\) is the systolic diameter and \(A_{\text{min}}\) is the diastolic diameter.
We plotted the mean pulmonary artery diameter data obtained by the procedures outlined above against the mean age of the patient sample of the corresponding study. We employed weighted regression analysis to derive the best-fit trend line using a physiologically realistic function. The data points in the regression analysis were weighted according to the sample size of the study from which the data was extracted. We also plotted the mean BSA of the patient samples against the mean age of the patient samples and performed a similar weighted regression analysis to derive the best-fit trend line for the somatic growth data. By combining the two aforementioned mathematical relationships, we obtained the PAI versus age function. Finally, we assumed the growth of the pulmonary arteries is negligible beyond the age of 18, and hence have presented the fitted models up to that time point.

<table>
<thead>
<tr>
<th>Ref No.</th>
<th>Authors</th>
<th>Sample Size</th>
<th>Distensibility</th>
<th>LPA Distensibility</th>
<th>RPA Distensibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>26*</td>
<td>Morgan et al.(RA Group)(1998)</td>
<td>6</td>
<td>-</td>
<td>0.41</td>
<td>0.45</td>
</tr>
<tr>
<td>26*</td>
<td>Morgan et al.(BC Group)(1998)</td>
<td>5</td>
<td>-</td>
<td>0.37</td>
<td>0.33</td>
</tr>
<tr>
<td>19</td>
<td>Robbers-Visser et al. (2008)</td>
<td>14</td>
<td>0.22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>Bossers et al. (2016)</td>
<td>23</td>
<td>0.15</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

LPA, Left Pulmonary Artery; RPA, Right Pulmonary Artery;
* Morgan et al. classified their patient sample into two groups and reported their findings separately for each group.

2.3 Results and Discussion:

Our fitted model for Fontan pulmonary artery size shows retarded pulmonary artery growth in Fontan patients compared to normal children (Figure 2.2); however, the somatic growth of Fontan patients closely follows that of normal children (Figure 2.3). The combination of retarded pulmonary artery growth and close-to-normal somatic growth leads to a precipitous drop in PAI over time (Figure 2.4).
Figure 2.2: Pulmonary artery diameter versus age

Figure 2.3: Body Surface Area versus age

Figure 2.4: Pulmonary Artery Index versus age
The pulmonary artery diameter versus age relationship for Fontan patients predicts a severe underdevelopment of the pulmonary arteries as compared to normal children. This prediction of retarded growth is consistent with previous literature findings that in Fontan patients the pulmonary artery growth is negligible[37] or at least not proportional to the somatic growth[35,40]. Making use of the scarce measurement data available, we compared the fitted model for the pulmonary artery diameter, which is derived using mean data, to the data reported by publications in Table 2.1: Section C, which primarily report median data (Table 2.5). The maximum difference of 21.8% corresponds to the data reported by Robbers-Visser et al.[36] This difference could be due to the difference in the location at which the pulmonary arteries have been measured and the fact that the median rather than mean was reported in the data. The difference between the model’s prediction and reported data in the rest of the comparisons ranges from 1.72% to 14.28%.

<table>
<thead>
<tr>
<th>Ref No.</th>
<th>Authors</th>
<th>Measurement Age (years)</th>
<th>Reported Diameter (mm)</th>
<th>Model Predicted Diameter (mm)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Ovroutski et al.(2009)</td>
<td>3.95</td>
<td>10.15</td>
<td>10.32</td>
<td>-1.72</td>
</tr>
<tr>
<td>20</td>
<td>Ovroutski et al.(2009)</td>
<td>8.6</td>
<td>10.18</td>
<td>11.63</td>
<td>-14.28</td>
</tr>
<tr>
<td>21</td>
<td>Bossers et al.(2016)</td>
<td>11.1</td>
<td>12.86</td>
<td>12.34</td>
<td>4.07</td>
</tr>
<tr>
<td>21</td>
<td>Bossers et al.(2016)</td>
<td>15.5</td>
<td>14.84</td>
<td>13.57</td>
<td>8.5</td>
</tr>
</tbody>
</table>

LPA, Left Pulmonary Artery; RPA, Right Pulmonary Artery;
For the “Measurement Age” and “Diameter” reported in previous literature, bold, italicized values represent median data and other values represent mean data

The PAI, which indexes the sum of the LPA and RPA area to the BSA, can provide a measure of the pulmonary artery growth in context of the somatic growth. In the case of healthy children, the PAI is expected to increase slightly as they mature to adulthood[40]. In Fontan patients, our mathematical models predict retarded pulmonary artery growth and close-to-normal somatic growth, the combination of which results in a precipitous drop in the PAI over time. This trend is consistent with the observations made by Adachi et al[40]. The substantial difference in the temporal evolution of PAI in Fontan patients as compared to normal children demonstrates a severe insufficiency of pulmonary artery growth relative to somatic growth, indicating a potential to restrict blood flow and adversely affect cardiac output.

Single ventricle patients have been reported to exhibit significantly reduced height-for-age and weight-for-age prior to the Fontan operation. Although they exhibit catch-up growth[41,42], long-term post-operative follow-up reveals a lasting deficiency in terms of the height-for-age[41–43] and a trend toward normalization of the weight-for-
Persistent deficiencies in height combined with the trend toward normalization of the weight would lead to close-to-normal BSA as our somatic growth model predicts. Quantitatively, the model presented here for somatic growth agrees with the observations made by Hasan et al. [43] (differences ranging from 5.97% to 13.56%) and Cohen et al. [44] (difference of 8.2%).

The phenomenon of the late failure of the Fontan is poorly understood and requires investigation of the adult Fontan physiology. Computational fluid dynamic modeling involving the use of patient-specific geometry is an invaluable tool for simulating the Fontan haemodynamics. The mathematical models presented in this study enable the scaling of anatomic geometries of the pulmonary vasculature according to age or body surface area. Hence, these models allow the formulation of evolving anatomic models without the necessity of acquiring patient imaging data at multiple time points.
CHAPTER THREE: SELECTIVE SCALING

3.1 Introduction:

Since the first description of the Fontan procedure in 1971[1], several variations of this procedure have been performed. Of these variations, the total cavopulmonary connection with an extracardiac conduit introduced in the 1990s (Figure 1.2-C) is now employed by most surgical centers[45]. This variant of the Fontan procedure utilizes a graft composed of a synthetic material to connect the flow from the IVC to the PA. The extra cardiac conduit does not grow with the patient[46]. In chapter two, we highlight the fact that the pulmonary arteries of Fontan patients do grow, albeit at a rate different compared to normal patients. The patient-specific geometries that form our initial dataset include both the graft and the pulmonary arteries. Therefore, in order to scale up these geometries realistically, it is necessary that only the pulmonary arteries be enlarged while the graft is held constant. In this chapter, we present the selective scaling procedure applied to one patient-specific geometry to demonstrate its capability to produce realistic adult Fontan junction geometry.

3.2 Methods:

To demonstrate the selective scaling we choose one patient-specific geometry with an extracardiac conduit. Autodesk Meshmixer (Autodesk Research, San Francisco, CA) was used to scale the geometry and establish a smooth connection between the scaled pulmonary arteries and unscaled graft portion (Refer Appendix A for a detailed description of the commands involved in the process). We then discretized the selectively scaled geometry and performed a steady flow simulation to test for discontinuities and voids in the mesh. For the steady flow simulation, realistic inlet flow rates were prescribed to the SVC and IVC (Figure 3.1). The pulmonary artery outlets were prescribed a zero pressure boundary condition and a no-slip boundary condition was applied to the walls of the geometry (Figure 3.1).
3.3 Results:

The initial unscaled geometry is shown in Figure 3.2-A. In Figure 3.2-B, the blue zone includes the pulmonary arteries, which will be scaled up, and the brown zone is the graft whose size remains constant. For this example we scaled up the pulmonary artery zone by 20% and the result is shown in Figure 3.2-C. The two zones were then joined together as shown in Figure 3.2-D (the orange portion represents the join zone) and Figure 3.2-E. After running the steady flow simulation, we compared the mass flow rates at the inlets and outlets, and we found that mass conservation was satisfied, which indicates that the joining process produced no voids or defects in the geometry.
Figure 3.2: The process of selective scaling: (A) initial unscaled geometry; (B) geometry divided into pulmonary artery zone to be scaled (blue) and synthetic graft which is to remain unscaled (brown); (C) pulmonary artery zone (blue) after being scaled up by 20%; (D) the two zones being joined with the union zone highlighted in orange; (E) close up view of the union of the unscaled graft and the scaled up pulmonary artery zone.
3.4 Discussion:

In this chapter, we have described how it is possible to use Autodesk Meshmixer to scale selectively the Fontan geometries that we have obtained from our collaborators. The geometries that are produced by this process do not contain voids or discontinuities, making them viable for use in multi-scale simulations. We intend to consult surgeons to ensure the final geometries produced are as anatomically realistic as possible.
CHAPTER FOUR: AUTOMATED ITERATIVE ADAPTIVE MESHING

4.1 Introduction:

For any numerical simulations involving the finite element method, it is critical that solution (i.e. the parameter of interest) be independent of the mesh size. In practice, this involves the process of progressively refining an isotropic mesh until the solution remains constant irrespective of mesh size. A disadvantage of using a conventional isotropic mesh for such geometries is the fact that the extracardiac conduit (ECC) or the Y-graft comprise a significant fraction of the total volume of the geometry. An isotropic mesh would devote a disproportionately large number of elements to the upstream portion (i.e. the ECC or Y-graft) of the geometry where the flow is relatively less complex when compared to downstream region (i.e. the Fontan junction and pulmonary arteries), where we expect to see complex flow interactions.

While several studies have utilized adaptive meshing algorithms to optimize the discretization of complex patient specific geometry, they rarely describe the parameters supplied to the meshing algorithm. In this chapter, we will summarize our experiences with iterative adaptive meshing and suggest preliminary guidelines that facilitate the generation of a converged adapted mesh. By utilizing an iterative Adaptive Meshing Protocol (AMP) that we propose here, it is possible to produce meshes of various sizes in discrete steps. The user then chooses the appropriate mesh based on the convergence of the parameter of interest. Additionally, the AMP progressively refines the mesh through each iteration, which progressively improves the capability of the adapted meshes to capture the physics of the flow field.

4.2 Methods:

The SimVascular package[47] includes an adaptive meshing algorithm (AMA) which performs an a posteriori evaluation of the Mean Interpolation Error (MIE) of a finite element solution[48]. SimVascular allows the user to choose one of two meshing strategies, isotropic and anisotropic adaptive meshing strategies. Our protocol utilizes this AMA to reduce iteratively, the MIE by progressively refining the mesh through each iteration. The AMA is applied to the steady flow solution of an isotropic mesh (of edge size \( H_0 \)) for the initial iteration and attempts to reduce the MIE by a reduction factor (R). Constraints for the size of the adapted mesh elements generated by the AMA are specified by the minimum & maximum edge size parameters. The minimum edge size \( (H_{1\text{min}}) \) and maximum edge size \( (H_{1\text{max}}) \) are specified for the first iteration. In subsequent iterations, \( H_{1\text{min}} \) and \( H_{1\text{max}} \) are reduced by a refinement factors F1 and F2 respectively,
and the process of the first iteration is repeated. The protocol continues in a similar manner for a user specified number of iterations. In the subsequent section, we present a trial of the AMP as an example. We carried out multiple trials of the AMP for both isotropic and anisotropic mesh strategies to determine a set of recommendations, which we describe in the results section.

We characterized the behavior of the protocol by using the same geometry, identical boundary conditions and varying the input parameters to observe its effect on mesh convergence. In case of multi-scale simulations, it is essential that the information exchanged at the boundaries between the LPN and the 3-D domain be converged. Since the thesis goal is to measure energy loss, we monitored the pressures developed at the inlet faces of the steady flow solution during each iteration of adaptation to determine if the mesh has converged. In this study, we considered the mesh to be converged if the pressures developed at the inlet faces of the steady flow solution varied by less than 5% between each iteration of the protocol.

In all cases the fluid was assumed to be Newtonian with a density of 1092.4 kg/m$^3$ and a dynamic viscosity of 0.0041 Pa·s, similar to that of blood. We prescribed the following boundary conditions in all cases: steady flow of magnitude 1.24 l/min and 2.58 l/min to the SVC and IVC faces respectively, zero pressure boundary conditions to the pulmonary outlet faces, and a no-slip boundary condition on the walls (Figure 4.1).

![Figure 4.1- Boundary conditions applied for all trials of the adaptive meshing protocol](image-url)
4.3 Results and Discussion:

Our broad observations of the behavior of the AMP are described below:

1. The isotropic mesh adaptation strategy is of scant utility. All trials with the isotropic mesh adaption strategy led to an initial decrease, followed by steady increases in the MIE (Figure 4.2) to magnitudes greater than the initial isotropic mesh.

2. Specifying a maximum edge greater than the initial edge size of the isotropic mesh led to a reduction in the number of elements after adaptation, often leading to a loss of geometrical accuracy (figure 4.3).

3. For any iteration of the adaptive meshing protocol, if the difference between the maximum and minimum edge sizes is of the same order of magnitude as the initial edge size of the isotropic mesh, distorted elements will be formed (Figure 4.4). Additionally, a loss of fidelity in capturing geometric characteristics of the input volume may occur.

4. If a boundary layer mesh is generated, the AMA does not influence it (Figure 4.5).

![Figure 4.2- Isotropic mesh adaption strategy](image-url) Evolution of the mean interpolation error and number of elements from through each iteration; iteration zero refers to the initial mesh.
Figure 4.3- Loss of geometrical accuracy; (A) Initial isotropic mesh; (B) Mesh produced after a single adaption with max edge size greater than the initial isotropic edge size.

Figure 4.4- Formation of distorted elements (dashed box) due to a large difference between the maximum and minimum edge size.

Based on these observations we believe that the following guidelines are useful to those who would wish to apply the adaptive meshing capabilities of SimVascular iteratively:

1. Use the anisotropic mesh adaption strategy.
2. The maximum edge size prescribed to the AMA should always be lesser than the initial isotropic mesh edge size, to prevent mesh coarsening.
3. The initial mesh should be fine enough to capture the geometric features of the input volume adequately. Face meshing is particularly useful since it refines only the surface without significantly affecting the body of the mesh.
4. It may be useful to prescribe a boundary layer mesh in addition to a fine face mesh for faces that are geometrically complex. The boundary layer mesh will
exclude that particular face from the adaptive meshing preventing a loss of quality.

5. The mesh for the gross volume can be quite coarse. The edge size for the initial mesh can be one order of magnitude larger than the edge size prescribed to the faces.

6. The boundary conditions prescribed should be such that the steady flow simulation experiences approximately the same maximum flow and pressure gradients that would be expected in the actual simulation.

7. As much as possible, ensure that the solver settings and residual control match those that will be used in the actual simulation.

8. We recommend the reduction of both maximum and minimum edge size through each iteration to refine the mesh progressively. In addition, we recommend that the difference between the maximum and minimum edge size be of the same order of magnitude as the minimum edge size, preferably smaller to prevent element distortion.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Symbol</th>
<th>Values (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotropic Mesh Edge Size</td>
<td>H₀</td>
<td>2.0</td>
</tr>
<tr>
<td>Max Edge size for iteration 1</td>
<td>H₁max</td>
<td>0.665</td>
</tr>
<tr>
<td>Min Edge size for iteration 1</td>
<td>H₁min</td>
<td>0.56</td>
</tr>
<tr>
<td>Max Edge Size Reduction Factor</td>
<td>F₁</td>
<td>0.95</td>
</tr>
<tr>
<td>Min Edge Size Reduction Factor</td>
<td>F₂</td>
<td>0.8</td>
</tr>
<tr>
<td>Error Reduction Factor</td>
<td>R</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Table 4.1** – Parameters specified for the adaptive meshing protocol for the example trial.

In order to demonstrate the application of these guidelines, we present an example here. The boundary conditions and fluid properties for this trial were set according to the details mentioned in section 4.2. Table 4.1 lists the parameters assigned to adaptive meshing protocol. For this particular example, we have specified boundary layer meshing for all faces. The boundary layer parameters are presented in the form of the input to SimVascular. The terms “negative 2 0.125 0.25” indicate the boundary layer will grow inward from the surface, it will have two layers, the height of the first layer being 0.125mm and the total height of the boundary layer mesh being 0.25mm. The objective
for this setting is to create a “thin shell” of fine mesh elements from the outer boundary of the geometry inward, which will not be affected by the AMA. The adaptive meshing algorithm is free to manipulate and refine the bulk of the mesh.

Since the fluid power loss is the parameter of interest in this thesis, we have used the pressure developed at the SVC face as a surrogate mesh convergence criteria. Figures 4.5 and 4.6 exhibit the evolution of the mean interpolation error, the pressure developed at the SVC face, and the number of elements for each iteration of the adaptive meshing protocol in this example. We observed the MIE decrease steadily through each iteration with the largest drop occurring in the very first iteration. This can be explained by the fact that \( H_{1\text{max}} \) is one order of magnitude smaller than the \( H_0 \) in this particular example. The number of elements increased steadily until the fifth iteration with the last two iterations accounting for an increase of nearly 3 million elements. The optimal mesh size is dependent on the parameter of interest. If the SVC face pressure is the parameter of interest, the meshes produced in the second and third iteration show negligible differences when compared to the mesh produced in the sixth iteration. The mesh generated by the third iteration would be a good compromise of accuracy and mesh size.

\[ \text{Figure 4.5} \quad \text{– Evolution of mean interpolation error and number of elements through six iterations of the adaptive meshing protocol. Iteration 0 corresponds to the initial mesh.} \]
Figure 4.6 – Evolution of pressure developed at the SVC face and number of elements through six iterations of the adaptive meshing protocol. Iteration 0 corresponds to the initial mesh.

To study the resolution of the internal flow field we investigated the 3-D output, specifically the results produced by the initial mesh and the meshes of iterations 1, 4, and 7. The confluence of the SVC and IVC flow is a zone of particular interest in the analysis of power loss in the Fontan junction; hence, we have taken a slice at the location shown in Figure 4.7(A). The improvement in the ability of the mesh to capture complex haemodynamics from the initial mesh to the final iteration is clearly visible from the velocity maps (Figure 4.7 (C)).

In conclusion, the AMP is capable of producing meshes tailored to the situation being modeled. The AMP allows the user to generate adapted meshes relatively quickly with discrete increases in the mesh size, with the final choice of the mesh being governed by the convergence of the parameter of interest.
Figure 4.7 – (A) Slice location, (B) Slice showing detail view location, (C) Detail view of velocity maps superimposed on the mesh for various iterations at the location specified in (B).
CHAPTER FIVE: MULTISCALE SIMULATIONS OF IVC STENOSES IN FONTAN PATIENTS

5.1 Introduction:

Multi-scale simulations consist of a two-way coupling between a 3-D CFD component and a 0-D lumped parameter component. The 3-D CFD component provides detailed local haemodynamic information such as power loss, while the 0-D lumped parameter component provides critical global haemodynamic data such as cardiac output. This capability of providing both local and global haemodynamic data is necessary for achieving the thesis goal stated in section 1.6. The objective of this chapter is to demonstrate the capability of performing multi-scale simulations of the Fontan circulation at various levels of exercise and interpret the results in terms of local and global haemodynamic parameters.

The scenario modeled here is the obstruction of the extracardiac conduit in Fontan patients due to calcium deposition and/or longitudinal torsion because of somatic growth. The multiscale simulations involved here are similar to those that we will perform to achieve the long-term goal stated in section 1.6; the difference being the coupling location between the 3D geometry and the physiological model, in addition to the number of inlets and outlets. An additional advantage of modeling this particular scenario is that it allowed us to corroborate the output of a novel computational-experimental hybrid framework against previously validated multi-scale techniques[22–25].

5.2 Methods:

We considered test cases for 85% and 65% (area reduction) stenoses for physiologic conditions of one, three, and five metabolic equivalent (MET). The location at which the stenoses geometry were inserted into the LPN is shown in Figure 5.1. The geometries have a patent diameter of 19mm and an elongated outflow section (Figure 4.1) to allow the stabilization of the complex flow field downstream of the stenoses and the dissipation of vortices. The geometries of the two stenoses were anisotropically discretized (Figure 5.2) using linear tetrahedral elements with a commercial meshing module (MeshSim, Simmetrix Inc., NY) which is available with the SimVascular software package[47]. The resulting meshes were comprised of $11.1 \times 10^6$ and $11.8 \times 10^6$ elements for the 85% and 60% stenoses geometries, respectively. The number of elements for these meshes is one order of magnitude larger (Table 4.1) than a previous computational study involving stenoses of comparable size and Reynolds number[49]. A no-slip boundary condition was imposed on the walls of the geometry, and the pressures from the physiology simulations were coupled to the inlet and outlet faces as Neumann boundary conditions. The working fluid was assumed to be Newtonian, with a density of
1092.4 kg/m³, and a dynamic viscosity of 0.0041 Pa.s, similar to that of blood. The 3-D solver solves for the incompressible Navier-Stokes equations using a previously validated, stabilized finite element method[24,25,50]. We employed a time-step size of 0.001s in all simulations. Stable periodicity was achieved after 4 and 5 respiration cycles for 1 MET and 5 MET cases, respectively. The results of the last respiration cycle were used for analysis. The NRMSE of the last and the second to last respiration cycles were <0.6%, which confirms that the simulations attained stable periodicity. We compared the output of these simulations against the prediction of the physiology simulations alone to highlight the impact of these stenoses on global haemodynamic parameters.

Figure 5.1: Multiscale model of an IVC stenosis in a Fontan patient. Dashed box represents the IVC stenosis.
Figure 5.2 –The stenosis geometries; (A) 60% and, (B) 85% stenosis 3D geometries. Distances shown are in mm. Zones 1 and 2 are meshed with a maximum edge size of 0.5 mm and 0.2 mm, respectively. The inlet and outlet faces are meshed with a maximum edge size of 0.4 mm.

5.3 Results:

Table 5.1 details the results obtained from the multiscale simulations at one, three, and five MET, where 1 MET represents the resting condition and 5 MET corresponds to
vigorous exercise. Cardiac Output and IVC pressure are the global haemodynamic parameters of interest, while the local power loss information is provided in terms of the input power.

<table>
<thead>
<tr>
<th></th>
<th>MET 1</th>
<th>MET 3</th>
<th>MET 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Output (L/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85% IVC Stenosis</td>
<td>3.34</td>
<td>4.56</td>
<td>5.37</td>
</tr>
<tr>
<td>60% IVC Stenosis</td>
<td>3.55</td>
<td>5.35</td>
<td>6.78</td>
</tr>
<tr>
<td>No Stenosis Fontan</td>
<td>3.56</td>
<td>5.39</td>
<td>6.98</td>
</tr>
<tr>
<td><strong>IVC Pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85% IVC Stenosis</td>
<td>14.91</td>
<td>19.97</td>
<td>24.67</td>
</tr>
<tr>
<td>60% IVC Stenosis</td>
<td>13.71</td>
<td>16.69</td>
<td>19.46</td>
</tr>
<tr>
<td>No Stenosis Fontan</td>
<td>13.33</td>
<td>15.95</td>
<td>18.3</td>
</tr>
<tr>
<td><strong>Power Loss (% of input)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85% IVC Stenosis</td>
<td>14.72</td>
<td>31.69</td>
<td>38.8</td>
</tr>
<tr>
<td>60% IVC Stenosis</td>
<td>2.53</td>
<td>7.99</td>
<td>15.96</td>
</tr>
<tr>
<td>No Stenosis Fontan</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Table 5.1: Evolution of local and global haemodynamic parameters for different exercise levels and degrees of IVC stenosis.*

CO is a measure of oxygen delivery to the tissues and hence is of significant clinical importance. With an increase in CO, oxygen delivery rate to the tissues increases, improving exercise capacity. Another global haemodynamic parameter of importance to clinicians is IVC pressure. The importance of the IVC pressure stems from the fact that the liver drains to the IVC. Higher IVC pressures hamper drainage from the liver causing a highly vascularized organ to be chronically congested, leading to irreversible liver damage. A high IVC pressure is of clinical importance due to its detrimental effects on the long-term health of a Fontan patient.

We observed a decrease in the CO when a stenosis is present both at rest and during exercise. The reduction in the CO increases with increasing severity of the stenosis at all levels of exercise with a 23% reduction for the 85% stenosis and a 3% reduction for the 65% stenosis at five MET. In case of the IVC pressure, the presence of stenoses are accompanied by increases in IVC pressure for both resting and exercise conditions. An increase in the severity of the stenosis is marked by an escalation of the IVC pressure, 34% in the case of 85% stenosis and 6% in the case of the 65% stenosis.
The local power loss tends to escalate with increasing levels of exercise for both stenoses. The severity of stenosis, however, has a significant impact on the power loss at all levels of exercise with a minimum upsurge of 143% at five MET and a maximum escalation of 582% at rest, when the 85% stenosis is compared to the 60% stenosis.

**Figure 5.3: Pertinent results of the multiscale simulations.** (A) Velocity map across the length of the geometry and velocity contours at the inlet, after the stenosis and at the outlet; (B) Normalized vorticity map along the geometry and a plot of maximum normalized vorticity at different slices of geometry; Vorticity is normalized against vorticity at inlet face.
In terms of the local haemodynamics, the velocity map and velocity profiles at specific points across the stenosis geometry were obtained (Figure 5.3(A)). These results correspond to the highest flow rate at time-step 8380 of the last respiration cycle, for the 85% stenosis geometry at an exercise level of 5 MET. In order to ensure that the outlet length was sufficient to allow the dissipation of vortices, Figure 5.3B shows a vorticity map along the length of the stenosis. Additionally, we have plotted the normalized vorticity (normalized to inlet flow vorticity) along the length of the stenosis. The normalized vorticity at the outlet is not significantly larger than at the inlet, indicating the dissipation of the complex flow field downstream of the stenosis.

5.4 Discussion:

The analysis of IVC stenoses in Fontan patients presented here demonstrates the capability to conduct multi-scale simulations to obtain both local and global haemodynamic information. The results clearly illustrate the detrimental effects of an IVC stenosis in a Fontan patient by quantifying changes in global haemodynamic parameters at rest and during exercise. This quantification also allows for the comparison between the two types of stenoses. Both stenoses result in a reduction of cardiac output and an elevation in the IVC pressure, which are detrimental to the health of the patient. The 85% stenosis, however, causes a significantly larger detriment to global haemodynamics as compared to the 60% stenosis. The detailed local haemodynamic information allows the computation of the power loss as a fraction of the inlet power loss, the visualization of the flow field, and the computation of quantities such as the vorticity, which may be of interest. Applying the multiscale framework to patient specific Fontan geometries will provide local power loss and global haemodynamic information in an analogous manner.
CHAPTER SIX: FUTURE WORK

6.1 Future Work:

1. The models produced in Chapter 2 need to be validated and expanded. To that end, we have acquired data for pulmonary artery diameters, age and BSA in Fontan patients through our collaborators. Validation and improvement of the model is currently in progress.

2. We will contact surgeons to ensure that the procedure defined in Chapter 3 produces anatomically correct geometry.

3. We will apply the techniques presented here to quantify the junction power loss for the various surgical configurations available to us and examine its effect on global haemodynamics.
REFERENCES


