I, Ashish Das, hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Mechanical Engineering.

It is entitled:
Development of Energy-Based Endpoints for diagnosis of Pulmonary Valve Insufficiency

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Development of Energy-Based Endpoints for diagnosis of Pulmonary Valve Insufficiency

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ABSTRACT

Introduction. Pulmonary insufficiency (PI) causes myocardial dysfunction and hypertrophy in the right ventricle; with fatal consequences in some cases. The only remedy is pulmonary valve (PV) replacement surgery, the timing of which is critical. Surgery performed earlier than necessary leads to a re-emergence of PI, whereas a delayed intervention can potentially render the replacement futile. There are no physiological markers to determine the correct window for this surgery. Clinicians currently rely on subjective assessment of cardiac MRI scans and evaluation of a few ad-hoc measures, such as end-diastolic pressure, cardiac volume and regurgitant fraction. The use of these different measures often results in conflicting conclusions and error-prone decisions. Thus, a quantitative index is required to unambiguously assess the progression of PI to determine the correct window for the PV replacement surgery. In this research, a set of energy-based endpoint were investigated that combined the pressure and volumetric measures. Right ventricular (RV) stroke work, energy loss in the branch pulmonary artery (PA) and a new endpoint, energy transfer ratio defined as the ratio of the total blood energy at the main PA and stroke work were developed and tested as a proof-of-concept.

Methods. The energy based endpoints were obtained for a normal and a diseased subject. Pressure measurements obtained invasively from cardiac catheterization, and flow rate and ventricular volume obtained non-invasively from MRI scans were utilized for the calculation.

Subsequently, methodologies to obtain these endpoints in a completely non-invasive approach, using patient-specific image-based hemodynamic models were developed to eliminate the requirement of invasive catheterization. Angiographic MRI was used for geometry reconstruction for image-based models. Actual time- and spatially- varying velocity profiles, directly obtained from phase-contrast MRI were used for patient-specific velocity boundary conditions.
Flow rates from the numerical models were validated with ones obtained from a standard of care measurement. Finally, the arterial wall compliance was incorporated in the computational models. The *in-vivo* wall pre-stress was calculated by developing a nonlinear least-square based inverse elastostatics algorithm called the *shrink-and-fit inverse* method. An idealized geometry of a canine femoral artery adopted from our prior publication was adopted for testing.

**Results.** The RV *stroke work* for the normal subject (0.115 J) was 32% higher than that of the subject with PI (0.078 J). The *energy transfer ratio* for the normal subject (1.06) was nearly two times that of the subject with PI (0.56). Similarly, the *loss of total energy* over one cardiac cycle for the normal subject (0.014 J) was also 64% lower than that of the subject with PI (0.023 J).

*Validation of non-invasive method:* The maximum difference between the flow rate from computation with time- and spatially-varying velocity boundary conditions and the one from standard of care measurement was 7 ml/sec at the main PA of the diseased subject. The computed flow rates for the normal subject were within 3.4% (2 ml/sec) of the measured values at each of the inlet and outlets and those of the diseased subject were within 22.6% (7 ml/sec). The double digit percentage differences for the diseased subject were due to lower baseline mean flow rates due to excessive regurgitation. For the *compliant arterial wall model*, the shrink-and-fit inverse algorithm matched the *in-vivo* and pre-stressed artery geometry within 0.0015 mm. The outer wall diameter of the pre-stressed wall was 4.3% higher than the load-free wall. The time-averaged longitudinal Cauchy stress under the pulsatile pressure condition was 42.5% higher than the corresponding circumferential stress.

**Conclusions.** The energy-based endpoints were able to delineate a normal physiology from a PI pathophysiology. These endpoints have the potential to improve the diagnosis of PI by eliminating the ambiguity resulting from the use of either pressure-based or volume-based measures.
To

Shishir, Mihir, Anindita
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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS

1. Introduction............................................................................................................................. 1
   1.1 Pulmonary Valve Insufficiency......................................................................................... 1
   1.2 Motivation and Objective.................................................................................................. 5
       1.2.1 Central hypothesis................................................................................................... 7
       1.2.2 Specific Aims.......................................................................................................... 7
   1.3 Research Plan and the Outline of the Dissertation.......................................................... 12

2. Background and Literature Review.................................................................................... 15
   2.1 Introduction ............................................................................................................... ...... 15
   2.2 Tetralogy of Fallot........................................................................................................... 16
       2.2.1 Normal Heart ........................................................................................................ 17
       2.2.2 Tetralogy Heart ..................................................................................................... 19
       2.2.3 Tetralogy Repair Surgery...................................................................................... 21
       2.2.4 Long Term Post Surgical Complications.............................................................. 22
       2.2.5 Clinical Diagnosis of Pulmonary Insufficiency .................................................... 23
   2.3 Cardiac Function Energetics ........................................................................................... 25
       2.3.1 Force-Velocity Relationship ................................................................................. 25
       2.3.2 Pump Characteristics ............................................................................................ 29
       2.3.3 Biochemical Processes.......................................................................................... 33
   2.4 Clinical Use of Cardiac MRI........................................................................................... 34
   2.5 Image-Based Models of Arterial Hemodynamics ........................................................... 35
       2.5.1 Geometry Reconstruction ..................................................................................... 36
       2.5.2 Boundary Conditions ............................................................................................ 39
   2.6 Blood Flow with Compliant Arterial Wall...................................................................... 41
       2.6.1 Wall Geometry and Thickness.............................................................................. 43
       2.6.2 Arterial Stress States .............................................................................................. 44
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6.3</td>
<td>Load-free Arterial Geometry</td>
<td>46</td>
</tr>
<tr>
<td>2.7</td>
<td>Conclusions</td>
<td>50</td>
</tr>
<tr>
<td>3.</td>
<td>Energy-Based Endpoints</td>
<td>52</td>
</tr>
<tr>
<td>3.1</td>
<td>Introduction</td>
<td>52</td>
</tr>
<tr>
<td>3.2</td>
<td>Rationale for using of Energy-Based Endpoints</td>
<td>53</td>
</tr>
<tr>
<td>3.3</td>
<td>Ventricular Stroke-Work</td>
<td>54</td>
</tr>
<tr>
<td>3.3.1</td>
<td>Cardiac cycle</td>
<td>54</td>
</tr>
<tr>
<td>3.3.2</td>
<td>Pressure-Volume Diagram</td>
<td>58</td>
</tr>
<tr>
<td>3.3.3</td>
<td>Ventricular Stroke Work</td>
<td>59</td>
</tr>
<tr>
<td>3.3.4</td>
<td>Cardiac Pressure and Volume Measurement</td>
<td>60</td>
</tr>
<tr>
<td>3.3.5</td>
<td>Co-registration of Pressure and Volume Data</td>
<td>62</td>
</tr>
<tr>
<td>3.3.6</td>
<td>Stroke Work Calculation</td>
<td>65</td>
</tr>
<tr>
<td>3.4</td>
<td>Total Energy at an Arterial Cross-Section</td>
<td>66</td>
</tr>
<tr>
<td>3.5</td>
<td>Energy Transfer Ratio</td>
<td>67</td>
</tr>
<tr>
<td>3.6</td>
<td>Energy Loss in Branch Pulmonary Artery</td>
<td>69</td>
</tr>
<tr>
<td>3.7</td>
<td>Concluding Remarks</td>
<td>70</td>
</tr>
<tr>
<td>4.</td>
<td>Patient-Specific Hemodynamics using Womersley Profile from PC-MRI</td>
<td>71</td>
</tr>
<tr>
<td>4.1</td>
<td>Introduction</td>
<td>71</td>
</tr>
<tr>
<td>4.2</td>
<td>Methods</td>
<td>72</td>
</tr>
<tr>
<td>4.2.1</td>
<td>Study Population</td>
<td>72</td>
</tr>
<tr>
<td>4.2.2</td>
<td>Data Acquisition</td>
<td>73</td>
</tr>
<tr>
<td>4.2.3</td>
<td>Analysis of Pressure and Flow Data</td>
<td>75</td>
</tr>
<tr>
<td>4.2.4</td>
<td>Patient-specific Geometry Reconstruction</td>
<td>75</td>
</tr>
<tr>
<td>4.2.5</td>
<td>Mathematical Model</td>
<td>78</td>
</tr>
<tr>
<td>4.2.6</td>
<td>Numerical Computation</td>
<td>85</td>
</tr>
<tr>
<td>4.3</td>
<td>Results</td>
<td>87</td>
</tr>
<tr>
<td>4.3.1</td>
<td>Regurgitant Fraction at MPA and RPA</td>
<td>87</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Validation of LPA Flow Rate</td>
<td>88</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Validation of Pressure</td>
<td>91</td>
</tr>
<tr>
<td>4.4</td>
<td>Discussion</td>
<td>93</td>
</tr>
<tr>
<td>4.5</td>
<td>Conclusion</td>
<td>96</td>
</tr>
</tbody>
</table>
5. Results: Energy-Based Endpoints

5.1 Introduction

5.2 Subject Population

5.3 Data Acquisition

5.3.1 Cardiac MRI

5.3.2 Cardiac Catheterization

5.4 Calculation of Energy-Based Endpoints

5.5 Results: Right Ventricular Stroke Work

5.5.1 RV Pressure and Volume Characteristics

5.5.2 RV Pressure-Volume Loops and RV Stroke Work Calculations

5.6 Results: Total Blood Flow Energy at MPA

5.7 Results: Energy Loss in Pulmonary Artery

5.8 Discussion

5.9 Limitations

5.10 Conclusions

6. Patient-Specific Hemodynamics using Time- and Spatially-Varying Velocity Profiles

6.1 Introduction

6.2 Method

6.2.1 Patient Selection

6.2.2 Cardiac and Flow MRI

6.2.3 Sequential block diagram of the overall methodology

6.2.4 PA geometry from Angiographic MRI

6.2.5 Locate inlet and outlet from PC-MRI

6.2.6 Patient-specific velocity profile from PC-MRI

6.2.7 Flow rate measurement

6.2.8 Hemodynamic model

6.3 Results

6.3.1 Comparison of flow rate: QFlow versus PCMR-Direct

6.3.2 Verification of the implementation: Boundary condition from PC-MRI data

6.3.3 Flow balance between inlet and outlet of branch PA
8. Conclusions and Future Work ........................................................................................................ 211
   8.1 Summary ................................................................................................................................... 211
   8.2 Future Work ............................................................................................................................... 214

BIBLIOGRAPHY ............................................................................................................................. 215
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>A) Schematic diagram of the heart showing different chambers and valves. B) A transverse section through the heart at the location of the pulmonary valve showing the valve leaflets. (<a href="http://en.wikipedia.org/wiki/File:Diagram_of_the_human_heart_(cropped).svg">http://en.wikipedia.org/wiki/File:Diagram_of_the_human_heart_(cropped).svg</a>)</td>
<td>2</td>
</tr>
<tr>
<td>1.2</td>
<td>A) Anatomical MRI of the right ventricle of a normal subject, and B) that of a subject with pulmonary insufficiency, showing the effect of volume overloading. C) Progressive enlargement of the right ventricle of a subject with pulmonary insufficiency over time.</td>
<td>4</td>
</tr>
<tr>
<td>1.3</td>
<td>Research plan and the summary of specific aims and objectives. The dashed lines associate a particular energy-based endpoint to the corresponding pulmonary flow related cardiac anatomy. The solid lines show the link between specific aims.</td>
<td>14</td>
</tr>
<tr>
<td>2.1</td>
<td>A) A normal heart with directions of blood shown by blue and red arrows. B) Schematic representation of the normal heart using a block diagram. The blue arrow represents flow of deoxygenated blood, whereas the red ones represent oxygenated blood. (<a href="https://health.google.com/health/ref/graphic/1056">https://health.google.com/health/ref/graphic/1056</a>)</td>
<td>17</td>
</tr>
<tr>
<td>2.2</td>
<td>A) A heart of a tetralogy of Fallot subject with directions of blood flow through the VSD. B) Its schematic representation using block diagram. The blue arrows represent the flow of deoxygenated blood; and the red ones, the oxygenated blood. (<a href="https://health.google.com">https://health.google.com</a>)</td>
<td>20</td>
</tr>
<tr>
<td>2.3</td>
<td>Schematic representation of the heart of a subject after tetralogy of Fallot repair surgery. The VSD is closed with a VSD patch. The stenosed PA is widened by cutting open the right ventricular outflow track (RVOT) and closed with RVOT patch.</td>
<td>22</td>
</tr>
<tr>
<td>2.4</td>
<td>Some of the commonly used phenomenological material models of cardiac tissues [1-3]. A) the Hill model, B) the Maxwell model and C) the Voigt model.</td>
<td>26</td>
</tr>
<tr>
<td>2.5</td>
<td>Various mechanical models of the cardiac muscle contraction process. A) Isometric contraction. B) Isotonic contraction. C) Isotonic afterload. The preload is denoted by PL, and AL represents afterload.</td>
<td>28</td>
</tr>
<tr>
<td>2.6</td>
<td>Schematic pressure-volume diagram for an isolated ventricle showing ESPV, ESPVR line and EDVPR curve. (<a href="http://www.ccnmtl.columbia.edu/projects/heart">www.ccnmtl.columbia.edu/projects/heart</a>)</td>
<td>32</td>
</tr>
<tr>
<td>2.7</td>
<td>Schematic diagram showing the different state of stresses in an arterial segment;</td>
<td>46</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>A) <em>in-vivo</em> in pre-stressed state, B) load-free without arterial pressure ( p ), and C) excised and cut longitudinally in stress-free state.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Schematic diagram of heart showing the control volumes used for the calculation of different energy-based endpoints.</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>3.2 The Wiggers diagram for the left ventricle of the heart showing the electrical activity as recorded with echocardiogram and the corresponding variation of the ventricular pressure and volume. The last row of heart icons shows the sequence of atrial and ventricular filling at different time points in the cardiac cycle. (Redrawn from Silverthorn, D.U., <em>Human Physiology: An Integrated Approach</em>, 2nd ed., Prentice Hall, NJ)</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>3.4 Volume and pressure measurement in the right and left ventricle.</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>3.5 A) A typical short-axis anatomical MRI through human heart at a given phase and slice location. B) Right ventricle inner wall boundary on images at different slice locations but at same phase. C) Representation of the right ventricular inner wall contours in 3D space. D) Right ventricular volume variation with time.</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>3.6 Co-registration of the asynchronous pressure and the RV volume versus time pulses (or the LPA/MPA/RPA flow as appropriate) using ECG. The time ( t = 0 ) sec, in our calculations correspond to the start of a systole and is identified from the start of the QRS complex of the ECG tracing. Start of two consecutive QRS complex on the ECG pulse of the patient define one cycle of the pressure pulse.</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>3.7 A) Schematic representation of control volume for energy ratio and energy loss calculation. B) Locations of velocity and pressure measurements at the inlets and outlets of branch pulmonary artery.</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>4.1 Geometry reconstruction from the patient specific MRI images: (A) Stack of 3D MRI of subject’s chest used for PA geometry reconstruction; (B), (C), (D) show the coronal, axial and sagittal views, respectively. The PA was identified by a coloring mask specified by setting a range of grey scale value from the image. (E) The reconstructed branch PA geometry without clearly defined inlet and outlets.</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>
| 4.2 Geometrical reconstruction for (A) Normal and (B) rTOF subject. The main PA domain is created from STL triangles. Cylindrical extensions are created to al-xiii
low for flow development. Transition piece connects the cylindrical extension to the respective non-circular inlet or outlet.

4.3 LPA Pressure measured using fluid filled catheter in normal and rTOF subject. 80

4.4 PC-MRI based flow rate measurement for the normal and rTOF subject at A) MPA and B) RPA. Womersley velocity profiles for velocity boundary conditions were computed from these flow rates.

4.5 Validation of the computed flow rates at LPA with the PC-MRI measurement for both the normal and rTOF subject. 89

4.6 Comparison of the numerically computed pressure with one obtained by catheter measurement, at (A) MPA and (B) RPA of the normal subject. The horizontal lines depict the time averaged values. 92

5.1 Schematic diagram of the heart of (A) rTOF subject, (B) normal subject and (C) intermediate subject. The rTOF subject (A) has defective PV and overloaded RV because of back flow. The normal subject (B) has functioning PV and normal RV. The intermediate subject (C) suffers from a partial anomalous PV return and thus has an overloaded RV but functioning PV. 100

5.2 Variation of RV pressure and volume with time for (A) the normal subject, (B) for the rTOF subject and (C) for the intermediate subject. It may be noted that RV of the rTOF subject operates at higher average pressure and is volume overloaded. 105

5.3 Right ventricular PV diagram for the normal, the rTOF and the intermediate subject. The RV of the normal subject is able to perform higher stroke work than that of the rTOF subject in spite of operating at lower average pressure. PV loop for the rTOF subject is shifted to right because of volume overloading. The SW value for the intermediate subject falls in between the normal and the rTOF subject. 108

5.4 Comparison of the rate of total energy output at the MPA for the normal, the rTOF and the intermediate subject. Power rate has a large negative component for rTOF subject as a result of high MPA regurgitation because of dysfunctional PV that results in the loss of power to the forward flow over the complete cardiac cycle. 109

5.5 Comparison of stroke work and net energy transfer to the blood at MPA for normal and rTOF subject. 110
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>Variation of the rate of A) pressure-flow energy loss and B) total energy loss in the branch PA over one cardiac cycle. (Note that the cardiac cycle period was different for the two subjects)</td>
<td>112</td>
</tr>
<tr>
<td>5.7</td>
<td>Total energy lost over one cardiac cycle in branch PA blood flow for the normal and the rTOF subject.</td>
<td>113</td>
</tr>
<tr>
<td>6.1</td>
<td>A) A typical stack of R (R=48) spatial angiographic MRI that were used for PA geometry reconstruction. The images represent a series of sagittal slices at a different spatial location along the z axis as indicated by different z values. B) A typical velocity encoded PC-MRI phase image (30 phases over a cardiac cycle).</td>
<td>124</td>
</tr>
<tr>
<td>6.2</td>
<td>Sequential block diagram: A) of the proposed methodology; B) for calculating PC-MRI plane location for each inlet and outlet in the domain of reconstructed geometry; C) to develop interpolation function for patient-specific velocity profiles from PC-MRI phase values.</td>
<td>126</td>
</tr>
<tr>
<td>6.3</td>
<td>Reconstructed geometry of branch PA from angiographic MR images in form of STL surface triangles (for rTOF subject).</td>
<td>127</td>
</tr>
<tr>
<td>6.4</td>
<td>A) Reconstructed geometry along with the different image coordinate systems (Patient: a₁, a₂, a₃; PA Geometry reconstruction: g₁, g₂, g₃ and PC-MRI: e₁, e₂, e₃). B) Velocity measurement planes from PC-MRI located in the space of geometry reconstruction. C) Geometry for computation with planar inlet and outlets (truncated with the PC-MRI planes at the inlet and outlets); arrows showing the blood flow direction.</td>
<td>129</td>
</tr>
<tr>
<td>6.5</td>
<td>Calculation of the velocity profiles from PC-MRI data. Figures 5A-5C show the result for background noise correction. A) Distribution of standard deviation $\sigma(\alpha, \beta)$ of velocity (red&lt;1%; 1.5&lt;Green&lt;3%; 3%&lt;Blue&lt;5%; 5%&lt;Yellow&lt;10% of the min to max range). B) Static region ($\Omega_s$) shown in blue on the phase image. C) Anatomical image showing tissues.</td>
<td>132</td>
</tr>
<tr>
<td>6.6</td>
<td>A) Points generated on the artery boundary of each of the inlet and outlets of the computational domain. B) Result of mapping the boundary points on to the corresponding PC-MRI.</td>
<td>135</td>
</tr>
<tr>
<td>6.7</td>
<td>A) A hybrid mesh of triangular and rectangular elements in the arterial domain to construct velocity profile. B) Rectangular and triangular element with their respective local coordinate systems.</td>
<td>137</td>
</tr>
<tr>
<td>6.8</td>
<td>A) Flow rate versus time graph from PC-MRI data showing different phases (for our rTOF subject at LPA). B)-G) Velocity profile at phases: 2, 4, 7, 11, 17,</td>
<td>139</td>
</tr>
</tbody>
</table>
20 as marked in Fig. A (units: z-axis is velocity in cm/sec; x and y axes distances on LPA PC-MRI plane are in mm).

6.9 A) Artery boundary drawn on PC-MR magnitude image at different phases N (total 30). B) A line segment drawn across the boundary. C) Velocity profile along the line segment drawn in B, showing velocity close to walls to be almost 0.0 cm/sec.

6.10 Finite volume mesh used for numerical computation (shown here for the rTOF subject). Time and spatially varying velocity profiles from PC-MRI measurement was applied as boundary condition at the MPA inlet and RPA outlet. A stress free out-flow boundary condition was applied at the end of the RPA extension. Numerically computed flow rate and velocity profiles at RPA (interior) were validated with PC-MRI measurements at the same location.

6.11 Comparison of flow rate from QFlow with those from PCMR-Direct: A) at MPA, B) at LPA and C) at RPA of the normal subject. D) For rTOF subject at MPA, E) at LPA and F) at RPA. Graphs designated “LPA+RPA” are sum of the LPA and RPA flow rates.

6.12 Comparison of flow rate from PCMR-Direct with those from numerical computation: A) at MPA, B) at LPA and C) at RPA of the normal subject. D) For rTOF subject at MPA, E) at LPA and F) at RPA. Graphs designated “LPA+RPA” are sum of the LPA and RPA flow rates. Note that the flow rate graphs for PCMR-Direct are same as Fig. 5.11; and the velocity profiles from PCMR-Direct were applied as boundary condition at LPA and MPA for numerical computation.

6.13 Comparison of out of plane velocity contours at RPA from PC-MRI data with those from numerical computation at: Times, $t=0.04$ sec (accelerating flow), $t=0.102$ sec (accelerating flow), $t=0.133$ sec (decelerating flow) and $t=0.256$ sec (decelerating flow). Units are in m/sec.

6.14 Comparison of out of plane velocity contours of the rTOF subject at RPA from PC-MRI data with those from numerical computation. Times are, $t=0.06$ sec, $t=0.08$ sec and $t=0.15$ sec (accelerating flow) and $t=0.22$ sec (decelerating flow). Units are in m/sec.

7.1 Block diagram of the shrink-and-fit algorithm to compute the load-free and pre-stressed geometry from the in-vivo geometry, load, and longitudinal shrinkage.

7.2 Pictorial representation of the shrink-and-fit algorithm.
7.3 Intermediate steps of the *shrink-and-fit* algorithm. A) Lumen surface in form of triangular mesh of STL triangles obtained by geometry reconstruction. B) Arterial wall geometry in form of STL-mesh of surface triangles. C) Finite element mesh of the wall geometry using 8 node hexahedral elements. D) Constraints imposed on the arterial wall motion in each shrink and fit iteration. Rigid contact surface superimposed on the outer arterial wall surface and extended at the ends, to maintain arterial shape during the longitudinal (axial) shrink or stretch operation. Contact surface meshed with 4-noded quadrilateral elements. Only in-plane radial motion in \(d_r-d_\theta\) plane allowed for the nodes of the inlet and outlet surfaces. Additionally, nodes of the outlets are allowed to move in \(d_z\) direction during longitudinal stretch or shrink operation.

7.4 Construction of the *in-vivo* 3D arterial wall geometry from lumen surface triangles.

7.5 Convergence of the shrink-and-fit optimization algorithm in terms of the objective function value and the number of function evaluation.

7.6 Geometry used for the compliant arterial wall-blood flow interaction with arterial pre-stress. The arterial dimensions of this straight, uniform diameter, canine femoral artery were adopted from Sinha-Roy et al., 2008.

7.7 (A) Experimental data and curve-fit of the circumferential Cauchy stress and stretch data of dog femoral artery from Attinger et al., 1968. The curve-fit generated using generalized Mooney-Rivlin model with \(N=2\). (B) Contour plot of the corresponding strain energy density function.

7.8 Finite element model for transient blood-flow-arterial wall interaction computation. The geometry is the load-free geometry obtained from the shrink-and-fit algorithm.

7.9 Pulsatile pressure boundary condition \(p_{in}(t)\) at the inlet, and \(p_{out}(t)\) at the outlet, applied as normal traction for blood flow-wall interaction.


7.11 Results from the shrink-and-fit inverse algorithm to compute the load-free and the pre-stressed geometry for the idealized, straight, uniform diameter dog femoral artery model.
Dimensions of: A) *in-vivo* wall; B) load-free wall; C) pre-stressed arterial wall with load-free wall superimposed on it. D) Details of the load-free and the pre-stressed cross-section. E) Shows the match between the pre-stressed artery and the *in-vivo* artery to be within 0.0015 mm deviation (the two almost superimpose on one another).

7.12 Cauchy stresses (in N/mm²) and engineering strains in pre-stressed artery with linear elastic material: A) and B) in the circumferential direction; C) and D) in the longitudinal direction. The different color bands for $\sigma_{zz}$ are within 0.5% between the maximum and minimum value.

7.13 Cauchy stresses (in N/mm²) and logarithmic strains in pre-stressed artery with hyperelastic material: A) and B) in the circumferential direction; C) and D) in the longitudinal direction.

7.14 Radial and axial deformations in mm from load-free configuration for wall with hyperelastic material.

7.15 Cauchy stresses at the mid-wall location in the circumferential and longitudinal direction at the inlet and outlet.
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Patient demographics and clinical data.</td>
</tr>
<tr>
<td>4.2</td>
<td>Fourier coefficients and Womersley numbers ($\alpha_n$) used to compute MPA and RPA flow profiles for the normal subject and rTOF subject. Fourier coefficients expressed in polar form $2Q_n = M_n e^{i\phi_n}$. The fundamental frequency $\omega_0 = 8.49$ rad/sec and the $M_n$ values are in ml/sec</td>
</tr>
<tr>
<td>4.3</td>
<td>Forward flow volume $Q_f$, and back flow volume $Q_b$, per cardiac cycle calculated from PC-MRI flow rate measurement at MPA and RPA. Regurgitant fraction (%) $f = 100 \times Q_b / Q_f$.</td>
</tr>
<tr>
<td>4.4</td>
<td>Comparison of the values of $Q_f$, $Q_b$ and regurgitant fraction $f$ at LPA, obtained from numerical computation and from PC-MRI measurements. Regurgitant fraction (%) $f$ defined as $100 \times Q_b / Q_f$.</td>
</tr>
<tr>
<td>4.5</td>
<td>Validation of the numerically computed time averaged MPA and RPA pressure with measured data for the normal subject.</td>
</tr>
<tr>
<td>5.1</td>
<td>Patient demographics and clinical data.</td>
</tr>
<tr>
<td>5.2</td>
<td>RV peak pressure, volume, stroke volume and computed RV stroke work (SW) and BSA indexed stroke work (SW/BSA)</td>
</tr>
<tr>
<td>6.1</td>
<td>Time averaged flow rate at the inlet (MPA) and the outlets (LPA and RPA) for the normal subject (where bar denotes average and the subscript $j$ denotes the inlet or outlet). The last row gives the absolute value of flow imbalance between inlet and outlets ($</td>
</tr>
<tr>
<td>6.2</td>
<td>Time averaged flow rate at the inlet (MPA) and the outlets (LPA and RPA) for the rTOF subject (where bar denotes average and the subscript $j$ denotes the inlet or outlet). The last row gives the absolute value of flow imbalance between inlet and outlets ($</td>
</tr>
<tr>
<td>7.1</td>
<td>The dimensions of load-free geometry calculated by the shrink-and-fit inverse algorithm and those obtained by the manual trial and error procedure by Sinha-Roy et al., 2008.</td>
</tr>
</tbody>
</table>
7.2 Stresses, strains and radial deformation on the inner and outer arterial wall. Results for arterial model with linear-elastic material and those for the pre-stressed artery with hyperelastic material for canine femoral artery. Strains under the column of linear elastic artery are engineering strains; those under the hyperelastic materials are logarithmic strains. For small deformations, logarithmic strains are close to engineering strains in magnitude. Units for deformations are in mm and stresses in N/mm².
LIST OF SYMBOLS

\( a_i \)  Unit vectors of patient space \((i = 1, 2, 3); a_1 = (1,0,0), a_2 = (0,1,0) \) and \( a_3 = (0,0,1). \)

\( A(x_i, \theta) \)  In-vivo arterial wall reconstructed from imaging in the \( \theta \) stress state.

\( A(x_L, \theta) \)  Load-free Artery: load-free and un-tethered artery in \( \theta \) state of stress.

\( A(x, \sigma) \)  Pre-stressed artery: In-vivo arterial wall in physiological state of stress, \( \sigma \).

BSA  Body surface area.

\( e_i \)  Unit vectors of PC-MRI space \((i = 1, 2, 3).\)

EDPVR  End-diastolic pressure volume relation.

EDV  End-diastolic volume.

ESPV  End-systolic pressure volume point.

ESPVR  End-systolic pressure volume relation.

ESV  End-systolic volume.

\( E^P(\alpha, \beta) \)  Background noise in velocity at the pixel location \((\alpha, \beta)\) at phase \( p \) \((p = 1 \text{ to } N)\).

\( \dot{E}_s \)  Rate of total energy transfer at a section \( s \).

\( \dot{E}_m \)  Rate of total energy transfer at MPA.

\( \dot{E}_l \)  Rate of total energy transfer at LPA.

\( \dot{E}_r \)  Rate of total energy transfer at RPA.

\( \dot{E}_{loss} \)  Rate of energy loss in branch PA.

\( E_{net} \)  Net energy transferred over a cardiac cycle at a given cross section.

\( f \)  Regurgitant fraction.

\( F \)  Fit operator to apply longitudinal stretch followed by radial stretch followed by during shrink-and-fit iteration \((\chi_{LS} \circ \chi_{RS})\).

\( FN_M \)  Numerically computed MPA flow rate.

\( FN_R \)  Numerically computed RPA flow rate.

\( FN_L \)  Numerically computed LPA flow rate.

\( FP_M \)  MPA flow rate using the reported methodology (PCMR-Direct with MPA PC-MRI).

\( FP_R \)  RPA flow rate using the reported methodology (PCMR-Direct with RPA PC-MRI).

\( FP_L \)  LPA flow rate using the reported methodology (PCMR-Direct with LPA PC-MRI).

\( FQ_M \)  Flow rate at MPA obtained using standard of care software QFlow.

\( FQ_R \)  Flow rate at RPA obtained using standard of care software Qflow.

\( FQ_L \)  Flow rate at LPA obtained using standard of care software Qflow.

\( g_i \)  Unit vectors of geometry reconstruction space \((i = 1, 2, 3).\)

\( K \)  Number of corner nodes of an element \((K = 4 \text{ for rectangles and } K = 3 \text{ for triangles})\).

LA  Left atrium.
LPA  Left pulmonary artery.
MPA  Main pulmonary artery.
MRI  Magnetic resonance image.
\( \hat{n} \)  Unit normal vector.
\( N \)  Number of phase images in PC-MRI set.
\( O \)  Top left corner pixel of an image in PC-MRI set.
\( P_g \)  A point on the reconstructed geometry with coordinates \((\hat{x}, \hat{y}, \hat{z})\) w.r.t \( g_1, g_2, g_3 \).
\( P_e \)  A point on the PC-MRI plane with coordinates \((x, y, z=0)\) w.r.t \( e_1, e_2, e_3 \).
PA  Pulmonary artery.
PC-MRI  Phase-contrast Magnetic Resonance Image.
PI  Pulmonary insufficiency.
PV  Pulmonary valve.
\( Q_S \)  Flow rate at a cross-section S.
\( Q_f \)  Forward flow over a cardiac cycle.
\( Q_b \)  Backward flow over a cardiac cycle.
RA  Right atrium.
RPA  Right pulmonary artery.
RV  Right ventricle.
rTOF  Repaired tetralogy of Fallot.
\( s \)  Number of PC-MRI pixels in the static region \( \Omega_s \).
\( S \)  Shrink operator to apply radial shrink followed by longitudinal shrink during shrink-and-fit iteration \( S_{RS} \circ S_{LS} \).
SW  Ventricular stroke work.
\( t^p \)  Physical time instant of a PC-MRI phase image at phase \( p (p=1…N) \).
TOF  Tetralogy of Fallot.
\( T_{ag} \)  Transformation matrix from the patient space to the geometry reconstruction space.
\( T_{ae} \)  Transformation matrix from the patient space to PC-MRI space.
\( u_i \)  Velocity components \( i=1, 2, 3 \) w.r.t vectors \( g_1, g_2, g_3 \).
\( V^p(\alpha, \beta) \)  PC-MRI pixel velocity for pixel at the location \((\alpha, \beta)\) and phase \( p (p=1 \text{ to } N) \).
\( \bar{V}(\alpha, \beta) \)  Mean of velocity \( V^1(\alpha, \beta), \ldots, V^N(\alpha, \beta) \) at pixel location \((\alpha, \beta)\).
VSD  Ventricular septal defect.
\( w^p(\alpha, \beta) \)  Background-noise-corrected velocity at pixel location \((\alpha, \beta)\) and phase \( p \).
\( w(\hat{x}, \hat{y}, \hat{z}, t) \)  Velocity at a point \((\hat{x}, \hat{y}, \hat{z})\) and time \( t \) interpolated from PC-MRI data.
\( w_i^p \)  Background noise corrected velocity value at node \( i (i=1,2,3 \text{ for \ triangle \ and \ } 1,2,3,4 \text{ for \ tetrahedron}) \).
for rectangle) of an element (formed by PC-MRI pixels) and at phase \( p (p=1, \ldots, N) \).

\( x, y \) Coordinates of a point on PC-MRI plane \( w.r.t \) vectors \( e_1, e_2 \), of PC-MRI image coordinate system.

\( \hat{x}, \hat{y}, \hat{z} \) Coordinate of a point on the reconstructed geometry \( w.r.t \) vectors \( g_1, g_2, g_3 \) of the geometry reconstruction space.

\( x_I \) A point in the \textit{in-vivo} arterial wall that was obtained by image reconstruction.

\( x_L \) A point in the load-free wall.

\( x \) A point in the pre-stressed wall.

\( x_{RS} \) A point on radially defined (stretch or shrink) artery.

\( X \) A point in arterial wall (used for indicating the geometry being referred to).

\( \omega_0 \) Fundamental frequency of pressure gradient or flow rate pulse.

\( \sigma(\alpha, \beta) \) Standard deviation of velocity, \( V^1(\alpha, \beta), \ldots, V^N(\alpha, \beta) \) at pixel location \( (\alpha, \beta) \).

\( \Omega_s \) Set of PC-MRI image pixels that form static region.

\( \psi_i \) Basis function at node \( i (i = 1, 2, 3 \text{ for triangle and } i = 1, 2, 3, 4 \text{ for rectangle}) \).

(\( \zeta, \eta \)) Normalized local element coordinate of point \((x, y)\).

\( \alpha_n \) Womersley number for the \( n \)th harmonics of flow rate or pressure gradient pulse.

(\( \alpha, \beta \)) Location of PC-MRI pixel on the image \( w.r.t \) \( e_1, e_2 \) of PC-MRI image coordinate system.

\( \Delta E \) Net energy loss over one cardiac cycle.

\( x_I \) A point in the \textit{in-vivo} arterial wall that was obtained by image reconstruction.

\( \textbf{0} \) Null tensor. To represent identically zero state of stress in the arterial wall.

\( A(x_I, \textbf{0}) \) Represents an \textit{in-vivo} wall reconstructed from imaging in \( \textbf{0} \) stress state.

\( \lambda_z \) Principal stretch ratio in the longitudinal direction. Longitudinal stretch.

\( \delta_I \) \textit{In-vivo} longitudinal stretch from load-free artery length.

\( \delta_l \) Increment or decrement in the longitudinal arterial length during shrink-and-fit iteration.

\( \delta_r \) Increment or decrement in the radial arterial length during shrink-and-fit iteration.

\( \chi_{RS} \) Radial deformation operator.

\( \chi_{LS} \) Longitudinal deformation operator.

\( d_r, d_\theta, d_z \) Displacement in radial \((r)\), circumferential \((\theta)\), and axial direction \((z)\), respectively.
Chapter 1

Introduction

1.1 Pulmonary Valve Insufficiency

The pulmonary valve (PV) is a tri-leaflet valve located between the right ventricle (RV) and the pulmonary artery (PA). A normally functioning pulmonary valve allows forward movement of blood from the right ventricle into the pulmonary artery during systole, but prevents the flow reversal during diastole (Fig. 1.1). As a result, there is a net forward flow of blood from the right ventricle to the lungs for oxygenation. A dysfunctional pulmonary valve causes backflow of blood from the pulmonary artery back into the right ventricle.

The clinical term for the pathophysiology of dysfunctional or nonexistent pulmonary valve is known as pulmonary insufficiency (PI). The symptoms of pulmonary insufficiency are the usual symptoms associated with exercise intolerance. These include fatigue, shortness of breath under physical exertion, chest pain, palpitation, and fainting. Mild pulmonary insufficiency is caused by the dilatation of the pulmonic valve ring, whereas the severe insufficiency results from malformed or nonexistent valve. Typically, malformed or nonexistent valve is the result of a congenital heart defect.
Although, mild pulmonary insufficiency does not pose any life threatening emergency, a severe one can be fatal, if left untreated. Severe forms of pulmonary insufficiency develop in patients born with tetralogy of Fallot [4-6]. Tetralogy of Fallot is a cyanotic heart disorder in which patients die because of lack of oxygen to organs and tissues. According to the statistics compiled by the Center for Disease Control and Prevention (CDC), about 1 in every 2500 babies is born with tetralogy each year in the United States alone [7]. This amounts to approximately 1660 tetralogy births per year in the United States.

Fig. 1.1: A) Schematic diagram of the heart showing different chambers and valves. B) A transverse section through the heart at the location of the pulmonary valve showing the valve leaflets. (http://en.wikipedia.org/wiki/File:Diagram_of_the_human_heart_(cropped).svg)

Tetralogy can only be repaired with surgical intervention. The surgery is known as tetralogy of Fallot repair surgery. Over the last few decades, this surgery has been successful in saving the lives of infants born with tetralogy. As a result, there currently are about 100,000 sur-
viving tetralogy subjects in the United States alone. In spite of the success of the tetralogy repair surgery as an immediate life saving measure, the long term sequelaes of this defect are coming to the forefront only now [8]. One such sequela is the development of severe pulmonary insufficiency [9,10].

The infants born with tetralogy of Fallot have malformed or non-existent pulmonary valve; a condition known as pulmonary atresia. As a part of the tetralogy repair surgery, a pulmonary patch is left to function as a make-shift prosthetic pulmonary valve. This make-shift pulmonary valve wears out as the patient ages. In other words, the patient’s body and heart simply outgrow the pulmonary patch since it does not grow with the patient’s somatic growth. This results in the onset of pulmonary insufficiency that progressively deteriorates over time.

The pulmonary insufficiency in repaired tetralogy of Fallot patients results in excessive flow regurgitation and back flow into the right ventricle. This regurgitation leads to the volume overloading of the right ventricle (Fig. 1.2). The volume overloading causes the onset of right ventricle hypertrophy. Overtime, this hypertrophy becomes acute and results in excessive stresses in the myocardium. This leads to permanent impairment of the ventricular functioning and can lead to sudden death [8,9,11].

Pulmonary valve replacement surgery is performed to alleviate the adverse effects of right ventricular hypertrophy and renormalize the myocardial stresses induced by hypertrophy [12]. However, the timing of this surgery is critical. Performing this surgery too early may result in a need for later re-operation since the prosthetic pulmonary valve does not grow with patient’s somatic growth. Therefore, clinicians often prefer to defer this procedure as long as possible, especially in growing children and adolescents. However, if this surgery is deferred too long, the myocardial contractile dysfunction of the right ventricle can become irreversible.
Therefore, determining the right time for the valve replacement surgery is of paramount importance for the clinical diagnosis of the progression of pulmonary insufficiency (Fig. 1.2C).

Fig. 1.2: A) Anatomical MRI of the right ventricle of a normal subject, and B) that of a subject with pulmonary insufficiency, showing the effect of volume overloading. C) Progressive enlargement of the right ventricle of a subject with pulmonary insufficiency over time.

This research focuses on later life complications arising from pulmonary insufficiency in the repaired tetralogy of Fallot patients. With the increasing number of tetralogy survivors, the development of such late-life pathophysiology is now becoming an important clinical problem. In this dissertation, the repaired tetralogy of Fallot (rTOF) patients with pulmonary insufficiency are referred to as rTOF patients.
1.2 Motivation and Objective

As previously mentioned, the debilitating effect of pulmonary insufficiency on the right ventricle can be rectified by pulmonary valve replacement surgery. For practicing clinicians deciding on the right time to perform the surgery has been difficult. There are no physiological markers other than the enlargement of the right ventricle, for deciding the timeline for the surgery. Currently, echocardiography [13] and cardiac MRI are two most commonly employed clinical techniques to diagnose the deteriorating condition of the right ventricle in such subjects. However, determining the right time for pulmonary valve replacement surgery using these two techniques has been subjective and prone to misdiagnosis. Echocardiography provides inaccurate results when applied to the right ventricle due to the poor acoustic signal caused by the complex shape of the right ventricle [13]. Cardiac MRI is a burgeoning field that is being increasingly employed to assess right ventricular volume in patients with pulmonary insufficiency. Currently, limited quantitative information such as ventricular dimensions, flow rate and volume measurements are all that is obtained from it. Due to its inability to provide physics-based quantifiable diagnostic indices, it has remained fairly descriptive and not deterministic in its ability to assess the future health of right ventricle.

It is evident from the discussion above that the clinical tools currently employed for the diagnosis of PI do not provide a clear guidance in deciding on the timing of the pulmonary valve replacement surgery. The decision making is subjective and mainly based on the assessment of cardiac MRI scans and evaluation of a few ad-hoc measures. These measures fall in two categories: 1) pressure-based measures such as end-diastolic pressure, and 2) volume-based measures, such as cardiac volume and regurgitant fraction. The use of different measures often results in conflicting conclusions and error-prone decisions. Thus, a quantitative index is required to un-
ambiguously assess the progression of pulmonary insufficiency. Therefore, the long-term goal of this research is to improve the clinical outcome of the diagnosis to establish the right time for pulmonary valve replacement surgery.

The symptoms associated with pulmonary insufficiency could result from the lack of blood flow to the lungs for oxygenation. The remodeling of the right ventricle caused by hypertrophy and the elevated level of myocardial stresses induced by the volume overloading could be contributing to structural inefficiencies. The resulting flow inefficiencies could be preventing the blood flow to the lungs for oxygenation under hyperemia caused by exercise conditions. Hence, it was hypothesized that energy-based indices derived from fundamental fluid mechanics could be useful in studying these inefficiencies. The quantification of flow inefficiencies using energy-based indices may provide endpoints to assess the status of the right ventricle. This may in future lead to more indices that can determine the right time for pulmonary valve replacement surgery. The objective of this research was to compute these indices from the available clinical data and improve the methodology for assessment of pulmonary insufficiency by using energy-based indices from patient-specific hemodynamic data. This in turn will help clinicians to define a more suitable clinical window for pulmonary valve replacement surgery in rTOF patients.

It will be shown later that the equations for the energy-based endpoints include both pressure as well as volume or flow rate. Therefore, these endpoints incorporate both the pressure-based measures as well as the volume and flow rate based measures into one single endpoint. Therefore, they eliminate the ambiguity that arises in choosing between the pressure-based and volume-based measures. In addition to that, these endpoints include theoretical principles of engineering mechanics.
1.2.1 Central hypothesis

The central hypothesis of this dissertation is that energy-based indices will delineate the inefficiencies in pulmonary arterial hemodynamics between normal subjects and subjects with pulmonary insufficiency.

1.2.2 Specific Aims

The specific aims of this research were formulated to test the central hypothesis. Appropriate energy-based indices relevant to pulmonary arterial flow were identified. Since pulmonary arterial flow is driven by the right ventricle, stroke work was chosen as an appropriate index to assess the performance of the right ventricle. At the junction between the right ventricle and the main pulmonary artery, a new index named energy transfer ratio was defined. This index was defined as the ratio of the total energy of the blood at a cross-section in the main pulmonary artery and the stroke work performed by the right ventricle. Finally, the index of energy loss for the flow through branch pulmonary artery was defined. This way, an energy-based endpoint was defined for each of the anatomical sections of the pulmonary arterial flow.

The specific aims were designed to calculate these indices using clinical data and hemodynamic computations [14]. Thus, the specific aims for this research work can be summarized as:

Specific Aim 1: To calculate and compare the right ventricular stroke work and energy transfer ratio for a normal subject and a subject with pulmonary insufficiency. The objective of this specific aim was to test the energy based indices: 1) right ventricular stroke work and 2) energy transfer ratio, for its ability to delineate the performance of the right ventricle of a normal subject from that of a subject with pulmonary insufficiency. Stroke work requires
simultaneous measurement of right ventricular pressure and volume [15]. Energy transfer ratio involves calculation of total energy of the blood at the main pulmonary artery and requires simultaneous measurement of pressure and flow rate. Under a clinical setting, pressure is measured by cardiac catheterization. On the other hand, the ventricular volume is obtained non-invasively using short-axis cardiac MRI. The flow rate can be obtained non-invasively using phase-contrast MRI. However, there are no clinical protocols to simultaneously perform both cardiac catheterization and MRI in humans. In other words, it is not possible in clinical settings to measure cardiac pressure and ventricular volume or flow rate simultaneously. Therefore, an ECG-gating based methodology was developed to calculate the stroke work and energy transfer ratio from non-simultaneously measured ventricular pressure, volume and pulmonary arterial flow rate data. Using this method, these two energy-based endpoints were calculated for a normal subject and a patient with pulmonary insufficiency.

Specific Aim 2: To calculate the energy loss in the branch pulmonary artery of a normal subject and a subject with pulmonary insufficiency. The overall objective of this specific aim was to evaluate the energy loss in the branch pulmonary artery of a normal subject and of a subject with pulmonary insufficiency using their respective patient-specific data. The objective was to evaluate the energy loss endpoint in a normal subject and a subject with pulmonary insufficiency to test whether this endpoint will be able to delineate the pulmonary insufficiency pathophysiology from a normal one.

A sub task in this objective was to establish the proof-of-concept for calculating energy loss using clinically measured pressure and flow rate data. Similar to the previous specific aim, the first requirement of this specific aim was to design a methodology to obtain the energy loss from non-simultaneously measured pressure and flow rate data. The second objective was to
minimize the required number of pressure measurements for the calculation of energy loss from three to one, as explained below.

Energy loss calculation requires simultaneous measurements of pressure and flow rate at all the inlet and outlets of the arterial segment of interest. Therefore, for a bifurcated pulmonary artery, a total of three pressure and flow rate measurements were required. These locations of measurements were the main, left and the right pulmonary arteries, respectively. Using patient-specific hemodynamics, energy loss calculation can be performed with only one pressure boundary condition and two velocity boundary conditions. Therefore, the number of required pressure measurements can be reduced from three to one. For this specific aim, the velocity boundary conditions for hemodynamic computations were specified using an idealized Womersley profiles that were calculated from time varying flow rate obtained from phase contrast MRI. It may be noted that a minimum of one pressure boundary condition was used because the Womersley velocity profile is not the true representation of the time and spatially varying velocity profile that is actually observed in the vicinity of pulmonary valve.

Specific Aim 3: To develop a methodology for patient-specific hemodynamic analysis of complex developing flow in the pulmonary artery by directly incorporating time- and spatially-varying velocity data from PC-MRI. The pulmonary arterial flow distal to the pulmonary valve is a developing flow. The velocity field for such a flow is complex as it is in the vicinity of the pulmonary valve. At an arterial cross-section close to the pulmonary valve, the flow field is both time- and spatially-varying in the three dimensional space. In the last specific aim, Womersley velocity profile was used to specify the velocity boundary condition for hemodynamic computation for calculating energy loss in branch pulmonary artery as a proof-of-concept. The Womersley velocity is a developing flow profile and was only used as an ap-
proximation for developing flow near pulmonary valve. Therefore, the overall objective of this specific aim was to directly incorporate time- and spatially-varying patient-specific velocity data obtained from phase-contrast MRI for hemodynamic computation.

The use of patient-specific time- and spatially- varying velocity data in hemodynamic computation was intended to serves two purposes. Firstly, it can improve the accuracy of the results of hemodynamic computation from the one performed in Specific Aim 2. Secondly, it yields a methodology to perform the patient-specific hemodynamics with non-invasively obtained data since all the boundary conditions were obtained from PC-MRI. At the same time, the patient-specific geometry of the pulmonary artery was also obtained from angiographic MRI. Therefore, the methodology for hemodynamic computation developed in this specific aim is non-invasive and combines the patient-specific geometry with patient-specific velocity measurements.

**Specific Aim 4: Develop methodology for hemodynamic computation with compliant arterial wall model incorporating in-vivo wall pre-stress.** The hemodynamic computation in Specific Aim 3 was performed with rigid arterial wall assumption. The pulmonary artery is known to be distensible. Therefore, to accurately simulate the physics of pulmonary arterial blood flow, the interaction between the compliant vessel wall and blood flow needs to be incorporated in the computational model. Thus, the main objective of this specific aim was to develop a methodology to perform hemodynamic computation with patient-specific arterial geometry incorporating wall compliance.

The arterial wall was assumed to be of constant thickness. The stress-strain constitutive law for the wall material was modeled using an isotropic, incompressible, hyperelastic, generalized Mooney-Rivlin strain energy density function. Moreover, arteries are known to be pre-
stressed in their in-vivo state. As a result, an excised arterial segment is known to shrink longitudinally and contract radially due to the release of the internal stresses induced by the mean in-vivo pressure and tethering from the surrounding tissues. The excised state, which is also known as the load-free state, is required for the calculation of the pre-stressed state. The physiological stresses in the pre-stressed state are induced by the mean arterial pressure and in-vivo longitudinal stretch.

As a part of this specific aim, two tasks were accomplished. First task was to develop an inverse elastostatic algorithm to calculate the load-free arterial geometry from the in-vivo (unstressed) arterial geometry for the patient-specific scenario. This inverse method was implemented using a nonlinear least square optimization formulation. The second task was to perform the hemodynamic computation with a compliant arterial wall model, subjected to pulsatile pressure boundary conditions, and incorporating the physiological wall stresses.

To perform the computations with compliant arterial wall, patient-specific wall thickness, in-vivo axial and radial shrinkage, and wall material property data was required. Due to the unavailability of this complete patient-specific pulmonary arterial data for the subjects in our sample, the scope of this Specific Aim was limited. The methodology was tested using an idealized arterial wall geometry. Therefore, the results for this specific aim only demonstrate the methodology using a simplistic idealized arterial geometry of canine femoral artery adopted from an earlier publication from our group [Sinha-roy et al., 2008]. Although this idealized arterial geometry is axi-symmetric, a 3D wall model will be utilized to demonstrate the computation of the load-free and pre-stressed arterial geometry using the inverse method. This will mimic the application of the inverse algorithm to a real patient-specific case. However, for simplicity the
transient arterial response under pulsatile pressure will be computed using an axisymmetric model. The results will be compared with those presented in the aforementioned publication.

1.3 Research Plan and the Outline of the Dissertation

To accomplish the Specific Aims presented above, first, the calculation of RV stroke work, energy transfer ratio and branch PA energy loss from clinically measured pressure, volume and flow rate data was investigated. The proposed energy based endpoints were calculated for a normal subject and a subject with pulmonary insufficiency. Next, as a part of Specific Aim 2, methodologies were developed to estimate these indices using clinical data. Finally, in Specific Aims 3 and 4, the appropriate methodologies for patient specific blood flow computations were developed with both rigid wall and compliant wall assumptions, respectively.

The connections between various specific aims of this research are shown in Fig. 1.3 using a block diagram. The first box at the top of the figure shows the physiologic segments of pulmonary arterial flow that are of interest for this research. The second set of boxes show the energy-based hemodynamic end points that are proposed in this research. The dashed lines with arrow connect a particular physiologic feature with the energy-based endpoint that is designed for it. The solid lines link a particular end point to the individual Specific Aim and also show the link between different Specific Aims.

The organization of the chapters in this dissertation follow the sequence of research steps that were undertaken to accomplish the individual Specific Aims outlined above. This dissertation is divided into the following chapters:

1. Background and literature review is presented in Chapter 2.
2. Details of the energy-based indices are presented in Chapter 3. The methodology developed to calculate these indices from non-simultaneously measured pressure, cardiac volume and flow rate is also presented.

3. The methodology to perform patient-specific hemodynamic computation with Womersley-type velocity boundary condition is described in Chapter 4.

4. Chapter 5 presents the results for the energy based indices for a normal and the subject with pulmonary insufficiency.

5. Chapter 6 describes the methodology to directly incorporate the time- and spatially-varying phase-contrast MRI data for patient-specific hemodynamic computations. The mathematical details of combining the patient-specific geometry from the angiographic MRI with the phase-contrast MRI data are presented.

6. Chapter 7 presents the details for performing hemodynamic computation with compliant arterial wall. It also describes the proposed inverse elastostatics algorithm for computing arterial pre-stress in patient-specific wall geometry.

It is evident from the description so far that the later life problems resulting from pulmonary insufficiency are the main topic of this dissertation. As was mentioned above, there are many causes of pulmonary insufficiency that result in congenital heart defect. One such congenital heart defect is tetralogy of Fallot, which is the motivation of this research. The condition of the pulmonary valve and the accompanying stenosis of the pulmonary artery, which directly affect the pulmonary arterial hemodynamics, are the hallmark of the original birth defect of tetralogy of Fallot. The pulmonary insufficiency is a post tetralogy repair surgery manifestation. Therefore, the next chapter begins with a detailed description of the tetralogy of Fallot, while presenting the literature review of the previously performed related research.
Research plan

Specific Aim 1:
• Calculate stroke work and energy transfer ratio.

Objectives:
• Feasibility and applicability of the indices.
• To delineate normal and pulmonary insufficiency (PI) physiology.
• Use non-simultaneously measured RV pressure, RV volume and main PA flow rate.

Specific Aim 2:
• Calculate energy loss in branch PA.

Objectives:
• Feasibility and applicability of the index.
• To delineate normal and PI physiology.
• Use non-simultaneously measured pressure, PA low rate.
• Use patient specific hemodynamic computation with Womersley profile obtained from PC-MRI.

Specific Aim 3:
• Patient specific blood flow by directly using patient-specific time- and spatially- varying velocity data from PC-MRI.

Objectives:
• Improve our understanding of PA flow patterns with patient-specific data.
• Non-invasive methodology useful for quantifiable indices for clinical use.

Specific Aim 4:
• PA hemodynamics with compliant wall model and patient-specific geometry and boundary conditions.

Objectives:
• Simulate more realistic physics of PA hemodynamics incorporating blood-flow-arterial-wall interaction.
• Will result in improved quantification of the energy-based indices.

Fig. 1.3: Research plan and the summary of specific aims and objectives. The dashed lines associate a particular energy-based endpoint to the corresponding pulmonary flow related cardiac anatomy. The solid lines show the link between specific aims.
Chapter 2

Background and Literature Review

2.1 Introduction

This research was undertaken to develop energy-based hemodynamic endpoints and to investigate their applicability in the clinical diagnosis of pulmonary insufficiency. The equations for the end-points were derived using the basic principles of engineering mechanics. Appropriate simplifications were made to these equations in order to perform the calculation of the endpoints using data obtained in clinical settings. These clinical data involved measurement of right ventricular pressure and its volume, and also pulmonary arterial pressure and flow rate. Magnetic resonance imaging was used to obtain right ventricular volume and pulmonary arterial flow rate data. The requirement of pressure measurement, which involves cardiac catheterization, an invasive procedure, restricts the applicability of these endpoints in clinical setting. Therefore, relevance of these endpoints in clinical settings requires the development of non-invasive methodology. The non-invasive methodologies developed in this research to compute these endpoints are based on image-based hemodynamic modeling. In other words, imaging was used not only as
a tool for measurement of ventricular volume and flow rate, but also to obtain patient-specific geometry reconstruction for hemodynamic computations.

It is clear from the above discussion that this research utilized tools and techniques from many different disciplines. Broadly, it required understanding of the physiology of pulmonary flow, application of engineering mechanics, application of magnetic resonance imaging, computation tools for hemodynamic computation, and image based modeling of cardiovascular flows. This chapter presents the literature review and background information on the tools and techniques used in this research. Some of the topics involved are too broad to cover them in their entirety. Therefore, the literature review presented here will be closely related to only the particular methodologies that have been adopted in this research. First, the pathophysiology of tetralogy of Fallot is described because it is the precursor to pulmonary insufficiency in patients studied in this research. Then on, the previously performed research on ventricular mechanics is presented. Finally, a review of the literature on image-based modeling is presented. This includes a detailed literature review of the past research on geometry reconstruction, and hemodynamic computation with both rigid as well as compliant arterial wall.

2.2 Tetralogy of Fallot

_Tetralogy of Fallot_ is one of the most complicated congenital heart defects. It is a complicated defect because, as will be described later, it is an amalgamation of four interrelated defects. The word “tetralogy” in its name is given to refer to these four defects. The word “Fallot” in its name is given after the French physician Étienne-Louis Arthur Fallot, who first described it in the year 1888. In order to explain the abnormal functioning and the underlying
congenital defect in the tetralogy heart, a description of the blood flow through a normally functioning heart is required.

2.2.1 Normal Heart

The body requires oxygen and nutrients for growth and survival. It also requires the disposal of waste products generated in the cells and tissues of the organs. The circulation of blood through the body performs oxygen and nutrients transport to the tissues and at the same time disposes the wastes generated in the cells. The heart performs the function of the pump to drive the systemic circulation [16,17].

![Diagram of the heart](https://health.google.com/health/ref/graphic/1056)

Fig. 2.1: A) A normal heart with directions of blood shown by blue and red arrows. B) Schematic representation of the normal heart using a block diagram. The blue arrow represent flow of deoxygenated blood, whereas the red ones represent oxygenated blood. (https://health.google.com/health/ref/graphic/1056)

The human heart consists of two pumps working in tandem (Fig. 2.1A). One collects the deoxygenated blood from the organs and tissues and pumps it to the lungs for oxygenation. The other pumps the oxygenated blood received from the lungs back to the rest of the body. These
two halves are also referred to as the right and left heart. The right heart pumps the blood to the lungs for oxygenation whereas the left is responsible for driving the systemic flow of oxygenated blood to organs and tissues. Each of the two halves of the heart consists of two chambers: 1) an atrium, which collects the blood and transfers it to the ventricle, and 2) the ventricle, which actually performs the pumping action (Fig. 2.1A). Therefore, the right ventricle pumps the blood to the lungs for oxygenation, whereas the left ventricle pumps the oxygenated blood collected from lungs to the organs and tissues.

As can be inferred from the above paragraph, a normal heart consists of four chambers (Fig. 2.1A): right atrium (RA), right ventricle (RV), left atrium (LA) and left ventricle (LV). The flow of blood through a normal heart is explained using a schematic diagram shown in Fig. 2.1B. The heart is represented in the form of a block diagram, where the four chambers of the heart, the right and the left atrium, and the right and the left ventricles are shown as blocks. The blue and red arrows depict the direction of blood flow. The blue and the red color are used to represent deoxygenated and oxygenated blood respectively.

The deoxygenated blood from the organs and tissues enters the right atrium through the superior and the inferior vena cava (SVC and IVC, respectively). From there it flows into the right ventricle, which then pumps it to the lungs for oxygenation via pulmonary arteries (PA). In a similar manner, the oxygenated blood from the lungs collects in the left atrium via pulmonary veins (PV). From the left atrium the blood is transferred to the left ventricle, which in turn pumps it to the rest of the body through the aorta.

It is clear from the Fig. 2.1 that there is no direct contact between the oxygenated and the deoxygenated blood in a normal heart. The two ventricles are connected in a series in a closed circuit of blood flow with the right ventricle feeding its output to the left ventricle, routed via
lungs. Each ventricle ejects the same amount of blood per unit time so as to maintain the cardiac output and prevent any accumulation of blood in the circuit.

2.2.2 Tetralogy Heart

In a tetralogy heart (Fig. 2.2A) the normal pathway of the blood flow is altered by a hole between the right and the left ventricle [4-6,18]. This hole between the right and the left ventricle is the result of a congenital defect and is termed as ventricular septal defect (VSD). The VSD is the root cause of the malfunction of the tetralogy heart (Fig. 2.2A). The altered pathway of blood flow through a tetralogy heart is shown in Fig. 2.2B, where the mixing of the deoxygenated blood with oxygenated blood is shown using the schematic block diagram. Due to VSD, very little volume of blood actually reaches the lungs for oxygenation, and most of it is directly shunted to the systemic circulation by the left ventricle through the aorta. Therefore, the septal defect causes recirculation of the predominantly deoxygenated blood passed through the VSD into the left ventricle back to the organs and tissues. As a result, the organs and tissues are deprived of the needed oxygen supply. Overtime, this oxygen deprivation causes the skin and tissue color in tetralogy subjects to develop a purple or bluish tinge.

The VSD in the heart of tetralogy infants also causes three other interrelated defects right from the prenatal stages of development. One of them is pulmonary stenosis which develops because most of the blood directly flows into the left ventricle through the VSD. The pulmonary arteries carry little blood to the lungs and thus become constricted right from the prenatal stages of heart development. The second consequence of the VSD is that the right ventricle performs little role in pumping blood to lungs. As a result, the right ventricular muscles become stiff and thicken, and develop a condition known as right ventricular hypertrophy. In contrast with the pulmonary artery, most of the blood volume flows into the left ventricle and through the aorta.
Under such condition, the aorta enlarges and structurally overrides the pulmonary artery to draw most of the blood. This condition is referred to as *over-riding aorta*.

This congenital defect is therefore aptly named *tetralogy* because it really is a combination of four interrelated abnormalities in the heart [5,6,18]: (1) ventricular septal defect, (2) pulmonary stenosis, (3) right ventricular hypertrophy, and (4) overriding aorta. These four defects thus make it one of the most complicated congenital heart defects. Its causes are not well understood. It is speculated to be the result of genetic abnormality occurring during the stages of fetal developmental.

The children born with tetralogy have a diminished life expectancy. The only recourse is *tetralogy repair surgery* [19]. For past few decades, tetralogy has been routinely repaired by this.

**Fig. 2.2:** A) A heart of a tetralogy of Fallot subject with directions of blood flow through the VSD. B) Its schematic representation using block diagram. The blue arrows represent the flow of deoxygenated blood; and the red ones, the oxygenated blood. (https://health.google.com)
surgery. The surgery has led to successful outcome in extending the life of these patients. However, after more than four decades of surgical treatment, the long-term complications resulting from this surgery are coming to the forefront only now [20]. A description of these long-term complications is presented after a brief description of the surgical procedure in the next subsection.

2.2.3 Tetralogy Repair Surgery

As a part of the tetralogy repair surgery, the VSD between the right and the left ventricle is closed by surgically implanting a patch known as the VSD patch. This prevents the mixing of the deoxygenated blood with the oxygenated blood, but also results in increased blood supply to the already stenosed pulmonary artery. The stenosed pulmonary artery is not capable of handling the increased blood volume, and in the native form, will be subjected to elevated PA wall stresses. The resulting stresses in the arterial walls are relieved by surgical incision by widening the pulmonary artery, and the right ventricular outflow track (RVOT). The PA and RVOT incision is closed by putting on an additional patch. Typically, a portion of this PA patch is left to function as a PV [21,22].

Tetralogy repair surgery has been routinely performed for the last few decades and has been successful in extending the productive life of tetralogy patients. As a result, there currently are more than 100,000 cases of subjects who underwent this surgery in their childhood [7]. At the same time, long term effects of the surgical intervention are manifesting themselves in the form of new post operative complications in adult life [8-10].
2.2.4 Long Term Post Surgical Complications

The “cure” of tetralogy heart defect after the tetralogy repair surgery has been a focus of extensive research and clinical studies [8,18,23-28]. The earliest longitudinal clinical studies that followed the recovery of patients after tetralogy repair surgery dates back to the decade of the 1950s [29-32]. The tetralogy repair surgery has been successful without any doubt in saving the lives of children born with this affliction, as is clearly evident from the rising number of currently surviving subjects [7]. However, it is a foregone conclusion that “tetralogy has been repaired but not cured” [8-10,26,28].

![Fig. 2.3: Schematic representation of the heart of a subject after tetralogy of Fallot repair surgery. The VSD is closed with a VSD patch. The stenosed PA is widened by cutting open the right ventricular outflow track (RVOT) and closed with RVOT patch.](image)
Pulmonary valve insufficiency (PI) is one of the complications that develop later in life of a tetralogy survivor. To begin with, the infants born with tetralogy have a malformed or non-existent pulmonary valve, a condition called pulmonary atresia. Often, a portion of the transannular patch, which is applied after surgical incision to relieve the pulmonary stenosis, is left in young children to perform the function of a make shift pulmonary valve. However, this “make-shift” valve either wears out with ageing or does not grow with somatic growth, and overtime leads to the leakage of blood back into the right ventricle. Therefore, the end result is a dysfunctional pulmonary valve as the patient grows into the adulthood.

A dysfunctional pulmonary valve leads to pulmonary regurgitation resulting in back flow of blood into the right ventricle. Over time, this regurgitation leads to ventricular overloading (Fig. 2.2), and causes hypertrophy due to the development of excessive myocardial stresses in the right ventricle. Untreated, right ventricular hypertrophy coupled with the overloading leads to irreversible myocardial contractile dysfunction. This often leads to the development of arrhythmias, and in extreme cases results in sudden death [8,9,11].

2.2.5 Clinical Diagnosis of Pulmonary Insufficiency

The only course of action to rectify the adverse consequences of pulmonary insufficiency is to replace the pulmonary valve. This is done by performing a pulmonary valve replacement surgery. The functioning pulmonary valve prevents the flow regurgitation and eventually alleviates the adverse effects of right ventricular hypertrophy by renormalizing the myocardial stresses induced by volume overloading [12]. However, the timing of this surgery is critical. Performing this surgery too early may result in a need for later re-operation because the prosthetic pulmonary valve does not grow with patient’s somatic growth. Therefore, clinicians often prefer to defer this procedure as long as possible, especially in growing children and ado-
lescents. However, if this surgery is deferred too long, the myocardial contractile dysfunction of the right ventricle can become irreversible [12,33].

With currently employed clinical techniques such as echocardiography [13] and cardiac MRI, determination of the right time for pulmonary valve replacement surgery has been subjective and prone to misdiagnosis. There are few quantifiable diagnostic indices to assess the progression of the deteriorating condition of the right ventricle or the pulmonary valve to determine the right time for pulmonary valve replacement surgery. Currently, most of the indices are either volumetric index, e.g., regurgitant fraction at the main pulmonary artery [34,35], or pressure based index such as end diastolic pressure in the right ventricle [36,37]. The preference of one over the other is not clearly established and both have been used by different clinicians with varying degree of success.

Energy based endpoints have been recently proposed for other heart defects such as total-cavo-pulmonary-connection (TCPC) and fontan. Energy based endpoints are promising because they combine both pressure and volumetric endpoints such as ventricular volume or flow rate into one index. However, they also have a drawback, as will be shown in next chapter, that they require significantly more measurements. The assessment of the condition of the heart in terms of the energetics of the cardiac function had been a major topic of research in the decades preceding 1980. It resulted in a significant advancement in the understanding of the fundamental mechanics of heart, but yielded few clinical tools for diagnosis. The renewed interest in this area over last decade has been to obtain the energy based endpoints using imaging and computational tools in a patient-specific setting. A brief review of the research on the cardiac function energetics is presented in the next section. The subsequent sections present a review of the research on
the applications of imaging in hemodynamic computations. The image-based modeling tools were utilized in this research for the computation of energy-based endpoints.

2.3 Cardiac Function Energetics

The long term goal of the research on the cardiac function energetics was to delineate a normal heart from a diseased one based on energy measurements. The research problem was to measure the amount of energy utilized by the heart while pumping blood, and relate it to the energy output to drive the blood flow. Among the earliest research in this area was performed by Frank and Starling in the year 1918. The key insight gained from their study was the idea that the performance of the heart as a pump was dependent on the contraction of the heart muscles. This idea distilled down to three different approaches. One of the approaches was to measure the energy consumption by individual muscle fibers, by developing a phenomenological model relating the muscle force to the velocity of contraction, and then compute the energy consumption by the whole heart. The second approach had been to study the pump characteristics in terms of the pressure, volume and flow rate endpoints of the individual ventricles that drive the flow. The third direction was to study the biochemical processes in the heart in terms of the oxygen consumption and mechanisms of protein interactions in the muscle fibers.

2.3.1 Force-Velocity Relationship

In the force-velocity approach, the velocity of contraction of an individual muscle fiber of the ventricle was related to the force required for shortening the fiber [38]. The force-velocity relationship of the individual muscle fiber thus obtained was then used for modeling the pressure-volume change of a ventricle. The mechanical work performed by the ventricle and the
flow rate resulting from the contraction process was calculated using the pressure-volume relationship from which ventricular work was calculated.

This approach required two sets of mechanical models [38,39]. One was the model of the material property of the muscle fibers, and the other was the model of the contraction process itself. The material property of the muscle fiber has been typically modeled using a phenomenological model such as the Hill model or the Maxwell model or the Viogt model [1-3] shown in Fig. 2.4. The cardiac contraction process on the other hand was modeled using one of the mechanical setups shown in Fig. 2.5 [38,39]. In most of these mechanical setups, the applied loads and the rate of change of muscle length (during stretching or contraction) have been recorded.

![Diagram of mechanical models](image)

**Fig. 2.4:** Some of the commonly used phenomenological material models of cardiac tissues [1-3]. A) the Hill model, B) the Maxwell model and C) the Viogt model.

Typically, most researchers adopted an assembly of spring and dashpot elements for the phenomenological models of tissues (Fig. 2.4). The spring element (SE or PE) was used to represent the elastic component of the muscle force and relate it to the instantaneous elastic deformation of the muscle fiber. The dashpot element (CC) was used to introduce a damping mecha-
nism for the passive dissipation of the energy in the contraction and relaxation of the tissue fibers. It related the forces developed in the individual muscle fibers to the instantaneous velocity of the fiber contraction. The earliest of these models was a two element model (Fig. 2.4A) for skeletal muscles, proposed by Hill based on experiments with frog sarcomere [40-42]. The mechanical behavior of cardiac muscles was found to be similar to that of the skeletal muscles, except that it developed a strong restoring force during cardiac activity [43,44]. To account for this additional restoring force, the Hill model was modified with an additional elastic element PE as shown in Fig. 2.4B and 2.4C. These models are known as: 1) the Maxwell model (Fig. 2.4B), and 2) Viogt model Fig. 2.4C). The Hefner et al., 1967 study [45] used the Maxwell model whereas, Yeatman et al., 1969 study used the Viogt model [46]. Equivalence of both the models was shown by Brady et al., 1971 [47,48].

The force-velocity concept for an isolated muscle fiber was extended to an intact heart by the work of many researchers; notable among them were: Levine et al., 1964 [49], Fry et al., 1964 [50], Covell et al., 1966 [51], and Nejad et al., 1970 [52], to mention a few. These studies demonstrated the inverse relationship between the myocardial wall stresses and velocity of shortening of the muscle fibers.

One key differentiator in the mechanical behavior of the cardiac muscles from the skeletal muscles was the mechanism of the muscle activation process. The cardiac muscles were found to have a “resting-state”, characterized by a “resting-length”, and an associated “preload”. The resting-length of the cardiac muscles was assumed to correspond to the end-diastolic volume, where the muscle fibers are elongated by the increased ventricular volume during diastolic filling. Therefore, the load on the muscle in the state of resting corresponds to end-diastolic pressure and is called preload. Through the pioneering work of Otto Frank and Ernest Starling,
the magnitude of the force of contraction developed in the muscle during the systolic phase was found to be directly proportional to this resting length of the muscle fiber. The simulation of this preload and resting length was part of any experimental setup to establish the force-velocity relationship.

![Diagram of experimental setups](image)

**Fig. 2.5:** Various mechanical models of the cardiac muscle contraction process. A) Isometric contraction. B) Isotonic contraction. C) Isotonic afterload. The preload is denoted by PL, and AL represents afterload.

The schematic diagram of a few experimental setups used by researchers to establish the force velocity relation observed in cardiac muscles is shown in Fig. 2.5. Three types of setups have been reported (Fig. 2.5): 1) Isometric contraction, 2) Isotonic contraction, and 3) Isotonic afterload. In all these setups, the muscles are stretched to its resting length and fixed at its ends before applying electrical stimulus to activate the muscle contraction process (Fig. 2.5A). In isometric contraction, the contraction force developed for different resting length was measured. Similarly, in the experimental setup called isotonic contraction (Fig. 2.5B), different preloads were applied to stretch the muscle to its resting length before the application of contraction.
stimulus. A series of research by Sonnenblick et al., from 1962 onwards had used the isotonic afterload setup shown in Fig. 2.5C to measure the force velocity relationship of cardiac muscle fibers [51,53-55]. In Sonnenblick’s experiments, the active contraction of the muscle took place against an additional afterload which is applied after stretching the muscle to a resting length using a preload. Elzinga and Westerhoff established the relation of the afterload to compliance and viscous resistance of the muscle [56,57].

The main drawback of this approach was that the verification of these models for an intact in-vivo ventricle is challenging. In the application of these models, the local stresses in the ventricular wall were calculated from the ventricular pressure by applying the law of Laplace. However, this could only be accomplished by assuming a rather simplistic shape of the ventricle, such as ellipsoidal or spherical. These theoretical calculations using these analytical geometries are questionable for a realistic ventricle that has complex shape and complicated orientation of the muscle fibers. Moreover, it is impossible to measure the local wall stresses along the muscle fibers in an intact ventricle in-vivo to verify the results predicted by these models. Therefore, the results are difficult to apply to a patient-specific scenario in clinical settings.

The force-velocity approach develops the pressure-volume relations for heart starting with models of individual muscle fiber contraction and incorporating them in models of cardiac process. An alternate approach was adopted by researchers such as Suga, Elginga, Westerhoff, etc., who studied the pressure and flow output using the metaphor of heart as a pump [58-62].

### 2.3.2 Pump Characteristics

The study of the performance characteristics of the heart as a pump was motivated by its functional analogy with a mechanical pump. Such studies measured the ventricular pressure and the flow rate output under varying operating conditions [39,63]. The operating conditions ex-
experienced by the heart consist of the condition of the heart itself, its muscles together with the blood vessels and the external arterial resistance imposed on it by the systemic circulation. These studies attempted to answer the research question: whether an optimal functioning law exists for the heart; i.e., a law that illustrates the optimal performance of the heart under a range of operating conditions. Experiments for measuring pump characteristics were typically performed with an isolated (canulized) heart. The flow circuitry consisted of tubes connected at one end to the major arteries of the heart and at the other end to mechanical devices that mimicked the arterial resistance and impedance in case of pulsatile flow [58,64]. Research by Westerhoff et al., 1971 [65] and Sunagawa et al., 1985 [61,66] have shed light on the difficulty of defining this question for reasons described in the following paragraph [61,65]. Needless to mention, these measurements have not been possible in an intact in-vivo heart and therefore it is difficult to extend these procedures to clinical protocols.

Mechanical pumps fall in two major categories. Either they operate as a pressure source, i.e., maintain a constant pressure head; or they operate as a flow source, i.e., maintain a constant flow rate [63]. Studies by Tan et al., 1981 [67] and Sdougos et al., 1982 [68], showed that the heart was neither a pressure source nor a flow source. Wilcken et al., 1964 study [69] and van den Horn et al, 1985 study [62] showed that the heart functioned to deliver maximum power to the blood under operating conditions by adjusting both the pressure and flow rate [62,69]. This meant that the cardiac work was a function of contractility as well as arterial loading. The difficulty in performing experiments to measure the pump performance characteristics of ventricles in a manner similar to that performed with a mechanical pump results from the difficulty in controlling pressure and volume changes. Unlike a mechanical pump, in the case of a heart, these
changes are caused by the autonomous control from the central nervous system during the measurement process itself [58,64].

The fundamental understanding of the pump function of a heart was based on the analysis of pressure-volume (P-V) relationship of the individual ventricles. Research conducted by Otto-Frank in the year 1895 using isolated frog heart and by Ernest Starling in 1914 using dog heart were the first to study the P-V relationship in a heart [70]. This research yielded a significant insight into the functioning of a heart and established the Frank-Starling law of heart. Many new fundamental concepts to describe the mechanical characteristics of heart emerged from their study. These include the concept of elastance (and contractility), end-systolic-pressure-volume relationship (ESPVR) and stroke work. Considerable research effort was directed to develop indices and criteria based on these mechanical concepts to discern a normal heart from a diseased one [58,64,71].

A typical schematic P-V diagram for the left ventricle, the main pump for systemic circulation is shown in Fig. 2.6. A brief description of the P-V diagram is presented here to introduce some of the concepts associated with it; a detailed description is presented in the next chapter. The two vertical lines almost parallel to the pressure axis represent the isovolumic contraction and relaxation. The line on the left side represents isovolumic relaxation during diastole where as the one on the right represents contraction during systole. The top-left corner point of the pressure volume diagram is known as end-systolic-pressure-volume (ESPV) point as it represents the end of the systole and the beginning of diastolic relaxation. Likewise, the bottom right corner point is known as end-diastolic-pressure-volume point as it represents the beginning of the systolic phase of the cardiac cycle. The area enclosed by the P-V curve loop represents stroke work performed by the ventricle.
The analysis of P-V diagram observed in isolated frog heart by Otto-Frank, established the importance of end-systolic-pressure-volume point. Many different indices have been used to characterize the ventricular performance. To mention a few: cardiac output, stroke volume, end-systolic pressure, stroke work, force-velocity relationship and other contractility based indices, etc. [64]

![Schematic pressure-volume diagram for an isolated ventricle showing ESPV, ESPVR line and EDVPR curve.](www.ccnmtl.columbia.edu/projects/heart)

Fig. 2.6: Schematic pressure-volume diagram for an isolated ventricle showing ESPV, ESPVR line and EDVPR curve. (www.ccnmtl.columbia.edu/projects/heart)

Although the indices such as ESPVR, elastance and stroke work have provided details of cardiac mechanics, and have been extensively used in research, their clinical application has been difficult. It is difficult to measure ESPVR for an *in vivo* heart. Firstly, the pressure measurement is invasive. Secondly, measurement of most of these indices requires simultaneous measurement of pressure and volume. Lastly, the computation of ESPVR by controlling the volume and pressure changes to alter the shape of the P-V loop in an intact *in-vivo* heart is difficult.
Shifting P-V curves have been used to study ventricular hypertrophy. The shift in the P-V loop towards larger pressure and increased volumes implies higher wall forces in the ventricle [60,72].

Dasi et al., 2009 [73,74] have proposed many energy-based indexes for Fontan and other cardiovascular flow applications. Another computational approach has been described recently that uses a control volume technique to analyze the mechanism of energy losses in functional single ventricle patients after Fontan palliation [75-78]. Recently, research has been devoted to pulmonary flow in tetralogy patients.

2.3.3 Biochemical Processes

The objective of analyzing the energy exchanges in biochemical processes associated with muscle contraction was to understand the changes in the mechanical behavior of the heart in terms of the alterations in the energy consumptions in associated processes. Blood flow through the heart is regulated by the contraction of cardiac muscles. Muscle contraction is a mechanical event. However, many biochemical reactions taking place between various proteins in the muscle fibers, and cells are responsible for the mechanical event. These chemical reactions are accompanied by energy exchanges [38].

The energy necessary for the shortening of muscle fibers during cardiac contraction is generated by metabolic activity in cardiac muscles. The metabolic activity is the result of aerobic reaction of hydrolysis of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) in the muscle fibers [79]. The regeneration of ATP in the myocardial cells requires oxygen [80,81]. Therefore, measurements of myocardial oxygen consumption have been used to characterize the energy needs of the heart. These measurements have been performed for isolated strips of myocardium [82] and also in papillary muscles [83]. Oxygen consumptions by an intact heart have
been determined from these measurements [84, 85]. Energy consumption in papillary muscles has also been studied by measuring the heat production in isolated muscle strand [86].

The determination of the energy utilized by the heart by the direct measurement of heat generated by the associated biochemical processes has been difficult in an intact heart. As a result, the oxygen consumption by an intact heart is often determined by pressure measurement in aorta or ventricular pressure volume loop [87]. Therefore, it is the mechanical events of pressure and volume rather than the measurement of biochemical activity that is used for the clinical determination of oxygen consumption [85]. This poses problems related to invasive pressure measurements and simultaneous measurement of pressure and volume as in the case of pump characteristics described above. Moreover, comparison of results between different individuals requires special indexing due to the differences in their heart rates [74].

2.4 Clinical Use of Cardiac MRI

In the current clinical practice, cardiac MRI has been primarily used as a visualization tool for depicting the interior anatomical features and for imaging of the blood flow using phase contract MRI. The quantitative data obtained from imaging for clinical practitioners has been limited to the measurements of size and shape of the internal organs, and for obtaining blood flow rate in the case of phase-contrast MRI. It is therefore this interest in clinical utilization of imaging beyond rudimentary anatomical and flow rate quantifications that has opened up a whole new field of image-based modeling. Image-based modeling utilizes geometry reconstruction from imaging to model the physics of biological processes to determine endpoints that may be a marker for specific diseases [88]. Image-based models have been used in many biomedical applications; from modeling of cardiovascular flows to orthopaedics as well as in surgical planning.
2.5 Image-Based Models of Arterial Hemodynamics

A patient-specific computational model of arterial blood flow constructed using imaging (MRI or CT) is referred to as image-based modeling of arterial hemodynamics. Accurate simulation of in-vivo physiologic conditions using computational models of arterial hemodynamics requires patient-specific geometry of the blood flow domain as well as patient-specific boundary conditions. The 3D arterial geometry used in these models is constructed from the imaging data by applying geometry reconstruction algorithms [89]. With the advent of phase-contrast MRI (PC-MRI), the velocity boundary conditions have also been derived from PC-MRI. It is possible to acquire the time- and spatially- varying velocity data through PC-MRI. However, due to the complexity of incorporating this data with patient-specific geometry, relatively few researchers have utilized it for hemodynamic computation [90-92].

In this research, pulmonary arterial flow is modeled using the angiographic MRI of the patient’s pulmonary anatomy and PC-MRI of the blood flow at the inlet and outlets of the pulmonary artery. A brief summary of the research applying image based modeling techniques to some of the important cases of cardiovascular flows is presented below.

Carotid bifurcation. The earliest published research using image-based hemodynamics was to assess the role of hemodynamic forces in the atherosclerosis in the carotid artery. Milner, et al., 1998 performed a hemodynamic computation of flow through carotid bifurcation assuming the walls to be rigid [93]. Their geometry of the carotid bifurcation was reconstructed from MRI. A much more sophisticated computational model of flow through patient-specific geometry of carotid bifurcation, incorporating compliant arterial walls has been studied by Huang et al., 2009 [94].
Coronary arterial flow. The study of coronary artery diseases has been another active area of research. The role of endothelial shear stresses in the development of atherosclerosis in human coronary artery was investigated by Krams et al, 1997 [95]. More recently, the rupture of vulnerable plaques has been studied by many researchers [96,97].

Aneurysm. Image-based models of blood flow through abdominal aortic aneurysm have been studied with both rigid, as well as compliant arterial wall models to investigate hemodynamic endpoints linked to an aneurysms rupture [98-100]. Li et al., 2005 have also investigated the role of peak shear stress and endoleaks in stented abdominal aortic aneurysms [101,102]. Similar techniques have been applied to analyze the hemodynamic forces in cerebral aneurysms [103,104].

Pulmonary flow. Pulmonary arterial hemodynamics has mainly received research attention from total cavo pulmonary flow in single ventricle flow [105,106]. Shandas et al., 2006 have used patient specific models to analyze pulmonary hypertension [107].

The first step in image based modeling of any arterial flow involves the reconstruction of the flow domain from the imaging data. The results obtained from image-based models depend on the accuracy with which the reconstructed geometry matches the in-vivo geometry. Noise in image pixel values and the coarseness or fineness of image resolution directly affects the quality of the reconstructed geometry. The issues that are encountered in geometry reconstruction from imaging data are presented in the next section.

2.5.1 Geometry Reconstruction

Reconstruction of the lumen geometry from imaging is a critical step for image-based models of arterial hemodynamics. The reconstructed geometry must closely match the in-vivo
The greater the mismatch between the reconstructed geometry and the in-vivo geometry, the lesser is the likelihood of the computed results to match with the in-vivo measurements. The geometry reconstruction methodologies adopted in the research literature can be classified into two categories: 1) bottom-up approach and 2) top-down approach [108].

In the bottom-up approach, an image segmentation algorithm is applied to each individual image in a set of spatially stacked images one at a time, to extract the lumen boundary on each image [109]. This process results in a series of planar arterial cross-sectional boundary curves on the individual images. Since the images in the set are spatially stacked, this result in a set of boundary curves aligned along the axis of the blood vessel. The 3D geometry of the lumen is then constructed by fitting a smooth tubular surface through those extracted boundaries [110,111]. The smoothness of the reconstructed surface depends on the smoothness of the individual boundary curves on each image. In the case of arterial bifurcations, first, surfaces are constructed using the curves of the individual branches of the bifurcation. Then a surface patch is constructed to join the surfaces created on the individual branches. For a complicated branch, fitting surface at the junction can pose tricky problems. As is clear from the above description, the bottom-up approach involves a significant number of manual steps.

In the top-down approach, the segmentation algorithm is applied to the 3D image volume formed by all the spatially stacked images at the same time. The segmentation algorithm extracts the 3D volume of the lumen based on an input range of intensity threshold. The resulting surface of the reconstructed geometry may have surface roughness and artifacts that require simplification and smoothening. For poor quality images, the automatically segmented 3D volume may often require manual cleanup by the removal of regions of artifacts [112,113]. The automatic
geometry reconstruction software MIMICS (Materialise, Inc., Leuven, Belgium) employs such an approach for creating 3D arterial geometry from MRI data.

It is clear from the above discussion that the geometry reconstructed from patient-specific images in the first attempt is expected to include some surface artifacts that require surface smoothening [114]. The assessment of the reconstructed geometry and the reliability with which it matches the *in-vivo* geometry has been the subject of much research effort. Statistics based approach to quantify the reliability of reconstruction has been followed by Sankaran et al., 2011 [115]. Others in past have attempted to quantify the inaccuracies in terms of a known geometry of a phantom or a cast of an *ex-vivo* artery sample. Moore et al., 1999 used a straight tubular phantom to show that the geometry reconstructed from coarser images of the phantom had more surface artifacts than those created using finer images [116]. The wall shear stresses obtained from models based on coarser images differ by 40% to 60% from those obtained using Poiseuille equation. Several researchers have reported that geometry reconstructed from MRI of cast of an *in-vivo* geometry produce sufficiently accurate results when used for image-based models [114,117]. Both, Zhao et al., 2003 and Moore et al., 1999 constructed their geometry from the phantom of a cast of carotid artery bifurcation. However, in a different study by Moore et al., 1999, the reconstructed geometry from the phantom of an aorto-iliac bifurcation that was obtained from the cast of sacrificed rabbits was found to have fewer artifacts than that obtained from the MRI of the same live animals [118]. This clearly shows that the MRI of live subjects has noise and artifacts caused by cardiac and respiratory motion affecting the accuracy of the reconstructed geometry.

The geometry smoothening that is generally applied to the initial result from image segmentation algorithms is subjective. Therefore, it is possible to have variability in the recon-
structed geometry obtained from the same set of images by two different persons or by the same person at two different times [119-121]. At the locations of bifurcations, the geometry is difficult to establish from the image and depends on the image quality. However, improving the image resolution and its contrast will improve the accuracy of the reconstructed geometry and also improve the reliability of the reconstruction.

In the area of image-based modeling, a significantly greater number of research has focused on geometry reconstruction compared to other aspects of the problem such as boundary conditions [88]. Using PC-MRI, it is possible to obtain velocity boundary conditions from imaging. Therefore, incorporation of patient-specific boundary conditions in hemodynamic computation is becoming an important research problem.

2.5.2 Boundary Conditions

Accurate patient-specific hemodynamics simulating in-vivo physiologic conditions require patient-specific geometry and patient-specific boundary conditions. While a significant number of publications have reported methodologies for obtaining patient-specific geometry for hemodynamic computation [108,114,119,122], there are not many publications that have used patient-specific velocity as boundary conditions. Therefore, there is a gap in the research on incorporating patient-specific boundary conditions for hemodynamic computations. Realistic in-vivo velocity profiles at any arterial cross-section exhibit significant temporal and spatial variations and are unlikely to have idealized profiles.

The boundary conditions adopted in most researches on image-based hemodynamic computations have been simplistic; namely idealized developed flow profiles such as uniform, parabolic or Womersley [14,123-127] type. Parabolic and Womersley profiles are developed flow velocity profiles and are defined only on a circular cross-section. For simplicity, researchers of-
ten assume developed flow conditions without any rigorous evidence [128,129]. Moreover, the in-vivo arterial cross-sections of many arteries such as the pulmonary artery are non-circular [39,130]. The main roadblock for using patient-specific velocity profiles with realistic vessel geometry arises from the fact that simultaneous incorporation of patient-specific velocity and arterial geometry is not trivial.

The flows in the proximity of heart valves pose additional challenge for specifying boundary conditions as they have complex three dimensional velocity fields. Such flows are generally of the developing type; for example, the flow in the proximity of the pulmonary valve. It is well known that the results of hemodynamic computation are questionable, when the developed velocity profiles are used as boundary conditions for flow near heart valves [14]. For such flows, the velocity profiles at different cross-sections along the length of the artery vary. In the case of the pulmonary artery, the short length of the main PA distal to the pulmonary valve is insufficient for the flow to become a fully developed flow. Therefore, for performing an accurate hemodynamic computation, the complex velocity profile must be applied as boundary condition at the precise location of its measurement, while simultaneously capturing its spatial and temporal variation over the non-circular arterial cross-section under in-vivo conditions. Most of the published researches apply velocity boundary condition at the outlet of long artificial extensions that can cause inaccuracies in the computed flow field for developing flows [14,125,126,131,132].

The in-vivo hemodynamic conditions in an artery are simulated more accurately by using time- and spatially- varying patient-specific velocity data as boundary conditions. Due to the inherent complexity, only a limited number of studies have employed PC-MRI data directly for hemodynamic computation [111,133,134]. Further, these studies do not adequately report their
methodology for handling patient-specific velocity data. Therefore, it is not clear whether the velocity boundary conditions were applied at the location of PC-MRI measurement. Additionally, most of these studies do not compute the developing flows near valves.

Most researches apply the pulsatile pressure as normal traction on the inlet or outlet surface [94,99,100,132]. Since the pressure measurement requires invasive catheterization, it diminishes the attractiveness of the methodology in clinical settings. As an alternate approach, many researchers have also used a coupled lumped parameter model to specify outflow boundary conditions [106,135,136]. In these studies the downstream arterial vasculature is represented by a lumped parameter model involving a combination of resistance and capacitance [137,138]. The difficulty with these models is to determine the right values of the resistance and capacitance from patient-specific data. They are either determined based on impedance or numerically calculated by assuming a morphological structure of the downstream arterial vasculature [106,139].

In recent years there have been many reported research on hemodynamic computations with compliant models of arterial walls. Compliant wall models can incorporate modes of energy dissipation in wall motion and therefore expected to simulate more accurate physics. However, they also pose complexity due to their data requirements and need to incorporate arterial wall pre-stress.

2.6 Blood Flow with Compliant Arterial Wall

Studies by Ling et al., 1973 [140] on aortic flow in dogs, and by Atabek et al., 1975 [141] on flow through dog femoral artery clearly established the necessity to incorporate the compliance of the arterial wall along with the nonlinear terms of Navier-Stokes equation in the numerical models of blood flow. Without these, the mean flow rate was grossly over-predicted by numerical computation, even though the general shape of the flow rate versus time pulse was pre-
dicted fairly accurately. The two studies by Ling and Atabek [140,141] showed that the nonlin-
ear convective terms of Navier-Stokes equation accounted for the convection that arises due to
the additional velocity component in the radial direction. The convective terms arises naturally
whenever there is radial flow. This is the case as a result of wall motion induced by pulsatile
pressure on a compliant artery. It is also the case of a flow through a naturally tapering artery.
Ling and Atabek studies found that the magnitude of the flow in radial direction was small but
the contributions from the convective terms were too significant to ignore as had been previously
assumed by Womersley [142]. Therefore it is important that arterial hemodynamics incorporat-
ing wall compliance simulates the physics of blood flow more accurately than the one with rigid
wall assumption.

In recent years there has been considerable research on application of patient-specific
hemodynamics with compliant arterial wall to obtain diagnostic indices. Li et al., 2005 used
blood flow models with compliant wall for determining aneurysm-sac pressure and wall stresses
in abdominal aortic aneurysm (AAA) [98]. Using 3D-models similar to Li et al., with AAA
bulge geometry created using analytical shapes, Scotti et al., 2005 and 2008 [99,100] reported
20% higher stresses than rigid wall models. Blood flow through cerebral aneurysm has been
modeled by Torii et al., 2007, 2008 and 2011 [104,143,144]. Tang et al., 2005 and 2009 have
used high resolution MRI to reconstruct 3D geometry of coronary artery with plaque for their
compliant wall-blood flow models [145,146]. In a separate study from their research group,
Huang et al., 2009 [94,147] have modeled flow through a human carotid bifurcation with athero-
sclerotic plaque taking into account wall and plaque as deformable materials. Hunter et al., 2006
[148] have modeled flow through compliant pulmonary artery in patients with pulmonary hyper-
tension. Process optimization for pulmonary valve replacement surgery has been studied by
Tang et al., 2008 [149] using a compliant wall model of pulmonary artery with an external patch. Model of blood flow under both resting and exercise conditions with compliant arterial wall using patient-specific geometry of Fontan configuration has been studied by Bazilevs et al., 2009 [150].

In problems where 3D geometry is not required, axi-symmetric models of artery are easier to implement. Idealized axi-symmetric arterial geometry have been adopted by Bathe et al., 1997 [151] for stenosed artery, by Sinha-Roy et al., 2008 [152] to model flow through dog femoral artery, and Konala et. al., 2011 [153,154], for flow through stenosed coronary artery to study the effect of wall compliance on the values of diagnostic parameters [155,156].

Modeling of blood flow with arterial walls as compliant tubes is considerably more challenging than one with the rigid wall. Apart from issues described above, additional data requirements and physiologic problems cause the task to be more difficult. These include wall thickness, material properties and pre-stress in in-vivo artery. Determination of arterial pre-stress requires radial and axial shrinkage observed in an ex-vivo artery sample when extracted from in-vivo condition.

2.6.1 Wall Geometry and Thickness

In most of the compliant wall models, the wall geometry is constructed from angiographic MRI or CT scan images. These images are often averaged over the cardiac cycle and thus the geometry represents an averaged representation of the arterial geometry. It is possible to obtain time varying geometry at different times (MRI trigger time) during acquisition cycle, as in 4D-MRI. However, the cost of obtaining such images at a fine resolution is prohibitive. The image quality required to capture the anatomical physiology accurately becomes questionable due to longer acquisition time. Moreover, the longer image acquisition time makes it difficult
for the subjects to hold breath over such prolonged duration and consequently, cardiac motion and breathing results in poorer image quality. Reducing the image acquisition time means that the image resolution has to be compromised, which in turn, may not result in good quality of reconstructed geometry. As a result most researchers work with geometry reconstructed from angiographic MRI which are average image of the anatomy over the cardiac cycle.

Wall thickness is another data that is difficult to obtain \textit{in-vivo} [130]. Most of the thickness determination is done by performing histological studies of samples of arterial cross-sections [145]. Huang et al., 2009 have reported procedures to obtain 3D geometry of carotid artery along with plaque of variable thickness using MRI [94,147].

\textbf{2.6.2 Arterial Stress States}

Arteries in \textit{in-vivo} condition are in a state of pre-stress. The arterial pre-stress is believed to be caused by the tethering of the arteries in the surrounding tissues [157]. The arterial geometry obtained by image reconstruction is the \textit{in-vivo} geometry. The physical dimensions of a segment of artery, $L$, $D$ and $t$ obtained from the reconstructed geometry are known as \textit{in-vivo} length, diameter and thickness, respectively (Fig. 2.7A). In the \textit{in-vivo} state, such an artery element is subjected to a net axial force, $F_s$, which results in longitudinal stresses in the artery (Fig. 2.7A). Likewise, the \textit{in-vivo} diameter of the artery, $D$, is also the result of the \textit{in-vivo} pressure load, $p$, as well as the longitudinal pre-stress resulting from the force, $F_s$ [2,3,158].

Excision of an artery from the body causes a reduction in the axial length and a release of wall pre-stress. As a result, the arterial dimensions change in the \textit{ex-vivo} setting. The excised state without the arterial pressure is known as the load-free state (Fig. 2.7B). Specifically, an excised artery shrinks longitudinally as well as radially in the absence of the \textit{in-vivo} pressure
loading \((p=0)\) as well as the pre-stressing force \(F_s\). The dimensions, \(L_0, D_0,\) and \(t_0\) are the length, inner wall diameter and thickness of the load-free geometry. Due to the axial and radial contraction of the artery from its \(in-vivo\) state, the radial and the longitudinal dimensions of the load-free geometry, \(D_0\) and \(L_0\) are less than the corresponding \(in-vivo\) dimensions, \(L\) and \(D\). The length of the longitudinal shrinkage is typically determined by ex-vivo studies \([94,159,160]\). Longitudinal shrinkage of the order of 48\% has been reported by Van Loom, 1977 study for femoral artery of dogs \([159]\). Similar value of 33\% for longitudinal shrinkage and 12\% to 16\% circumferential shrinkage has been reported for human carotid arteries with plaque deposit by Huang et al., 2009 \([94]\). Similarly, considerable variation in \(in-vivo\) axial stretch along the arterial vasculature has been reported by Guo et al., 2011 and Algranti et al., 2011 for both, porcine aorta and coronary arteries \([160-163]\). The arterial wall materials are known to be incompressible \([2,3,158]\). Therefore the arterial wall thickness, \(t_0\) in the load-free state and \(t\) in the \(in-vivo\) state are related by volume incompressibility.

The longitudinal and radial contraction observed in excised artery samples implies the existence of longitudinal as well as circumferential pre-stresses in the \(in-vivo\) state \([2,3,158]\).

Zhang et al., 2005 \([164]\) have reported significantly larger increases in longitudinal stresses when arteries are subjected to \(in-vivo\) axial stretch. For porcine coronary LAD, they report that longitudinal stresses exceed circumferential stresses for axial stretch ratios greater than 1.4 (i.e., 40\% stretch from load-free length). However, it may be noted that the load-free state of the artery is not the stress-free state (Fig. 2.7C). A longitudinal incision made in the load-free artery results in the opening of the artery by an angle \(\alpha\) \([165,166]\). This is the result of residual stresses that exist in the load-free artery. The reason for existence of residual stress in the artery is not known.
The opening angle, $\alpha$, is reported to be a measure of the level of residual stress in the artery.

**Fig. 2.7:** Schematic diagram showing the different state of stresses in an arterial segment; A) *in-vivo* in pre-stressed state, B) load-free without arterial pressure $p$, and C) excised and cut longitudinally in stress-free state.

The arterial geometry obtained from image reconstruction is the time averaged *in-vivo* geometry. Since the artery in this state is pre-stressed, excessive deformation will result if *in-vivo* pressure load is applied to this *in-vivo* geometry without accounting for the arterial pre-stress. This causes the determination of arterial pre-stress important for accurate hemodynamic model with a compliant arterial wall (Fig. 2.7). To obtain the pre-stressed state of the artery, the load-free geometry needs to be determined followed by obtaining the pre-stressed configuration.

### 2.6.3 Load-free Arterial Geometry

In the load-free state (Fig. 2.7B), an arterial segment is free of any *in-vivo* load resulting from either blood flow or forces due to the tethering [157] of the artery in the surrounding tissues. The calculation of the load-free geometry from *in-vivo* geometry with known *in-vivo* loads
is an *inverse elastostatics* problem. In this problem, the undeformed (load-free) arterial wall geometry is computed from the *in-vivo* wall geometry (i.e., the deformed or the *in-vivo* geometry) using the *in-vivo* loads and axial shrinkage data. In concept the load-free geometry can be obtained from the *in-vivo* geometry by radially and axially shrinking the *in-vivo* geometry. It is a computationally challenging problem due to issues of numerical stability of the inverse algorithms [168]. The methods for solving the *inverse elastostatics* problem can be classified into two categories: 1) direct numerical *solution of the inverse equations*, and 2) optimization based *inverse* solution.

In the first method, the inverse problem is solved as a boundary value problem with the unknown function being the deformation field. In an inverse problem, the unknown deformation field is the displacement from the *deformed* configuration back to the *undeformed* configuration [168]. In *inverse-elastostatics* literature, this deformation field is termed as the *inverse* deformation field and it is defined with respect to the current or the deformed configuration (*in-vivo* geometry). Therefore, for inverse problems the deformed (*in-vivo*) configuration is taken as the reference configuration [169]. The load boundary conditions for the inverse boundary value problem are derived from the *in-vivo* load; but they do not have a physical significance. This method was originally developed by Govindjee et al., 1998 [168] for shape design of automobile tires and was later adopted by Lu et al., 2007 [170,171] for computing the load-free geometry for a patient-specific abdominal aortic aneurysm (AAA) case. The mathematical formulation of the method incorporates large deformation along with material nonlinearity. However, numerical convergence has been reported to be an issue in many cases; e.g., Govindjee et al., 1998 [168] have reported instability in the cases involving incompressible materials.
The optimization-based inverse methods find an approximate solution of the inverse problem by least-squared minimization. The objective function for the least-square minimization is typically the error norm of the distance between the points of the in-vivo geometry and those of the deformed geometry, resulting from the application of the in-vivo loads on an assumed load-free geometry. The constraints for optimization for inverse-elastotastics problems are typically the equations of elasticity. The optimization based inverse is easier to implement as a numerical code compared to the direct solution approach described above. Therefore, based on the number of published research, this optimization based approach, although approximate, has been the preferred approach for the computation of load-free arterial geometry [172-176].

Raghavan et al., 2006 was the first research to report an optimization based method to account for pre-stress in a patient-specific AAA geometry [173,177]. In their method, first the deformation field, $U$ of the in-vivo geometry under mean in-vivo arterial pressure was computed. Their methodology assumed that the pattern of AAA wall deformation under a range of pressure loads was similar. Using this assumption, the coordinates of the load free geometry point $X$, were calculated as $X = x - kU$ using the deformation, $U$, at each point, $x$, of the in-vivo wall [173]. Therefore, the optimization algorithm was reduced to a 1-D optimization problem over an independent variable $k$ with real values. The optimization algorithm calculated the value of $k$, such that the match between the in-vivo geometry and the deformed load-free geometry was within acceptable tolerance. The existence of a single unique value of $k$ for all points of the AAA wall geometry is an approximation, in particular, when the wall material can be nonlinear and anisotropic in nature.

A backward incremental algorithm has been proposed by de Putter et al., 2007 to compute the load-free geometry [175]. In this approach, deformation computed for the points of the
“assumed” load-free geometry in each iteration are applied backwards on the in-vivo geometry, but the mean in-vivo pressure is applied in an incremental manner to attain stress equilibrium under loading [175]. In other words, the in-vivo pressure is applied in small increments to the in-vivo geometry in each iteration, \( i \); and the resulting point displacements, \( U_i \), were applied back to the in-vivo geometry point, \( x_I \), to calculate the load-free geometry point \( X \), as \( X = x_I - U_i \). It may be noted that in the Putter et al., 2007 method [175], the backward deformation is applied to the points of the in-vivo geometry \( (x_I) \); whereas, in the Raghavan et al., 2006 method [173], the backward displacement is applied to the points of the deformed geometry \( (x) \) that results from the application of the in-vivo pressure to the in-vivo geometry. The iterations in de Putter et al., 2007 method converge when the stress equilibrium is attained under in-vivo pressure load and at the same time matching the in-vivo geometry. Speelman et al., 2009 [172] adopted the de Putter et al., 2007 [175] for the case of AAA wall with the nonlinear material model proposed by Raghavan et al., 2000 [178].

Another methodology to calculate the load-free geometry that is referred to as fixed-point iteration procedure has been proposed by Bolls et al., 2013 [176]. This algorithm is similar to the de Putter et al., 2007 [175], algorithm described above in the approximation of the load-free geometry computed in each iteration using the point displacements, \( U_i \). As in de Putter algorithm, the point displacements, \( U_i \), are applied back to the in-vivo geometry point, \( x_I \), to calculate the trial load-free geometry point \( X \), as \( X = x_I - U_i \). However, the difference between this algorithm and the original de Putter et al., 2007 [175] algorithm is in the application of pressure load. In this algorithm, full in-vivo pressure is applied to the load-free geometry instead of incremental pressure after the completion of each iteration.
In the cases of AAA geometry, the predominant deformation is under pressure load. However, as mentioned above, femoral and carotid arteries are known to have significant shrinkage [94,159]. It is not clear from the above cited research whether the methodologies will be valid for an arterial geometry subjected to significant longitudinal stretching. A method of computation of load free geometry when significant longitudinal stretching is required has been reported by Huang et al., 2009 [94,147]. The methodology is a manual trial-and-error based procedure. Similar methodology has been adopted by Sinha-Roy et al., 2008 [152] for an idealization dog femoral artery with a straight tapered geometry, and by Konala et al., 2011 [154] for an axi-symmetric geometry of coronary plaque with anisotropic material model.

In this research, an optimization based inverse algorithm is implemented, and tested to obtain the load-free geometry. The algorithm is designed for a patient-specific artery geometry subjected to both pressure load as well as longitudinal stretch.

2.7 Conclusions

The pathophysiology of pulmonary insufficiency and its influence on the repaired tetralogy of Fallot subjects was discussed. A brief overview of the past research on cardiac energetics was presented. The background and the literature review of the topics related to the existing techniques were also presented. It is evident that the energy-based hemodynamic endpoints are less commonly adopted because of the difficulty in obtaining relevant clinical data. Recently, they have been employed in single ventricle flow in Fontan and total-cavo-pulmonary-connections.

It is evident from literature review of the past research that the field of image based hemodynamic modeling has been an active area of research for the last two decades. However, the
focus of much of the research in this area has primarily been on obtaining patient-specific geometry from imaging. As a result, there is a gap in the research in incorporating patient-specific \textit{in-vivo} boundary conditions in the image-based models. This is particularly true for the computations involving developing flows near valves where idealized velocity boundary conditions have been employed as simplification.

The next chapter presents the description of the hemodynamic endpoints introduced in this research and the methodologies to calculate them from clinical measurements.
Chapter 3

Energy-Based Endpoints

3.1 Introduction

This chapter presents a brief description of the energy-based hemodynamic endpoints that are proposed in this research for analysing the pathophysiology of pulmonary insufficiency. These endpoints are: 1) right ventricular stroke work, 2) a new endpoint, energy transfer ratio and 3) the energy loss in branch pulmonary artery. The rationale for using these endpoints to analyze pulmonary insufficiency is previously explained in Chapter 1. This chapter presents only the theoretical basis of these endpoints along with their derivation from basic fluid mechanics. The equations for the endpoints obtained from basic fluid mechanics require appropriate simplifications so that they can accommodate clinically measured pressure, flow rate and volume data. Therefore, a methodology to calculate these endpoints from clinically obtained pressure, volume and flow rate measurements in patients are also described in this chapter. The results of applying these endpoints to delineate the pathophysiology of a normal subject from one with pulmonary insufficiency are presented in Chapter 5.
3.2 Rationale for using of Energy-Based Endpoints

The patients with tetralogy repair surgery performed at a young age develop severe pulmonary insufficiency in their adult life. As a result, they experience fatigue, shortness of breath and fainting under exercise condition. In this research, it was postulated that these symptoms could be the result of the inadequate oxygenation of the blood in these patients. In other words, inefficiencies in the pulmonary circulation could be responsible for the insufficient flow of blood to the lungs for oxygenation. Therefore, in order to understand and quantify these inefficiencies in the flow of blood to the lungs, energy-based hemodynamic endpoints were proposed.

![Diagram of heart showing control volumes](image)

**Fig. 3.1:** Schematic diagram of heart showing the control volumes used for the calculation of different energy-based endpoints.

The right ventricle drives the pulmonary arterial flow to the lungs for oxygenation. The other structural components of the pulmonary flow system are: the right ventricular outflow track with the malformed pulmonary valve, the branch pulmonary artery (Fig. 3.1), and finally the downstream pulmonary artery vasculature beyond the left and right pulmonary artery branches. The root cause of pulmonary insufficiency is the defective pulmonary valve which does not af-
fect the downstream pulmonary vasculature tree. Therefore, this research did not investigate the effect of the resistance offered by the pulmonary vasculature on blood flow to lungs. The focus of this research work was on the inefficiencies in ventricular output, pulmonary artery and the join between the ventricle and the main pulmonary artery.

The energy-based indices proposed in this dissertation are designed for each of the above mentioned physiologic components. For the right ventricle, stroke work was used as a measure of the ventricular pumping inefficiency. For the junction between the right ventricle and the main pulmonary artery, a new endpoint: energy transfer ratio was defined. Finally, energy-loss in the flow through the pulmonary artery was used as the measure of flow inefficiency.

3.3 Ventricular Stroke-Work

The two ventricles of the heart drive the flow. The right ventricle is the driver for the pulmonary arterial flow of blood to the lungs, whereas, the left ventricle is responsible for the systemic flow to the organs and tissues. The energy imparted to the blood by the ventricle is responsible for its continuous flow through the circulatory system. The pumping action of the ventricles produces the necessary mechanical work to circulate blood throughout the body. This pumping action is the result of a sequence of mechanical events in the ventricle. The right as well as the left ventricle of the heart go through a similar mechanical cycle. In the following section, the cardiac cycle of the left ventricle is described because some of the mechanical events are more clearly observable there than the right ventricle.

3.3.1 Cardiac cycle

The cardiac cycle consists of a sequence of mechanical events in the heart that produces the pumping action. The mechanical events constitute closing and opening of the valves at ap-
propriate time during the cycle, relaxation, and contraction of the cardiac muscles, etc., to regulate the flow of blood. These events occur in two phases: 1) diastolic phase and 2) systolic phase. During the diastolic phase the cardiac muscles relax; whereas, in the systolic phase the muscles contract to pump blood out of the ventricle.

**Fig. 3.2:** The Wiggers diagram for the left ventricle of the heart showing the electrical activity as recorded with echocardiogram and the corresponding variation of the ventricular pressure and volume. The last row of heart icons shows the sequence of atrial and ventricular filling at different time points in the cardiac cycle. (Redrawn from Silverthorn, D.U., *Human Physiology: An Integrated Approach*, 2nd ed., Prentice Hall, NJ)
The functioning of a normal human heart over one cardiac cycle is shown schematically using the Wiggers diagram (Fig. 3.2). For a normal human heart, the duration of the cardiac cycle under resting condition is typically from 700 ms to 900 ms. The contraction and relaxation of the heart muscles are triggered by electrical signals which are recorded as electrocardiogram (Fig. 3.2). This contraction and relaxation of the cardiac muscles is responsible for the isovolumic contraction and relaxation of the ventricle, which in turn regulates the ventricular pressure. The opening and the closing of the valves is a passive response to the pressure differential that builds-up across the ventricle and the outlet valve. In other words, it is the electrical activity in the heart that triggers the contraction and relaxation of heart muscles. And, that in turn is responsible for the build-up of the ventricular pressure, which again regulates the opening and closing of the heart valves.

The variation of the left ventricular pressure and volume over the cardiac cycle along with the resulting aortic pressure is also shown in Fig. 3.2. The row of heart pictures at the bottom of Fig. 3.2 depicts the approximate time points for ventricular filling and ejection.

It is clear from the Wiggers diagram that there are two parallel pumping processes taking place in the heart simultaneously. One is the pumping by the right heart using the right atrium and the right ventricle, and the other by the left heart using the left atrium and the left ventricle. The deoxygenated blood from organs and tissues collects in the right atrium via superior and inferior vena cava (SVC and IVC). The right heart pumps the deoxygenated blood from organs and tissues to the lungs for oxygenation. After oxygenation, the blood comes in the left atrium via pulmonary veins. Thus, the left heart is responsible for the systemic circulation by which the oxygenated blood from the lungs is pumped back to the organs and tissues.
At the start of the cardiac cycle, blood collects in the right and the left atrium. The valves between the atrium and ventricle (tricuspid and mitral) remain closed at this moment. The higher pressure in the ventricles at this point prevents the valves from opening. This is because, the ventricles are undergoing ejection and the pressure levels in the ventricles are high enough to keep the valves closed. With the increase in the atrial volume, the atrium undergoes atrial systole. The pressure in the atrium increases and forces the blood into the respective ventricles. This leads to a steady increase in the ventricular volume until a point when the volume increase subsides. This moment marks the beginning of the ventricular systolic phase.

The beginning of the systolic phase in the ventricle is accompanied by a very sharp rise in the ventricular pressure without the corresponding change in the ventricular volume. As seen from the Wiggers diagram, the volume versus time is almost horizontal during this short period. During this period, the pressure build-up in the ventricle is the caused by the contraction of the cardiac muscles. This short period of pressure build-up in the ventricle at a constant volume is known as isovolumic contraction. In this duration, the valves at the inlet (tricuspid and mitral valve) as well as the outlet of the ventricle (pulmonary and aortic valve) are closed. The build-up in the ventricular pressure forces the opening of the outlet valves (pulmonary and aortic) resulting in the ejection of blood out of the ventricle.

The ventricular pressure drops following the ejection. This drop in the ventricular pressure marks the beginning of the diastolic phase. As in the case of systolic phase, for a very short period of time, the cardiac muscles relax after contraction during which the ventricular volume remains constant. This stage is known as isovolumic contraction. At this point the ventricular pressure decreases to the level that the mitral and the tricuspid valve open and ventricular filling starts and the cycle is repeated.
3.3.2 Pressure-Volume Diagram

The time variation of the ventricular pressure and volume, shown in Fig. 3.2 can be plotted on a single graph showing the variation of pressure with volume. This diagram is called ventricular pressure-volume diagram (Fig. 3.2). An idealized pressure-volume diagram for a left ventricle is presented in Fig. 3.3. It is referred to as idealized pressure-volume diagram, because the isovolumic contractions and relaxations phases are shown by vertical straight lines. The cardiac cycle shown the in Fig. 3.2 starts at the point A when the mitral (and tricuspid) valve opens and the ventricular filling begins. In the isovolumic phase B to C both the inlet and the outlet valves are closed. The segment B-C-D on the pressure-volume diagram (Fig. 3.3) represents the systolic phase in the cardiac cycle whereas, the segment D-A-B represents the diastolic phase.

![Diagram](image1.png)

**Fig. 3.3:** A schematic representation of the pressure-volume diagram for the left ventricle. (Redrawn from Silverthorn, D.U., *Human Physiology: An Integrated Approach, 2nd ed.*, Prentice Hall, NJ)
Actual pressure-volume loops obtained from clinical data have a slightly distorted shape. Pressure-volume diagrams for right ventricle are known to be much rounded in shape and have indistinguishable isovolumic stages (D-A and B-C; Fig. 3.3). The disease conditions of the ventricle can also affect the shape and the area enclosed by the pressure-volume loop.

3.3.3 Ventricular Stroke Work

The area enclosed by the loop of the pressure-volume diagram is defined as ventricular stroke work. Therefore, the stroke work can be obtained by:

\[
SW = \int_C pdV
\]

(3.1)

where, \(p\) and \(V\) are the ventricular pressure and volume, respectively, and \(C\) the closed loop of the pressure-volume diagram. It is a measure of the energy imparted to the blood by the ventricle.

The calculation of stroke work, by definition, requires simultaneous measurement of ventricular pressure and volume. In the clinical setting, the pressure measurement is obtained by cardiac catheterization, which is an invasive procedure. The ventricular volume is obtained non-invasively by cardiac MRI. However, there are no clinical protocols to perform cardiac MRI and catheterization simultaneously in humans. In other words, it is difficult to simultaneously measure pressure and volume in humans under clinical settings. Therefore, a methodology needs to be developed to compute the ventricular stroke work from non-simultaneously measured pressure and volume data. This methodology was developed as a part of Specific Aim 1 and is presented in one of the following sections.
3.3.4 Cardiac Pressure and Volume Measurement

Pressure measurement. The pressure in the ventricle is measured by catheters. This procedure is invasive and requires insertion of the catheter into the ventricle of interest. For the left ventricle, the catheter can be advanced into the ventricle through the aorta. For the right ventricle it is typically inserted through the superior or inferior vena-cave (Fig. 3.4).

Volume measurement. The volume of the ventricle can be measured by both invasive as well as non-invasive methods. Invasive methodologies use a conductance catheter (Fig. 3.4). Non-invasive volume measurements are performed using imaging techniques such as bi-planar angiography, echo-cardiography, CT, and MRI. In the current clinical settings, short-axis MRI is accepted as the standard of care technique.

As shown in Fig. 3.5A, the shape of the cross-section of the left ventricle is elliptical; whereas, that of the right ventricle is like a crescent (Fig. 3.5A). The left ventricle of the heart
has an ellipsoidal shape in the three dimensional space. On the other hand, the right ventricle has a complex shape that wraps around the left ventricle (Fig. 3.5A). In the clinical settings, the volume of the left ventricle can be measured more easily and accurately than the right ventricle due to its ellipsoidal shape. The shape (complex) of the right ventricle in the three dimensional space makes the accurate measurement of its volume using conductance catheter difficult and error prone. Similarly, bi-planar angiography works well with the left ventricle but is inaccurate when applied to the right ventricle. The projected image of the crescent shaped right ventricle onto the two orthogonal planes perpendicular to the long axis of the ventricle gives inaccurate volume.

The ventricular volume measurement using conductance catheter requires invasive procedure of inserting the catheter into the ventricle. Thus, it is clinically less appealing. Bi-planar angiography requires injection of radio-opaque contrast agent into blood stream and involves X-ray fluoroscopy. Therefore, it subjects the patient to potentially harmful side effects of chemical agents and exposure to X-rays. In contrast, short axis magnetic resonance imaging provides accurate results with right as well as the left ventricle. Being non-invasive and free of any detrimental side effects it has become the standard-of-care clinical technique for ventricular volume calculation. The procedure of calculating the time varying ventricular volume data from MRI is described below.

*Volume Measurement from Cardiac MRI.* For this research work, right ventricular volume was measured using MRI. In this methodology, a spatially aligned stack of MRI along the short-axis of the ventricle was obtained at different times during the cardiac cycle. A typical image at a given slice location and time is shown in Fig. 3.5A. A spatial stack of these images along the long axis of the ventricle are shown in Fig. 3.5B. The individual images in this stack were seg-
mented by semi-automatic method using QMass software to obtain the inner wall boundary of the right ventricle. This process was repeated for each slice at each of the time points (Fig. 3.5B). A three dimensional contour representation of the ventricle was obtained at each time point (Fig. 3.5C). Ventricular volume at the given instant of time was obtained by numerical integration using Simpson’s rule. The variation of the volume over the cardiac cycle was obtained by repeating the process for stack of images at each time point (Fig. 3.5D).

3.3.5 Co-registration of Pressure and Volume Data

As mentioned above, the calculation of ventricular stroke work requires simultaneous measurement of pressure and volume. This is difficult to achieve in clinical settings because there are no protocols to perform simultaneous MRI and invasive catheterization in humans. Therefore, cardiac catheterization and MRI data are acquired at separate sessions. It is expected to have differences in cardiac period between sessions of catheterization and cardiac MRI. As a result, the cardiac period of the pressure dataset and the volume dataset will have a small difference. For the present analyses, these data sets needed to be adjusted to account for differences in heart rate between the sessions for MRI and catheterization.

This was performed digitally based on the resident electrocardiographic (ECG) signal present in both the data sets (Fig. 3.6). This process required three steps. Initially, the hardcopy of the catheterization data which included: pressure versus time curves for the RV, MPA, and locations in the branch PAs, and ECG recording with time, were manually digitized between two consecutive ECG R-waves. The cardiac cycle period for the catheter data was assumed to be the duration of this time interval between these two consecutive R-waves. Noise content (random white noise) was low in our subjects. Most pulses were repeatable and not statistically different. A maximum of 3% variation was observed during time discretization between any pulses.
Fig. 3.5: A) A typical short-axis anatomical MRI through human heart at a given phase and slice location. B) Right ventricle inner wall boundary on images at different slice locations but at same phase. C) Representation of the right ventricular inner wall contours in 3D space. D) Right ventricular volume variation with time.
Fig. 3.6: Co-registration of the asynchronous pressure and the RV volume versus time pulses (or the LPA/MPA/RPA flow as appropriate) using ECG. The time $t = 0$ sec, in our calculations correspond to the start of a systole and is identified from the start of the QRS complex of the ECG tracing. Start of two consecutive QRS complex on the ECG pulse of the patient define one cycle of the pressure pulse.

The isolated pulses with high noise because of catheter movement were excluded by visual inspection of the pressure time plot. Next, the heart rate interval was measured from the digital CMR data (RV volume versus time and PA flow versus time), which by definition is recorded starting at the onset of the ECG R-wave. Finally, the CMR data was linearly scaled in the time
domain to match the cardiac catheterization time period. All digital measurements and adjustments were performed via a customized MATLAB®, (MATLAB, Inc., Waltham, MA) software.

### 3.3.6 Stroke Work Calculation

The digitized, synchronized right ventricular pressure and volume data were smoothed by fitting a Fourier series approximation, which was then used to construct a pressure-volume diagram for the ventricle.

The Fourier series of the co-registered and synchronized RV pressure and volume curves were sampled at a series of closely spaced consecutive time points, \( t_1, t_2, \ldots t_n \), over one cardiac period, \( T \), progressing from \( t = 0 \) sec to \( t = T \) sec. Thus, the pressure-volume loop points evaluated at the sampled time points, \( t_1, t_2, \ldots t_n \) are, \((p_1, V_1), (p_2, V_2), \ldots (p_n, V_n)\). The stroke work \((SW)\) given by Eq. 3.1, which is the area enclosed by the pressure-volume loop, is computed by straightforward application of Gauss theorem, reducing Eq. (3.1) to,

\[
SW = \frac{1}{2} \int_C (pdV - Vdp),
\]

a cyclic integral over the closed path, \( C \), and then reducing the right hand side of Eq. 3.2 to a summation over the closed path formed by the sampled pressure-volume loop points, \((p_1, V_1), (p_2, V_2), \ldots (p_n, V_n), (p_1, V_1)\) to,

\[
SW = \sum_{i=1}^{n-1} \frac{1}{2} \left( p_{i+1}V_{i+1} - p_{i+1}V_i \right) + \frac{1}{2} \left( p_nV_1 - p_1V_n \right)
\]

An in-house MATLAB script was developed to numerically compute the RV stroke work that, 1) co-registered the pressure and volume data using ECG time points for two consecutive systoles, 2) fitted Fourier series to the pressure and the volume curves and 3) computed the pressure-volume stroke work using Eq. 3.3, which is the discrete form of Eq. 3.1. The RV stroke work
(Eq. 3.1) is based on the assumption of quasi-static variation of pressure with volume and does
not take into account the inherent dynamic conditions in the RV.

3.4 Total Energy at an Arterial Cross-Section

The rate of energy transferred to the blood at an arterial cross-section $s$, can be derived in
a straightforward manner from the basic fluid mechanics. Let, $\vec{V}_s(\vec{x},t)$ be the distribution of
blood velocity at any point $x$ inside the arterial cross-section at an instant of time $t$. In general,
the velocity distribution inside an artery is complex and unlike any idealized profile such as uni-
form, or parabolic. Therefore, this velocity distribution, $\vec{V}_s(\vec{x},t)$, varies both spatially and tem-
porally over the cross-section. The rate of transfer of the total energy to the blood ($\dot{E}_s$) at the
cross-section $s$, neglecting the contribution of the potential energy due of gravity, is given by:

$$\dot{E}_s = \iint_{A_s} \left( p_s + \frac{1}{2} \rho \vec{V}_s \cdot \vec{V}_s \right) \vec{V}_s \cdot n dA_s,$$

(3.4)

where, $A_s$ is the area of the cross-sectional $s$; $n$ is an unit normal to the cross-section; $p_s$ is the
pulsatile pressure; and $\rho$, the density of the blood.

Since the distribution of $\vec{V}_s(\vec{x},t)$ is both time- and spatially varying over the arterial
cross-section, Eq. 3.4 can be simplified by approximating the velocity distribution $\vec{V}_s(\vec{x},t)$ by an
average velocity vector of magnitude $v_s$. The value of $v_s$ can be computed from flow rate $Q_s$
by $v_m = Q_s / A_s$. The flow rate $Q_s$ is given by:

$$Q_s = \iint_{A_s} \vec{V}_s(\vec{x},t) \cdot n dA_s.$$  

(3.5)

With these simplifications, the rate of total energy transferred to the blood pool at the cross-
section $s$, can be expressed as:
\[ \dot{E}_s = \left( p_s + \frac{1}{2} \rho v_s^2 \right) Q_s. \] (3.6)

The advantage of the approximation of \( \dot{E}_s \) by Eq. 3.6 is that it involves physical quantities \( Q_s \), \( p_s \), and \( v_s \), that can be measured in the clinical setting. It may be noted that the quantities \( Q_s \), \( p_s \), and \( v_s \) are functions of time. Therefore, \( \dot{E}_s \) is also a function of time. The rate of the transfer of energy by the ventricle to the blood pool never remains constant and varies over the cardiac cycle with the pulsatile variation of flow rate, pressure and velocity.

### 3.5 Energy Transfer Ratio

Energy transfer ratio is a new energy-based endpoint introduced in this research. It is defined as the ratio of the total energy transferred to the blood by the ventricle at a cross-sectional plane distal to the outlet valve, and the stroke work performed by the ventricle. The numerator term of energy transfer ratio, the total energy should be obtained at an arterial cross-sectional plane close to the outlet of the ventricle, distal to the outlet valve. Therefore, the energy transfer ration is defined at an arterial cross-sectional plane located at the outlet of the ventricle. For the left ventricle, it can be defined on a cross-sectional plane through the aorta, distal to aortic valve. For the right ventricle, it can be defined on a cross-sectional plane through the pulmonary artery distal to the pulmonary valve.

The net energy transferred to the blood pool (\( E_{net} \)) over the cardiac period \( T \), at a cross-section \( s \), distal to the outlet valve of the ventricle can be computed by:

\[ E_{net} = \int_0^T \dot{E}_s(\tau) d\tau. \] (3.7)
where, $\dot{E}_s$ is given by Eq. 3.6. Time averaged energy transfer rate ($\tilde{E}_{net}$) over one cardiac cycle at MPA can be defined as:

$$\tilde{E}_{net} = \frac{E_{net}}{T}. \quad (3.8)$$

The energy transfer ratio $e_s$ at the cross-section s is defined as:

$$e_s = \frac{E_{net}}{SW}. \quad (3.9)$$

Where, SW is the ventricular stroke work calculated using Eq. 3.3 and $E_{net}$ by Eq. 3.7.

**Fig. 3.7:** A) Schematic representation of control volume for energy ratio and energy loss calculation. B) Locations of velocity and pressure measurements at the inlets and outlets of branch pulmonary artery.

It may be noted that the stroke work (SW) and $E_{net}$ have dimensions of energy and may be affected by many factors including but not limited to, age, physiology, BSA, etc. For subjects with severe pulmonary insufficiency, SW might also be biased by high right ventricular pres-
sures inherent due to hypertrophy. The energy transfer ratio $e_s$, on the other hand is dimensionless.

The energy transfer ratio $e_s$ is an indicator of the efficiency of the transfer of energy from the ventricle to the blood being ejected out. A higher value of $e_s$ will indicate a more efficient ventricle. However, the ratio $e_s$ is strictly not a measure of efficiency. For example, the definition of stroke work underlies assumption of quasi-static variation of the ventricular pressure with the change in volume [15,73,74]. On contrary, the forces generated in the heart are very dynamic in nature. Although, the numerator term of energy transfer ratio, $E_{net}$ does incorporate the dynamic conditions of blood velocity, flow rate, and pressure, it does not directly account for many complex modes of energy dissipation. For example, it does not account for temporary energy storage (due to elasticity of tissues) and losses (friction between blood and tissue), turbulence and valve’s opening and closing, etc. Therefore, in the strict sense, energy transfer ratio is not a measure of efficiency. However, it may be noted that higher value of energy transfer ratio signifies larger energy imparted to the blood by the ventricle and thus a more efficient system.

### 3.6 Energy Loss in Branch Pulmonary Artery

The rate of energy input to the blood is given by $\dot{E}_m$. The rate of total energy at the outlet at the LPA and RPA can be obtained by $\dot{E}_l$ and $\dot{E}_r$, respectively. Therefore, the rate of energy loss in the branch pulmonary artery can be computed by:

$$\dot{E}_{loss} = \dot{E}_m - (\dot{E}_l + \dot{E}_r), \quad (3.10)$$

where, $\dot{E}_m$, $\dot{E}_l$ and $\dot{E}_r$ are calculated by using Eq. 3.4. The net loss over the cardiac cycle can be calculated using:
\[
\Delta E = \int_{\theta}^{T} \dot{E}_{\text{loss}} \, dt
\]

where, the integration is performed over the period \( T \) of the cardiac cycle.

### 3.7 Concluding Remarks

This chapter presented a theoretical framework for the hemodynamic endpoints of stroke work, energy transfer ratio and energy loss. The equations for these endpoints were developed starting with the basic principles of mechanics. The equations were simplified by making appropriate assumptions to incorporate clinically measured pressure, flow rate and ventricular volume data. The methodologies developed to calculate these endpoints from clinical measurements were presented. The results of applying these endpoints to a normal subject and one with pulmonary insufficiency are presented in Chapter 5.

In many clinical cases, it may not be possible to measure the pressures at all the required locations in an arterial segment to calculate endpoints such as energy transfer ratio, and energy loss. In such cases, it is possible to calculate the missing pressure data using patient-specific hemodynamic computation. Therefore, in the next chapter, a methodology to perform hemodynamic computation of the flow in the branch pulmonary artery using patient specific geometry and flow measurement using phase-contrast MRI will be presented.
Chapter 4

Patient-Specific Hemodynamics using Womersley Profile from PC-MRI

4.1 Introduction

Energy-based hemodynamic endpoints: energy transfer ratio and energy loss in the branch PA are defined in terms of pressure flow energy and kinetic energy. These endpoints require pressure measurement and flow rate or velocity measurement at the MPA inlet and LPA and RPA outlets. Flow rate data can be obtained non-invasively using velocity encoded PC-MRI and therefore pose no complexity in the clinical situation. However, the pressure data is currently obtained through cardiac catheterization which is challenging because it is an invasive procedure. The shape of the right ventricle, which actually warps around the left ventricle, is complex enough to make the advancement of catheter through it into the main PA difficult. Therefore, for some subjects, all the required pressure measurements (at each of the inlet and outlets of PA) may not be obtained during their cardiac catheterization. For such subjects, the unavailable pressure data may be obtained by patient-specific hemodynamic computation.

The central idea of this chapter is to use patient-specific hemodynamics to obtain pressure and velocity fields in the arterial segment of interest and use the results to calculate the energy-
based endpoints. For such an approach, the arterial geometry will have to be patient-specific and the boundary conditions for the numerical computation will also have to come from patient-specific clinical measurements. There are few researches that use the data of complex velocity field as boundary conditions. Therefore, in this chapter as a first pass, an idealized Womersley type of velocity profile will be computed from patient-specific flow rate measurement data and used as a boundary condition in the numerical computation. In later chapters, this approach will be extended to incorporate the actual time-and spatially-varying PC-MRI velocity measurement data directly into hemodynamic computation.

4.2 Methods

The main steps in the procedure are: 1) subject selection, 2) acquisition of pressure and flow rate data for the subjects, 3) geometry reconstruction and 4) development and solution of the computational model of the arterial hemodynamics. The pressure and flow rate calculated from the numerical model were compared with measured data.

4.2.1 Study Population

The subject population for this study was selected from the Cincinnati Children’s Hospital and Medical Center (CCHMC) patient database. Two age-, sex- and size-matched subjects, one normal (Age: 4 years, Sex: male, Wt.: 20.3 Kg, BSA: 0.78 m², Stroke volume: 52 ml) and the other rTOF (Age: 5 years, Sex: male, Wt.: 16.9 Kg, BSA: 0.72 m², Stroke volume: 56 ml) were selected. Data was retrospectively analyzed from records for each of the subjects who had undergone both clinical cine phase-contrast magnetic resonance imaging (PC-MRI) and cardiac catheterization within a span of 1 month at CCHMC (Table 4.1). This study was approved by
the Institutional Review Board of CCHMC. The “normal” subject in our study had a normal RV loading along with a functioning pulmonary valve (PV; as confirmed by exam and echocardiography).

The normal subject had relatively lower average LPA flow (1.85 ml/sec) compared to his RPA (46.6 ml/sec) and MPA flows (47.5 ml/sec) as obtained from phase contrast MRI measurements. The rTOF subject had been diagnosed with TOF and underwent clinical CMR at least 3 years after undergoing rTOF surgery in their infancy, including PV transannular patching, and had essentially a non-functional PV. The PV in the rTOF subject had been previously assessed by echocardiography and was found to be non-functional, with severe pulmonary insufficiency but no stenosis. Neither of the subjects showed more than mild tricuspid regurgitation on echo.

Table 4.1: Patient demographics and clinical data.

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (bpm)</th>
<th>MRI-Cath. Time Gap (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Catheter</td>
<td>MR I</td>
</tr>
<tr>
<td>Normal: Normal RV and PV</td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td>rTOF: Abnormal RV and PV</td>
<td>102</td>
<td>100</td>
</tr>
</tbody>
</table>

4.2.2 Data Acquisition

The patient data acquired for each subject consisted of: 1) pressure data from cardiac catheterization, 2) contrast enhanced MR angiograms, and 3) velocity encoded PC-MRI for flow rate measurements at the inlet (MPA) and outlets (LPA and RPA) of the pulmonary artery.
Pulmonary artery MR angiograms. A stack of 3D MRI coronal images of the individual patient’s chest that covered segments from the main, left and the right PA branch were acquired using a Siemens 3 Tesla MRI scanner (Fig. 4.1A). This set of images was used to construct the patient specific geometry of the branch PA of the individual subjects. This image series consisted of a spatially aligned stack of coronal images of the chest. Typically, this set of images for each subject consisted of 36-48 images at uniformly spaced slice locations. Typical echo time for the image acquisition was of 1.08 sec and repetition time was 2.84 sec. The typical image resolution was 1.17mm x 1.17mm to 1.33mm x 1.33mm. The slice thickness varied from 2.2mm to 5mm. All images were 256x256 pixels in size.

PC-MRI flow imaging. Pulmonary artery flow imaging was performed using retrospective ECG-gating, through-plane velocity-encoded phase contrast technique [179-185] on Siemens 3Tesla Trio Magnet (Siemens, Inc., Malvern, Germany), with an 8-channel cardiac coil equipment. Each subject underwent their cardiac MRI via general endotracheal anesthesia with breath holding technique. Velocity encoding limits were adjusted as needed for minimal peak to avoid aliasing of phase signal. This ensured flow images without phase wrapping error. PC-MRI was performed at the mid-point of the main and each of the branch pulmonary artery with 18-22 phases at each PA site: main, left and right PA. Data computed included peak velocity, area of flow and flow rate (antegrade and retrograde) at each PA site: MPA, LPA and RPA respectively (Fig. 4.1).

Cardiac catheterization. Subjects underwent cardiac catheterization under general endotracheal anesthesia. Hemodynamic measurements were performed during the catheterization by advancement of a fluid-filled catheter (Cook Medical Inc., Bloomington, Indiana, USA) under fluoroscopic guidance into the RV and at least one of the following: main (MPA), left (LPA), or
right (RPA) pulmonary artery. Pressure variation with time at each site was recorded along with the ECG tracing on hard (paper) copy over a few consecutive cardiac cycles.

4.2.3 Analysis of Pressure and Flow Data

Flow images in the PC-MRI series were analyzed to compute flow rate via standard flow assessment techniques using semi-automated computer software QFLOW (Medis Medical Imaging Systems, Inc., Leiden, Netherlands). Peak velocity, area of flow and flow rate (antegrade and retrograde) were calculated at MPA, LPA and RPA, respectively. Since the cardiac MRI and catheterization data were acquired at separate sessions, these data sets were adjusted to account for the differences in heart rate between the two sessions. This was performed digitally based on the resident electrocardiographic (ECG) signal present in both the data sets. This process required three steps for each subject. Initially, the hardcopy catheterization data (pressure versus time curves at MPA, and branch PA, and ECG versus time) were manually digitized between two consecutive ECG R-waves, from which the heart rate interval was determined. Next, the heart rate interval was measured from the digital cardiac MRI data (flow rate versus time), which by definition is recorded starting at the onset of the ECG R-wave. Finally, the flow rate versus time data was linearly scaled in the time domain to match the cardiac catheterization time period. All digital measurements and adjustments were performed via a customized MATLAB (MATLAB, Inc., Waltham, MA) program.

4.2.4 Patient-specific Geometry Reconstruction

Patient-specific geometry of the PA of each of the subjects was reconstructed from their individual contrast-enhanced 3D angiographic MRI (Fig. 4.1A). The geometry reconstruction
was done semi-automatically using MIMICS (Materialise, Inc., Leuven, Belgium). This geometry included the main PA, with its inlet located just distal to the pulmonary valve annular region, along with nearly equal lengths of the left and right pulmonary artery branches.

The angiographic MRI series consists of a stack of coronal images of the patient’s chest that capture the PA geometry as a single snap-shot over the cardiac cycle. These images were read into MIMICS image processing and geometry reconstruction software. The software automatically computed a spatial stack of axial and sagittal slices from the input coronal slices and showed the images on the three orthogonal views (coronal, axial and sagittal) as shown in the Fig. 4.1. The branch pulmonary artery was identified on any one of the views by visual inspection. The grey scale intensity values at the pulmonary artery location in the view were used to specify a threshold range for the region growing algorithm in MIMICS. The algorithm automatically created a volume of 3D voxels that match the specified intensity threshold range (Fig. 4.1B, 4.1C, 4.1D). Disjoint voxels that were not part of pulmonary artery volume were removed, resulting in one contiguous volume of PA geometry. This resulting volume still had surface roughness at many locations that were visually inspected and manually removed from the volume. Finally a surface mesh of triangles was fitted to the volume of voxel to yield a smoothened geometry of the branch PA. The accuracy of the meshed surface was checked by projecting a sample of points on the PA boundary and by checking the projected distance to be within reasonable tolerance. This process results in boundary reconstruction of the blood flow zone without clearly defined inlet and outlet planes (Fig. 4.1E). The surface of this reconstruction was then exported as a stereolithographic (STL) file of surface triangles to define inlet and outlet surfaces and generate tetrahedral mesh in the blood flow domain (using GAMBIT, ANSYS, Inc., Canonsburg, PA).
Fig 4.1: Geometry reconstruction from the patient specific MRI images: (A) Stack of 3D MRI of subject’s chest used for PA geometry reconstruction; (B), (C), (D) show the coronal, axial and sagittal views, respectively. The PA was identified by a coloring mask specified by setting a range of grey scale value from the image. (E) The reconstructed branch PA geometry without clearly defined inlet and outlets.
4.2.5 Mathematical Model

The differential equations governing the branch PA flow along with the boundary conditions and material model for blood are presented below.

Governing equations. The branch PA hemodynamics was modeled using unsteady, laminar, incompressible flow of non-Newtonian Carreau fluid [186] with rigid arterial wall assumption.

Following the standard tensorial notation, where, \( u_i, \ i=1, 2, 3 \) are the velocity components in the direction of the unit vectors of coordinate system of the model, the continuity equation:

\[
\frac{\partial u_i}{\partial t} = 0
\]  

and the mass-momentum equations (with body force neglected):

\[
\rho \left( \frac{\partial u_j}{\partial t} + u_j u_i, j \right) = - p, i + \left[ \mu (u_i, j + u_j, i) \right]_j
\]

were numerically solved using finite-volume method. In Eq. 4.2, \( \rho \) is the density of blood taken to be 1.05 gm/cc, \( p \) is the static pressure and \( \mu \) is the shear rate (\( \dot{\gamma} \)) dependent non-Newtonian blood viscosity:

\[
\mu (\dot{\gamma}) = \mu_\infty + (\mu_0 - \mu_\infty) (I + A \dot{\gamma}^2)^n
\]

with the parameters, \( \mu_\infty = 0.0345 \) poise, \( \mu_0 = 0.56 \) poise, \( A = 10.975 \) sec\(^2\), \( n = 0.3568 \), and the shear rate \( \dot{\gamma} \) (in sec\(^{-1}\)) is,

\[
\dot{\gamma} = \sqrt{\frac{1}{2} \sum_i \sum_j \dot{\gamma}_{ij} \dot{\gamma}_{ij}}.
\]

Boundary conditions. A combination of pressure and velocity boundary condition was applied at the inlet (MPA) and outlet (LPA and RPA) cross-sections of the blood flow domain (Fig. 4.2).

No slip condition was imposed on all other boundaries in contact with the flow.
**Fig 4.2:** Geometrical reconstruction for (A) Normal and (B) rTOF subject. The main PA domain is created from STL triangles. Cylindrical extensions are created to allow for flow development. Transition piece connects the cylindrical extension to the respective non-circular inlet or outlet.

At the LPA outlet, pulsatile pressure measured using catheter was imposed as boundary condition (Fig. 4.3). It was applied as spatially uniform normal traction (but pulsatile) on the LPA outlet cross-section.

At the outlet cross-section at the MPA inlet and RPA, velocity boundary condition was applied. The velocity profiles for these boundary conditions were, Womersley profile calculated from the pulsatile flow rate measurements (Fig. 4.4) obtained using PC-MRI at these locations. The equations used for calculating the Womersley profiles from pulsatile flow rate are described in the next section.

Womersley profile is a developed flow profile. Therefore, artificial extensions were created in the direction of outward normal at the MPA and RPA cross-section so as to allow for the
flow to develop. In addition to that, Womersley profiles are defined only on a circular cross-section. Therefore, each of the extensions were of cylindrical shape of same cross-sectional area as the cross-section of the patient-specific geometry on which they were constructed. A small transition segment was added to connect the cylindrical extension to the patient-specific cross-section (Fig. 4.2).

![Graph showing LPA Pressure measured using fluid filled catheter in normal and rTOF subject.](image)

**Fig. 4.3:** LPA Pressure measured using fluid filled catheter in normal and rTOF subject.

All of the pulsatile boundary conditions, which included velocity as well as pressure, were specified as Fourier series over the cardiac cycle. The total duration of these boundary condition pulses were extended over multiple cardiac cycle periods. To obtain the necessary Fourier coefficients, the raw digitized data for pressure and flow rate was preprocessed by methods described in the previous chapter. This included synchronization of the pressure and flow
rate pulses as they were acquired during separate sessions of cardiac catheterization and magnetic resonance imaging.

**Fig. 4.4:** PC-MRI based flow rate measurement for the normal and rTOF subject at A) MPA and B) RPA. Womersley velocity profiles for velocity boundary conditions were computed from these flow rates.
**Womersley velocity profile from flow rate.** Womersley velocity profile is the velocity profile observed at a cross-section of a developed pulsatile flow of a Newtonian fluid through a straight tube of constant radius under time-varying pressure gradient. Compared with a time-varying plug profile or a time varying parabolic profile, it can be a better choice of boundary condition for hemodynamic computation involving pulsatile conditions. In Womersley flow, inertial effects are considered in addition to the viscous effects. Therefore, this profile can model local flow reversal near arterial walls when the net flow is still in the forward direction.

The original paper by Womersley [123] expressed the velocity profile in terms of the Fourier series coefficients of the pressure gradient pulse. However, a simple mathematical manipulation allows it to be expressed in terms of the Fourier coefficients of the flow rate pulse [127,130]. The velocity profile thus obtained from the Fourier series coefficients of the flow rate pulse can be used for obtaining velocity boundary conditions from flow rate. In a typical clinical scenario, the flow rate data can be obtained more easily by non-invasive means such as PC-MRI, than the pressure gradient. Measurement of pressure gradient requires simultaneous measurement of time varying pressures at two locations along the artery and is more challenging. The details of the calculations are as follows.

Using the measured flow-rate versus time data (Fig. 4.4), the flow rate $Q(t)$ is approximated by a Fourier series with its coefficients computed from a set of $M$-1 uniformly sampled values of $Q(t)$. Thus, the period $T$ of the pulse (cardiac period) is divided into $M$ equal intervals of length $\Delta t$, with $\Delta t = T/M$, and the corresponding uniformly sampled time points $t_s$ given by $t_s = s\Delta t$, $s = 0, 1, 2, \ldots, M-1$, with the corresponding sampled flow rate values as, $q_0 = Q(t_0)$, $q_1 = Q(t_1)$, $\ldots$, $q_{M-1} = Q(t_{M-1})$ respectively. Using these $M$-1 uniformly sampled values of flow rate versus time pulse, at the most $N=(M-2)/2$ harmonics of the Fourier series,
\[ Q(t) = a_o + \sum_{k=1}^{N} \left\{ a_k \cos\left(k \frac{2\pi}{T} t\right) + b_k \sin\left(k \frac{2\pi}{T} t\right) \right\} \quad (4.5) \]

can be computed, and the corresponding Fourier series coefficients, \( a_o, a_1, \ldots, a_N \) and \( b_1, \ldots, b_N \) are given by,

\[
a_0 = \frac{1}{T} \int_{0}^{T} Q(t) dt = \frac{1}{M} \sum_{s=0}^{M-1} q_s \quad (4.6a)
\]

\[
a_k = \frac{2}{T} \int_{0}^{T} Q(t) \cos(k \omega_q t) dt = \frac{2}{M} \sum_{s=0}^{M-1} q_s \cos(k \omega_q t_s) \quad (4.6b)
\]

\[
b_k = \frac{2}{T} \int_{0}^{T} Q(t) \sin(k \omega_q t) dt = \frac{2}{M} \sum_{s=0}^{M-1} q_s \sin(k \omega_q t_s) \quad (4.6c)
\]

The corresponding complex valued coefficients, \( Q_n \)'s of the complex Fourier series,

\[ Q(t) = \sum_{n=-N}^{N} Q_n e^{in\omega_q t} \quad (4.7) \]

are computed using,

\[
Q_n = \begin{cases} 
\frac{1}{2} (a_k + ib_k) & k = -n, n < 0 \\
a_0 & n = 0 \\
\frac{1}{2} (a_k - ib_k) & k = n, n > 0 
\end{cases} \quad (4.8)
\]
Table 4.2A: Fourier coefficients and Womersley numbers ($\alpha_n$) used to compute MPA and RPA flow profiles for the normal subject. Fourier coefficients expressed in polar form $2Q_n = M_n e^{i\phi_n}$. The fundamental frequency $\omega_0 = 8.49$ rad/sec and the $M_n$ values are in ml/sec.

<table>
<thead>
<tr>
<th>Harmonics</th>
<th>Frequency (rad/sec)</th>
<th>MPA (Normal)</th>
<th>RPA (Normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>$\omega = n\omega_0$</td>
<td>$\alpha_n$</td>
<td>$M_n$</td>
</tr>
<tr>
<td>0</td>
<td>0.0</td>
<td>-</td>
<td>47.42</td>
</tr>
<tr>
<td>1</td>
<td>8.49</td>
<td>0.1598</td>
<td>65.45</td>
</tr>
<tr>
<td>2</td>
<td>16.98</td>
<td>0.2260</td>
<td>42.49</td>
</tr>
<tr>
<td>3</td>
<td>25.47</td>
<td>0.2768</td>
<td>21.07</td>
</tr>
<tr>
<td>4</td>
<td>33.96</td>
<td>0.3196</td>
<td>11.46</td>
</tr>
<tr>
<td>5</td>
<td>42.45</td>
<td>0.3573</td>
<td>8.59</td>
</tr>
<tr>
<td>6</td>
<td>50.94</td>
<td>0.3914</td>
<td>8.83</td>
</tr>
<tr>
<td>7</td>
<td>59.43</td>
<td>0.4227</td>
<td>7.96</td>
</tr>
</tbody>
</table>

Table 4.2B: Fourier coefficients and Womersley numbers ($\alpha_n$) used to compute MPA and RPA flow profiles for the rTOF subject. Fourier coefficients expressed in polar form $2Q_n = M_n e^{i\phi_n}$. The fundamental frequency $\omega_0 = 10.70$ rad/sec and the $M_n$ values are in ml/sec.

<table>
<thead>
<tr>
<th>Harmonics</th>
<th>Frequency (rad/sec)</th>
<th>MPA (rTOF)</th>
<th>RPA (rTOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>$\omega = n\omega_0$</td>
<td>$\alpha_n$</td>
<td>$M_n$</td>
</tr>
<tr>
<td>0</td>
<td>0.0</td>
<td>-</td>
<td>41.84</td>
</tr>
<tr>
<td>1</td>
<td>10.70</td>
<td>0.1642</td>
<td>116.48</td>
</tr>
<tr>
<td>2</td>
<td>21.40</td>
<td>0.2322</td>
<td>40.17</td>
</tr>
<tr>
<td>3</td>
<td>32.11</td>
<td>0.2844</td>
<td>1.91</td>
</tr>
<tr>
<td>4</td>
<td>42.81</td>
<td>0.3284</td>
<td>7.02</td>
</tr>
<tr>
<td>5</td>
<td>53.51</td>
<td>0.3672</td>
<td>2.96</td>
</tr>
<tr>
<td>6</td>
<td>64.22</td>
<td>0.4022</td>
<td>1.02</td>
</tr>
<tr>
<td>7</td>
<td>74.93</td>
<td>0.4345</td>
<td>1.18</td>
</tr>
</tbody>
</table>
The equation for the Womersley velocity profile \( u(r,t) \), at a radial location \( r \) from the face centroid and at a given instant of time \( t \) is given by [127],

\[
\begin{align*}
\frac{Q_0}{\pi R^2} & \left( 1 - \frac{r^2}{R^2} \right) + \sum_{n=1}^{N} \text{Real} \left\{ \frac{2Q_n}{\pi R^2} \left[ 
\begin{array}{c}
\frac{J_0 \left( \alpha_n \frac{r^{3/2}}{R} \right)}{1 - \frac{2J_1 \left( \alpha_n \frac{r^{3/2}}{R} \right)}{i^{3/2} \alpha_0 \left( i^{3/2} \alpha_n \right)}} 
\end{array}
\right] e^{i\alpha_n t} \right\} 
\end{align*}
\]

(4.9)

where, \( \text{Real}(\cdot) \) is the real part of a complex number, \( J_0 \) and \( J_1 \) are the Bessel function of first kind of order 0 and 1 respectively [187], and \( \alpha_n \) is the non-dimensional Womersley number defined by,

\[
\alpha_n = R \sqrt{\frac{2m \rho}{T \mu}} 
\]

(4.10)

with \( T \), \( R \), \( \rho \) and \( \mu \) being the period of the cardiac cycle, artery radius, blood density and viscosity respectively and \( N \) representing the number of harmonics used to fit the experimental flow rate versus time data. The Fourier series coefficients for the first six harmonics of the flow rate pulse MPA and the RPA along with the corresponding Womersley number are presented in Tables 4.2A and 4.2B for the normal and the rTOF subject respectively. The formula for \( u(r,t) \) given by Eq. 4.9 is implemented in the finite volume solver (FLUENT) as a boundary condition using a user defined subroutine.

4.2.6 Numerical Computation

Mesh generation. The PA geometry reconstructed in MIMICS was imported into GAMBIT (ANSYS, Inc., Canonsburg, PA) for mesh generation as an STL file of surface triangles. This reconstructed geometry did not have any planar inlet and outlet cross-sectional surfaces. The
locations and orientations inlet and outlet surfaces were obtained from the PC-MRI for velocity measurement at the MPA, LPA and RPA. Planes for the MPA inlet, and the LPA and RPA outlets, were created in GAMBIT by specifying the respective plane normal and location. Using the planes normal to the flow direction at the respective inlet and outlets, planar inlet and outlet surfaces were created in the flow volume. The region of the PA bounded by the inlet and outlet planes was meshed with linear tetrahedral elements of size 1 mm, resulting in typically a range of 150K-200K elements (Fig. 4.2). A finer mesh with elements in the range of 650K elements was used to check that the computed solution did not vary with mesh size. The non-circular inlet and outlet surface of the PA region were extruded to about 2-3 mm in the outward normal direction and also transitioned to a circular cross-section. The circular surface of the resulting transition piece was further extruded in the outward normal direction by 20 times the diameter to create cylindrical extensions (Fig. 4.2). Velocity boundary conditions were applied at the end of the cylindrical extensions.

**Numerical solution of the flow equations.** The solution for the governing equations using above boundary conditions were performed in finite volume solver FLUENT (ANSYS, Inc., Canonsburg, PA) using an unsteady laminar flow model. The peak Reynolds number for our flow was in the laminar range. Thus an unsteady laminar flow model was used. Considering such flows, we do not rule out possible local shear layer instabilities and organized vortical cells at the locations of flow reversal. However, we will not categorize these as turbulent flow having random fluctuations in the PA.

The computations were performed for three cardiac cycles. Convergence of the numerical solution for each case was verified by performing mesh convergence study by reducing the
mesh size from 1 mm to 0.5 mm and also by reducing the time steps from 0.001 sec to 0.0005 sec [188]. The flow rates and pressures from mesh convergence computations were verified to be between 1-5%. More specifically, the maximum difference in MPA pressure between results from computations with finer and the coarser mesh was found to be 3.4%.

The numerical computation was used to obtain velocity at LPA and pressures at RPA and MPA. The velocity field at LPA was used to compute LPA flow rate which was compared with the flow rate obtained from PC-MRI measurement for validation. From the result of numerically computed flow rate variation with time, the forward flow volume \( Q_f \) and reverse flow volume \( Q_b \) over one cardiac cycle were also computed. The regurgitant fraction \( f \) was calculated as the ratio of \( Q_b \) to \( Q_f \), expressed in percentage. Likewise, numerically computed MPA and RPA pressure were compared with the respective catheter measurements at those locations.

4.3 Results

Results are presented for the forward and reverse flow volume, \( Q_f \) and \( Q_b \), respectively, and regurgitant fraction \( f \) at the MPA, LPA and RPA. Since MPA and RPA are the cross-sections for applied velocity boundary condition, \( Q_f \), \( Q_b \), and \( f \) at MPA and RPA were calculated from PC-MRI data itself. The numerically computed flow rate at LPA was compared with the corresponding PC-MRI measurement. The numerically computed pressure at MPA and RPA was validated with the corresponding catheter measurement.

4.3.1 Regurgitant Fraction at MPA and RPA

The regurgitant fractions at the MPA and RPA for both the normal and rTOF subjects are presented in Table 4.3. These were obtained from the PC-MRI measurements of the flow rate
(Fig. 4.3A and 4.3B). The MPA regurgitant fraction ($f$) of the normal subject was 1.5% and that of the rTOF was 33.2%. The RPA, regurgitant fractions was 0% for the normal subject and 21.7% for the rTOF subject. The large value of the regurgitant fraction for the rTOF patient is expected; for example, similar $f$ values at MPA have been reported by other researchers [189].

Table 4.3: Forward flow volume $Q_f$, and back flow volume $Q_b$, per cardiac cycle calculated from PC-MRI flow rate measurement at MPA and RPA. Regurgitant fraction (%) $f = 100 \times \frac{Q_b}{Q_f}$.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th></th>
<th>rTOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_f$</td>
<td>$Q_b$</td>
<td>$f$ (%)</td>
<td>$Q_f$</td>
</tr>
<tr>
<td>MPA</td>
<td>35.0</td>
<td>0.50</td>
<td>1.5</td>
</tr>
<tr>
<td>RPA</td>
<td>34.4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

4.3.2 Validation of LPA Flow Rate

For both the subjects, the LPA flow rate from numerical computation is compared with the PC-MRI measurement in Fig. 4.5. The values of $Q_f$, $Q_b$ and the regurgitant fraction ($f$) are tabulated in Table 4.4 for both the subjects. In Table 4.4, the row designated numerical provides the $Q_f$, $Q_b$ and $f$, obtained from numerically computed flow rate versus time variation; the row designated measurements presents the values obtained from PC-MRI measurements.

For the normal subject, the forward flow volume ($Q_f$) per cardiac cycle at LPA, obtained from numerical computation was 6.52 ml compared to 6.09 ml from PC-MRI measurement (7% error). The reverse flow ($Q_b$) at LPA, obtained from numerical computation was 5.83 ml compared to 4.72 ml from PC-MRI (23% difference). The value of LPA regurgitant fraction ($f$) from
numerical computation was 89% compared to 77.5% from the PC-MRI data (15.5% higher). Although this high value of LPA regurgitant fraction for the normal subject who has a functioning pulmonary valve is counter intuitive, it is in agreement with results reported by other researchers [189,190].

**Fig 4.5**: Validation of the computed flow rates at LPA with the PC-MRI measurement for both the normal and rTOF subject.

The flow rate results from numerical computation are compared with PC-MRI measurements in terms of the minimum, maximum and the time averaged values over the cardiac cycle. For the normal subject, the maximum value of the LPA flow rate from numerical computation was 50.5 ml/sec compared with 45.2 ml/sec from PC-MRI measurement (Fig. 4.5). The mini-
The minimum value from numerical computation was -41.8 ml/sec, compared with -22.5 ml/sec from PC-MRI data. The time averaged LPA flow rate from the numerical computation was 0.92 ml/sec, compared with 1.85 ml/sec from PC-MRI measurement.

**Table 4.4:** Comparison of the values of $Q_f$, $Q_b$ and regurgitant fraction $f$ at LPA, obtained from numerical computation and from PC-MRI measurements. Regurgitant fraction (\%) $f$ defined as $100 \times Q_b / Q_f$.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>rTOF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$Q_f$ (ml)</td>
<td>$Q_b$ (ml)</td>
</tr>
<tr>
<td>Numerical</td>
<td>6.52</td>
<td>5.83</td>
</tr>
<tr>
<td>Measured</td>
<td>6.09</td>
<td>4.72</td>
</tr>
<tr>
<td>Error (%)</td>
<td>7.0</td>
<td>23.0</td>
</tr>
</tbody>
</table>

For the rTOF subject, the numerically computed forward flow $Q_f$ at the LPA per cardiac cycle was 23.1 ml compared with 14.3 ml from PC-MRI measurement (60% difference). The reverse flow volume $Q_b$ at the LPA from computation was 9.96 ml compared with 5.65 ml from PC-MRI (75% difference). Therefore, the numerically computed LPA regurgitant fraction was 43%, which differed by 8.7% from value of 39% obtained from PC-MRI. The time averaged LPA flow rate from the numerical computation was 22.4 ml/sec compared with the 14.6 ml/sec from PC-MRI data. The peak flow rate from the numerical computation was 131.8 ml/sec, and that from PC-MRI was 72.7 ml/sec. The minimum value of LPA flow rate from numerical computation was 80.3 ml/sec, whereas, the value obtained from PC-MRI measurement was 63 ml/sec.
4.3.3 Validation of Pressure

The numerically computed MPA variation with time for the normal subject is shown in Fig. 4.6A; the RPA pressure for the same subject is shown in Fig. 4.6B. The time averaged values over one cardiac cycle are presented in Table 4.5. The pressure measurement for the rTOF subject was only available at LPA. Therefore, the validation of numerical computed MPA and RPA pressure with catheter data was not possible.

**Table 4.5:** Validation of the numerically computed time averaged MPA and RPA pressure with measured data for the normal subject.

<table>
<thead>
<tr>
<th></th>
<th>MPA Pressure (mmHg)</th>
<th>RPA Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Min</td>
</tr>
<tr>
<td>Numerical</td>
<td>16.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Measured</td>
<td>16.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Error (%)</td>
<td>1.0</td>
<td>-6.0</td>
</tr>
</tbody>
</table>

The MPA pressure variation with time from numerical computation follows the same trend as the one obtained from catheter measurement (Fig. 4.6A). The time-averaged pressure of 16.5 mmHg from numerical computation was within 1% of the time average value of 16.3 mmHg from catheter measurement (Fig. 4.6A; Table 4.5). The maximum value of the computed MPA pressure over the cardiac cycle was 25.4 mmHg, which was 10% higher than the maximum value from catheter data (23 mmHg). Likewise, the minimum value of the MPA pressure from numerical computation, 8.7 mmHg, was within 6% of the minimum value of 9.3 mmHg from
measurement (Fig 4.6A). A sudden drop in MPA pressure seen in Fig 4.6A at time 0.38 sec was the result of sudden deceleration of flow at the point of closing of the PV for the normal subject.

![Graph A](image1)

**Average** = 16.5 mmHg (Computed)

**Average** = 16.3 mmHg (Measured)

![Graph B](image2)

**Average** = 14.6 mmHg (Measured)

**Average** = 13.8 mmHg (Numerical)

**Fig. 4.6:** Comparison of the numerically computed pressure with one obtained by catheter measurement, at (A) MPA and (B) RPA of the normal subject. The horizontal lines depict the time averaged values.
The numerically obtained RPA pressure versus time along with the corresponding catheter measurement is shown in Fig. 4.6B. As with the MPA pressure (Fig. 4.6A), the RPA pressure from the numerical computation and the catheter measurement follow a similar variation with time. The time average values are given in Table 4.5. They are: 13.8 mmHg from the numerical computation and 14.6 mmHg from catheter measurement (6% lower). Over the cardiac period, the numerical computation showed a peak RPA pressure of 22.7 mmHg, which was 17% higher than 19.4 mmHg obtained from measurement. Similarly, the minimum RPA pressure differed by 20% between 7.1 mmHg from numerical computation to 8.9 mmHg from catheter measurement.

4.4 Discussion

This study validates that numerical computation coupled with clinically acquired cardiac MRI and catheter data can be used to characterize the pulmonary arterial hemodynamics in both normal subjects and subjects with pulmonary insufficiency. The geometry reconstructed from patient’s angiographic MRI can be used for patient-specific hemodynamic computation; the results of which can be validated with measurements. This method is clearly more desirable over geometry reconstruction approach that involves artificial constructs which extrude assumed cross-sectional shapes along a path approximated from arterial centerline.

In the proposed methodology, the use of Womersley type velocity boundary conditions is more realistic for pulsatile flows as it accounts for the local flow reversal near the arterial walls; a phenomena noted in experimental in-vitro pulsatile flow studies in the branch PA [191-193]. Simplistic velocity profiles, such as, spatially uniform or parabolic profiles, do not account for local flow variations. Although long extensions have been used in the computational model,
they may not be required because the Womersley profile represents a developed flow condition. With non-Newtonian fluid, as in the proposed model, the Womersley profile will adjust to developed flow profile over a much shorter length compared to a parabolic or uniform profile, thus requiring much shorter extensions.

The graph of MPA flow rate with time, for rTOF subjects (Fig. 4.3) shows a steeper slope in the early systolic phase than the one for the normal subject. This implies a higher rate of acceleration in the flow rate in the case of the rTOF subject compared to the normal one. This could be speculated to be due to the presence of the functioning PV in the normal subject that offers hindrance to the flow acceleration.

The MPA regurgitant fraction for the normal subject (1.5%) was much lower in value than that of the rTOF subject (33.2%; Table 4.3). This is a well-known result and is obviously due to the functioning PV in the normal subject that prevents the backward flow of blood at MPA. However, the high LPA regurgitant fraction for the normal subject as evident from the numerical computation as well as PC-MRI measurement (Table 4.4) is not intuitive. The high value of LPA regurgitant fraction has indeed been reported by other researchers as well [189,190].

The difference between the results of numerical computation and PC-MRI measurement for forward flow volume (Qf), back-flow volume (Qb) and regurgitant fraction (f) at LPA require explanation (Table 4.4). The percentage differences reported in the Table 4.4, for Qf, Qb and f at LPA are affected by several factors. They include, smaller values of respective flow volumes (which make percentage differences large), flow imbalance between the inlet at MPA and outlets at LPA and RPA that is inherent in the PC-MRI measurement itself, and also the inaccuracy in the PC-MRI flow imaging in the diastolic stage of cardiac cycle (because of low flow velocity).
For example, it can be seen from Table 4.4 that for the normal subject, LPA $Q_t$ from numerical computation (6.52 ml) differed by only 7% from the value obtained from PC-MRI (6.09 ml). Whereas, in the diastolic phase, the LPA $Q_b$ from numerical computation (5.83 ml) differed by 23% from the value obtained from PC-MRI (4.72 ml). In this patient, the measured LPA flow rate was significantly lower than MPA and RPA flow rate. Thus, even though there was a significant agreement in LPA flow results between numerical and PC-MRI values in the systolic phase, the difference in the diastolic phase resulted in marginal difference in average flow rate (0.92 ml/sec from computation versus 1.85 ml/sec measured). It is also well known that PC-MRI can be less accurate in registering reverse flow across the measurement plane. Hence, further attention is needed for accurate flow measurement.

For the rTOF subject, Fig. 4.5 shows that the numerical results capture the time trend in the LPA flow rate. The regurgitant fraction ($f$) only shows a difference of 8.7%, showing that the flow rate trend is captured by the numerical calculation for the rTOF subject. The reason for this difference between the computed and measured LPA flow rate for the rTOF subject could be attributed to excessive regurgitation at MPA (MPA regurgitant fraction $f=33.2\%$ for the rTOF, versus 1.5% for the normal; Table 4.3).

Another potential contributor to this discrepancy can likely be due to the compliance effect of the PA wall (the functioning PV acts like a stiffener for the PA wall at the MPA), necessitating the need for a blood-PA wall interaction calculation and a more accurate velocity field estimation based on phase contrast MRI.

The non-simultaneous acquisition of pressure and flow rate data is one limitation of this study. Therefore, the pressure and the flow rate pulses were synchronized "offline" using the ECG wave. This can potentially introduce errors due to adjustment and scaling of the time peri-
ods of the pressure and flow rate pulse. Since, there are no clinical protocols to simultaneously perform cardiac catheterization and PC-MRI in a clinical setting, therefore synchronization using ECG is a reasonable approach.

The use of Womersley velocity profile for velocity boundary condition is an improvement over parabolic or plug profile in the sense that it incorporates flow reversal near arterial walls. However, it does not precisely capture the velocity field in an arterial cross-section. Both phase contrast MRI measurements [190], and in-vitro branch PA pulsatile flow studies [192,194] report asymmetry in velocity field near the pulmonary valve, whereas, Womersley flow profile is axially symmetric profile. A direct use of phase contrast MR data may provide better results, as it will be able to account for asymmetry as well as flow reversal near the PA walls.

Finally, in this pilot study, since our patient sample was retrospectively selected, we are limited by the availability of the measured data for our subjects. For example, for our rTOF subject, only the LPA pressure measurement was available, and thus validation of the numerical results for MPA and RPA pressures with the respective pressures measurements was not possible.

4.5 Conclusion

In this chapter, a methodology was developed and tested for performing a patient-specific hemodynamic calculation to obtain pressure and velocity in the branch PA using clinical data. The PA geometry of the blood flow domain was reconstructed from patient’s angiographic MRI. The velocity boundary conditions were computed from patient’s PC-MRI in form of Womersley profile. The pressure boundary condition was used at only one of the outlets of the flow domain. The results of flow rate and pressure obtained from the hemodynamic computation were validated with actual measurements.
The methodology developed in this chapter demonstrated the proof of concept to calculate the energy-based endpoints for subjects who only had partial pressure measurements in their pulmonary artery. Specifically, these subjects either did not, or could not have the complete pressure measurements at all the inlets and outlets of their branch pulmonary artery. Therefore, in the end, these numerically computed pressure and velocity data was used to calculate the values of energy-based endpoints. It may also be emphasized that the technique developed also has a broader application in the understanding of PA hemodynamics through numerical methods.

The results of the calculation of patient-specific values of the energy-based endpoints using the pressure and flow rate obtained from the numerical computation will be subject of next chapter. In subsequent chapter, the methodology will be improved by performing hemodynamic computation using the time- and spatially- varying velocity data directly obtained from PC-MRI.
Chapter 5

Results: Energy-Based Endpoints

5.1 Introduction

In the previous chapters, energy-based hemodynamic endpoints were developed from basic fluid mechanics. These endpoints were stroke work, energy transfer ratio and energy loss in the branch pulmonary artery. As a part of this research, methodologies were developed to calculate these endpoints from clinically measured pressure, and imaging data from MRI. As was mentioned in Chapter 1, the overall objective of this research was to test the applicability of these endpoints to delineate the performance of the right ventricle of a normal subject from that of a subject with pulmonary insufficiency.

This chapter presents the results of applying these endpoints to a sample of human subjects. This sample included both normal subject and a subject with pulmonary insufficiency. Although, for this pilot research, the size of the subject sample was small, the subjects were carefully selected by matching their physiological characteristics such as age, weight, stroke volume, etc. The underlying assumption was that, it was reasonable to qualitatively compare the energy-based endpoints for subjects with similar physiological characteristics.
The results presented here constitute the outcome of the research work undertaken to accomplish Specific-Aims 1 and 2 described in Chapter 1. This involved calculation of right ventricular stroke work, energy transfer ratio at the main pulmonary artery and energy loss calculation in the branch pulmonary artery. The calculations were performed using the procedure developed in this research, as described in Chapter 3. For some of the subjects, not all of the pressure and flow rate measurements needed for energy transfer ratio and energy loss calculations were available. Therefore, the missing measurements were obtained using patient-specific hemodynamics described in chapter 4.

5.2 Subject Population

The subject population for this study was selected after retrospectively analyzing the patient records from Cincinnati Children’s Hospital and Medical Center (CCHMC) patient database. This pilot group of subjects constituted three age-, size-, and gender-matched subjects who had undergone both clinical cardiac MRI and catheterization within a span of 1 month at our center (Table 5.1). The physiologic and demographic data for the subjects is provided in Table 5.1. The Institutional Review Board of our hospital approved the study.

The subject data was stratified based on the condition of the RV and the functioning state of the PV. More specifically, whether the RV condition was normal or abnormal, and whether the PV functioned normally or abnormally in the subjects. Based on these conditions, three groups were identified (Table 5.1, Fig. 5.1): “Normal”, repaired tetralogy of Fallot, “rTOF” and “Intermediate.” The “normal” subject had normal RV loading with normal PV function (as confirmed by exam and echocardiography). The rTOF subject had infantile transannular patch TOF
repair surgery, and had RV volume overloading due to a non-functional PV with severe pulmonary insufficiency. The rTOF subject did not suffer from severe pulmonary stenosis, as confirmed by echocardiography. The “intermediate” subject had RV volume overload due to a large atrial septal defect and partial anomalous pulmonary venous return, but had normal PV function (as confirmed by exam and echocardiography). Only stroke work was calculated for this subject. None of the subjects showed more than mild tricuspid regurgitation on echocardiography, and all had normal right and left ventricular ejection fraction on cardiac MRI.

**Fig. 5.1:** Schematic diagram of the heart of (A) rTOF subject, (B) normal subject and (C) intermediate subject. The rTOF subject (A) has defective PV and overloaded RV because of back flow. The normal subject (B) has functioning PV and normal RV. The intermediate subject (C) suffers from a partial anomalous PV return and thus has an overloaded RV but functioning PV.
Table 5.1: Patient demographics and clinical data.

<table>
<thead>
<tr>
<th></th>
<th>Age (year)</th>
<th>Height (m)</th>
<th>Weight (Kg)</th>
<th>BSA (m²)</th>
<th>Heart rate (bpm)</th>
<th>MRI-Cath. Time Gap (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal:</td>
<td>4</td>
<td>1.11</td>
<td>20.3</td>
<td>0.78</td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td>Normal RV and PV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rTOF:</td>
<td>5</td>
<td>1.07</td>
<td>16.9</td>
<td>0.72</td>
<td>102</td>
<td>100</td>
</tr>
<tr>
<td>Abnormal RV and PV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate:</td>
<td>5</td>
<td>1.05</td>
<td>16.6</td>
<td>0.68</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>Abnormal RV, Normal PV</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

5.3 Data Acquisition

For each of the subjects in the sample, three sets of data were acquired. These included:

1) RV volume, 2) flow rates at the inlet and outlets of PA, and 3) pressure data in the RV as well as in PA at one or more of its inlet or outlets. Patients underwent cardiac MRI from which RV volume and pulmonary arterial flow rates were obtained. The flow rate data was obtained at the inlet at the main PA as well as the outlets at the right and the left PA. Pressure data was acquired in the RV and at one or more locations of inlet or outlets of the branch PA.

5.3.1 Cardiac MRI

Clinical cardiac MRI studies were performed on a clinical 3 Tesla Siemens Trio Magnet (Siemens, Inc., Malvern, Germany) with an 8-channel cardiac coil. All subjects underwent their MRI via general endotracheal anesthesia with breath holding technique, which is a standard clinical practice.

MR based Ventricular Volumetry. Functional imaging for RV volume and function assessment was performed using retrospective ECG-gating, segmented Steady State Free Precession (SSFP)
technique after localized shimming and/or frequency adjusting. Subjects were breath-held according to their tolerance level. For those subjects who could not adequately hold their breath, a free breathing technique with multiple-signal-averaging was used. Standard imaging included a short axis stack of cine SSFP images from cardiac base to apex; the short axis was prescribed as the perpendicular plane to the left ventricular long axis in 2 and 4 chamber views as previously described[195-197]. Typical scan parameters included FOV = 32-38 cm, slice thickness = 5-6 mm, gap = 1-2 mm, NEX = 2 (breath hold; 4-5 for free breathing), TE/TR = 1.4/2.8, in-plane resolution = 1.2-2.2 mm. A minimum of 12 slices were performed, with 20 phases/slice. The typical temporal resolution of the cine SSFP images was 30-40 ms, adjusted according to the patient’s heart rate and ability to breath-hold. The RF flip angles were set between 50°-70° dependent on the patient weight, height and the SAR level.

Pulmonary Artery Flow Imaging. Pulmonary Artery Flow Imaging was performed using retrospective ECG-gating, through-plane velocity-encoded phase contrast MRI technique (PC-MRI) [179,182,185,198]. Appropriate breath-holding procedures [199] were followed as stated in the previous section. Typical scan parameters were similar to that described above. Velocity encoding limits were adjusted as needed for minimal peak to avoid aliasing of phase signal. PC-MRI was performed at the mid-point of the main and each branch pulmonary artery prescribed from preceding anatomical axial double inversion recovery images, with 18-22 phases at each site.

5.3.2 Cardiac Catheterization

Subjects underwent clinical cardiac catheterization using standard pediatric cardiac catheterization techniques while under general endotracheal anesthesia. Hemodynamic measurements were performed during the catheterization by advancement of a fluid-filled catheter (Cook Medi-
cal Inc., Bloomington, Indiana, USA) under fluoroscopic guidance into the RV and at least one of the following: main (MPA), left (LPA), or right (RPA) pulmonary artery. Pressure variation with time over the complete cardiac cycle at each site was recorded along with the ECG tracing on hard (paper) copy.

5.4 Calculation of Energy-Based Endpoints

The details of the methodologies for the calculation of the energy-based endpoints: stroke work, energy transfer ratio and energy loss have been provided in Chapter 3. The clinically obtained pressure and imaging data was analyzed by using the methodologies described there. Right ventricular volume and pulmonary arterial flow rate over the cardiac cycle were obtained from the MR imaging data. Co-registration of the RV pressure and RV volume as well as the respective PA flow rate and the corresponding pressure measurements was performed as described in the section 3.3.5.

The RV stroke work was calculated using Eq. 3.6. The energy transfer ratio and energy loss in the branch PA were calculated using Eq. 3.9 and 3.11, respectively. For the rTOF subject pressure measurement in the MPA and RPA was not performed. Therefore, the pressure variation over the cardiac cycle in the MPA and RPA was obtained by numerical computation using the patient-specific PA geometry. This procedure is described in detail in Chapter 4.

5.5 Results: Right Ventricular Stroke Work

The three subjects in our study had similar mean values for age (4.67 years), body surface area (0.73 m²), and weight (19.2 Kg), as shown in Table 5.1. Their RV pressure and RV volume as a function of time are compared in the sections below.
5.5.1 RV Pressure and Volume Characteristics

The variation of the RV pressure and volume over one cardiac cycle for each of the subjects is shown in Fig. 5.2. The x-axis of the graphs represent time duration; whereas, the data for pressure and volume are plotted on the two opposite y-axes of the same figure. The peak end-diastolic RV volume of the rTOF subject, 118.6 ml, is almost 40% higher than that of the normal subject (84.4 ml). This difference in the RV volume is striking because the two are of comparable physiological characteristics such as age, body surface area (BSA), and net stroke volume (SV; refer Table 5.2). This illustrates the inherent RV volume overloading in rTOF due to pulmonary insufficiency.

The RV pressure for the normal subject (Fig. 5.2A) ranges from a maximum value of 25 mmHg to a minimum value of 0.4 mmHg, whereas the values for the rTOF subject (Fig. 5.2B), RV pressure ranges from a maximum of 30 mmHg to a minimum of 2.0 mmHg. Despite the presence of the dysfunctional PV, both the peak and mean RV pressures are higher in the rTOF subject as compared to the normal subject.

The volume versus time relationship for the normal subject (Fig. 5.2A) shows that at the start of the systole (t = 0 sec), the slope of the tangent to the RV volume versus time curve is almost zero, whereas the RV pressure versus time curve (Fig. 5.2A) shows a rapid build up of the RV pressure. This rapid build-up of RV pressure over the duration when the RV volume change is minimal is the closest the RV comes to a true isovolumic contraction phase [200,201]. During this “near-isovolumic” RV contraction phase, both the RV inlet and outlet valves, i.e. the tricuspid valve (TV) and the PV, respectively, are closed. As a result, the contraction of the RV does not significantly change the RV volume. This represents the right lower quadrant of the RV pressure-volume curve in Fig. 5.3. In contrast, for the rTOF subject (Fig. 5.2B), the slope of the
Fig. 5.2: Variation of RV pressure and volume with time for (A) the normal subject, (B) for the rTOF subject and (C) for the intermediate subject. It may be noted that RV of the rTOF subject operates at higher average pressure and is volume overloaded.
RV volume versus time curve at the start of the systole (t = 0 sec) is not horizontal but instead is distinctly downward.

In other words, in the rTOF case, there is an immediate and significant drop in RV volume with the initiation of the contraction of the RV during the “near-isovolumic” contraction phase of the RV as described above. Thus, this data shows that the rTOF subject (with abnormal RV and PV) has a much greater drop in volume during the “near-isovolumic” contraction phase than does a normal subject.

Figure 5.2C shows the RV pressure and volume variation with time for the intermediate subject (Fig. 5.1). The peak pressure and peak volume are 26.6 mmHg and 111.8 ml respectively and fall somewhere between the rTOF and the normal subject (Table1). The volume overloading is evident from the pressure volume curve (Fig. 5.2C) compared with that of rTOF and the normal subject (Fig. 5.2A, 5.2B). The extent of volume overloading is lower than our rTOF subject.

5.5.2 RV Pressure-Volume Loops and RV Stroke Work Calculations

The pressure-volume loop for each of the subjects is shown in Fig. 5.3. It is clear from the figure that the pressure-volume loop for the rTOF subject is shifted rightward and upward of the one for the normal subject. This is consistent with the observation of higher RV volume and pressure in the RV of the rTOF subject. The nearly vertical segments of the pressure volume curve of the normal subject (Fig. 5.3) correspond to the isovolumic contraction and relaxation stages of the RV. As seen in the figure (Fig. 5.3), the pressure-volume loop of the normal subject has a much noticeable isovolumic contraction and relaxation phase as compared to that of the rTOF subject.
Table 5.2: RV peak pressure, volume, stroke volume and computed RV stroke work (SW) and BSA indexed stroke work (SW/BSA).

<table>
<thead>
<tr>
<th></th>
<th>Stroke Volume (ml)</th>
<th>Max. RV Pressure (mm Hg)</th>
<th>Max. RV Volume (ml)</th>
<th>SW (J)</th>
<th>SW/BSA (J/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: Normal RV &amp; PV</td>
<td>52.0</td>
<td>25.0</td>
<td>84.4</td>
<td>0.115</td>
<td>0.147</td>
</tr>
<tr>
<td>rTOF: Abnormal RV &amp; PV</td>
<td>56.4</td>
<td>30.0</td>
<td>118.6</td>
<td>0.078</td>
<td>0.109</td>
</tr>
<tr>
<td>Intermediate: Abnormal RV, Normal PV</td>
<td>70.3</td>
<td>26.6</td>
<td>111.8</td>
<td>0.083</td>
<td>0.123</td>
</tr>
</tbody>
</table>

The RV stroke work that pushes the blood into the PA is calculated by computing the area enclosed by the PV loop. The absolute values and the BSA normalized values of the RV stroke work are shown in Table 5.2. The RV stroke work for the normal subject was 0.1149 J and that for the rTOF subject was 0.0782 J. For our subjects (with similar age, BSA, and stroke volume), the magnitude of stroke work as well as the BSA-indexed stroke work follow a similar trend (Table 5.2).

As shown in Fig. 5.3, the pressure-volume loop for the intermediate subject also falls in between the rTOF and the normal subject, and hence the computed stroke work (0.8365 J) follows the same trend. Fig. 5.3 shows that the intermediate subject has a volume overloaded RV with patterns of filling that mirror rTOF, and yet operates at a relatively normal operating pressure (approx. 27 mmHg). As such, the increased pressure in rTOF RV is the result of regurgitant backflow from the PA. Interestingly, the quadrant of this PV loop between end systole and end diastole does not remain isovolumic. The reasons for these are unclear. It may however be noted that investigations by other researchers have shown that the RV contraction and relaxation is never truly isovolumic [201,202]. More importantly, Fig. 5.3 shows that, despite operating
with an abnormally higher volume than the normal subject RV, the intermediate subject RV does not operate at higher pressure than the normal subject RV.

**Fig. 5.3:** Right ventricular PV diagram for the normal, the rTOF and the intermediate subject. The RV of the normal subject is able to perform higher stroke work than that of the rTOF subject in spite of operating at lower average pressure. PV loop for the rTOF subject is shifted to right because of volume overloading. The SW value for the intermediate subject falls in between the normal and the rTOF subject.

### 5.6 Results: Total Blood Flow Energy at MPA

The variation of the rate of energy transferred to the blood was computed using Eq. 3.6 at the MPA over one cardiac cycle is shown in Fig. 5.4. The differences in the duration for different subjects are due to small differences in their heart rates. The point, $t = 0\text{ sec.}$, in Fig. 5.4 corresponds to the start of the systole, i.e. the start of the isovolumic contraction phase of the RV. The rate of energy transfer to the blood by the RV is not uniform over the entire cardiac cycle.
(Fig. 5.4). It increases with the contraction of the RV muscles during the systole and then decreases during the diastole.

**Fig. 5.4:** Comparison of the rate of total energy output at the MPA for the normal, the rTOF and the intermediate subject. Power rate has a large negative component for rTOF subject as a result of high MPA regurgitation because of dysfunctional PV that results in the loss of power to the forward flow over the complete cardiac cycle.

The positive portion of the energy curve is associated with the net forward flow of blood, away from the RV and into the PA. In contrast, the negative portion is associated with the back flow of the blood from the PA back into the RV. The kinetic energy contribution to the total energy rate ($\dot{E}_m$) at the MPA was insignificant compared to the pressure-flow component of the total energy transfer rate. For example, for the rTOF subject, the peak kinetic energy transfer rate was 0.013 J/sec compared to 0.4 J/sec (an order of magnitude difference) for pressure-flow energy transfer rate. Therefore, the simplification of the velocity field with an average velocity vector did not significantly change the calculation of energy computed using Eq. 3.6.
The rTOF subject also shows a significant negative contribution to the rate of energy transfer to the blood at MPA by the RV (Fig. 5.4). This negative contribution is associated with the back-flow of blood from the PA into the RV due to regurgitation resulting from the dysfunctional pulmonary valve. The rate of forward energy transfer (Eq. 3.6) at the MPA for the normal subject was found to peak at 0.623 J/sec, and that of the rTOF subject was 0.408 J/sec. The peak negative rate of energy transfer for the rTOF subject was -0.3653 J/sec, as opposed to -0.0686 J/sec for the normal subject. This is directly attributed to the degree of pulmonary insufficiency present in the subjects: very high for the rTOF subject; whereas, insignificant in the normal one. The time averaged value of the energy transfer rate over one cardiac cycle ($\overline{E_{net}}$) was 0.07 J/sec for the rTOF subject, compared to 0.17 J/sec for the normal subject.

**Fig. 5.5:** Comparison of stroke work and net energy transfer to the blood at MPA for normal and rTOF subject.
As mentioned above, the net energy transferred to the blood at the MPA over one cardiac cycle can be broken down into two components: one, associated with the forward flow, and the other associated with the reverse flow. The net energy associated with the forward and reverse flow for the normal subject was 0.124 J and 0.002 J, respectively. The same values for the rTOF subject were 0.085 J, for forward flow and 0.044 J, for the reverse flow. The net energy transferred at the MPA over one cardiac cycle, $E_{net}$, was computed to be 0.121 J for the normal subject and 0.044 J for the rTOF subject. The energy transfer ratio $e_{mpa}$, was 1.06 for the normal subject and 0.56 for the rTOF subject, indicating significant differences in efficiency for the rTOF RV compared to the normal RV.

The variation of the energy transfer rate at the MPA for the intermediate subject (Fig. 5.4) also is in between the normal and the rTOF subject. The minimum and the maximum values for the energy transfer rate being 0.033 J/sec and 0.482 J/sec, respectively. The graph for energy rate has no negative contribution, because the presence of the functioning PV prevents the back flow of the blood into the RV (Fig. 5.4). The time averaged energy transfer rate over one cardiac cycle ($\bar{E}_{net}$) was calculated to be 0.198 J/sec. As was noted earlier, the RV of the normal subject RV operates at a lower pressure than that of the rTOF subject. Therefore, we conclude that the increased pressure in the rTOF RV is necessary to overcome the loss of energy resulting from the back flow and regurgitation because of the incompetent PV.

### 5.7 Results: Energy Loss in Pulmonary Artery

The rate of energy-loss in the branch PA is shown in Fig. 5.6. The total energy of the blood has two components: 1) pressure-flow component and 2) kinetic energy component.
Therefore, the energy loss between the inlet and outlet can also be separated into these two

\[
\begin{align*}
\text{Average} &= 0.065 \text{ J/sec} \\
\text{Average} &= 0.038 \text{ J/sec}
\end{align*}
\]

\((\text{rTOF})\)

\[
\begin{align*}
\text{Average} &= 0.04 \text{ J/sec} \\
\text{Average} &= 0.02 \text{ J/sec}
\end{align*}
\]

\((\text{Normal})\)

**Fig. 5.6:** Variation of the rate of A) pressure-flow energy loss and B) total energy loss in the branch PA over one cardiac cycle. (Note that the cardiac cycle period was different for the two subjects)
components. Typically, the kinetic energy component for our subjects was small by orders of magnitude compared to the pressure flow component. Thus, the results for energy loss are presented in terms of loss in total energy and loss in pressure flow energy. The variation of the rate of energy loss between inlet and outlet for pressure flow energy is shown in Fig. 5.6A; whereas, Fig. 5.6B shows the same for the rate of total energy loss.

![Figure 5.7: Total energy lost over one cardiac cycle in branch PA blood flow for the normal and the rTOF subject.](image)

It can be seen from the figures that the energy losses for the rTOF subject attains a higher peak than the normal subject. The peak value of the rate of energy loss, for both, pressure flow losses (Fig. 5.6A) as well as the total energy loss (Fig. 5.6B), are attained at different time during the cardiac cycle. The reason for this is not clear and could be due to the nonexistent PV in the case of rTOF subject. The time averaged value of the pressure flow energy loss for the rTOF
subject is 0.065 J/sec compared to 0.038 J/sec for the normal one (almost 70% higher than normal; see Fig. 5.6A). Likewise the time averaged value for the total energy loss over the complete cardiac cycle for the rTOF subject was 0.04 J/sec compared with 0.02 J/sec for the normal one (Fig. 5.6B).

The net energy loss over the cardiac cycle can be computed by numerically integrating the graphs for rate of energy loss (Fig. 5.6) over the cardiac cycle. The net energy loss in both total energy as well as pressure flow energy for the rTOF and normal subject are shown in Fig. 5.7. The net losses in pressure flow energy for the normal subject are about 36% lower than the rTOF subject (Fig. 5.7). The total energy loss shows a similar trend with losses for normal subject almost 65% lower than the rTOF.

5.8 Discussion

The energy-based endpoints for the normal and rTOF subject were obtained using their clinically measured pressure and imaging data. This demonstrated the application of the methodologies developed in this research to calculate these endpoints, using data obtained from non-simultaneous catheterization and cardiac imaging. It also showed the use of patient specific hemodynamic computation to calculate pressure data at the inlet or outlets where pressure measurement was not available. This helped in reducing the required number of pressure measurements to only one location out of three: the inlet at MPA and the two outlets at LPA and RPA, respectively. Therefore, this pilot study has demonstrated that numerical methodology coupled with clinical imaging and catheterization can be employed to characterize pulmonary arterial hemodynamics in an abnormal RV and PA pressure-flow physiology. Our observations suggest
that parameters such as RV stroke work (SW), energy transfer ratio ($e_{mpa}$) and energy loss in the branch PA may be useful in assessing the RV dysfunction in rTOF patients.

Inefficiency in the rTOF RV is suggested by the lower value of $e_{mpa} = 0.56$ for the rTOF subject, compared to 1.06 for the normal subject, despite the fact that rTOF RV operates at higher pressure and volume. This finding is logical, as the rTOF RV has an incompetent outlet valve (PV). The incompetent PV causes diastolic RV volume overload. However, it is not the overloaded RV that is the primary source of the inefficiency; rather, it is the continuous PV backflow that significantly reduces the efficiency of the RV in rTOF.

The presence of a functioning PV in the normal subject enables the development of a pressure gradient between the RV and PA during iso-volumic contraction in early systole. When the pulmonary valve opens, the accumulated blood volume in RV is pushed into the PA with the motive force imparted on the blood pool by the RV, pushing that blood volume to the lungs. The work imparted by the RV can thus be transferred efficiently to the blood pool, and the blood flows through the branch PAs into the lungs. When the PV closes at end-systole, the blood pool in the PA is prevented from flow reversal into the RV, as the valve provides the resistance necessary to hold the volume.

As mentioned above, in normal PA physiology, the presence of the functioning pulmonary valve allows development of a larger pressure gradient under normal RV operating pressure than in rTOF pathophysiology. In rTOF physiology, the absence of a functioning PV prevents the development of a pressure gradient across the PV annular region, which thereby diminishes the work available for the RV to impart to the blood pool. The dysfunctional pulmonary valve allows blood to backflow into the RV, which causes the RV to be volume overloaded. This is further detrimental to the RV because higher RV operating pressures are required during ven-
tricular end-systole to pump blood. In other words, in the rTOF subjects, the presence of increased blood volume in the MPA offers a higher resistance to flow being pushed out of the RV compared to the case of normal RV with normally functioning PV.

The rate of energy loss in the branch PA over the cardiac cycle is not constant. This is expected because the flow is unsteady in the pulmonary artery downstream of the pulmonary valve. The maximum value of the rate of energy loss as well as its time averaged value over the cardiac cycle is higher for the rTOF subject than the normal one (Fig. 5.6). Specifically, the time averaged rate of loss in total energy for the rTOF subject (0.04 J/sec) was 50% higher than the normal subject (0.02 J/sec). It also follows that the net energy loss for the rTOF subject is higher than the normal subject (Fig. 5.7). Therefore, it clearly demonstrates that the energy-based hemodynamic endpoints can clearly delineate the flow characteristics of a normal subject from that of an rTOF subject with pulmonary insufficiency.

Most researchers have either used RV volume based endpoints [34,35] or RV pressure based endpoints [37,203] to diagnose pulmonary insufficiency in rTOF patients. The energy based endpoints have an advantage that they incorporate pressure as well as velocity (or flow rate and volumetric endpoint) into one index. The RV stroke work combines RV pressure and RV volume into one endpoint. The energy transfer ratio, which is defined as the ratio of total energy imparted to the blood over one cardiac cycle at MPA to the RV stroke work, takes into account both, the RV energy as well as the blood energy at MPA. It incorporates RV pressure, RV volume, MPA pressure and flow rate and kinetic energy of the blood at MPA. Therefore, it may be noted that the energy-based endpoints incorporate the dynamic characteristics of the flow into one single endpoint.
The disadvantage of the energy based endpoints is in their data requirements for their computation from clinically obtained data. For example, energy loss in the branch PA requires three pressure and three flow measurements at the inlet MPA and outlets LPA and RPA. Moreover, these endpoints require pressure data which at present can only be obtained by invasive catheterization. This makes the usefulness of these endpoints less appealing in current clinical practice. With the development of non-invasive pressure measurement techniques in future, energy-based endpoints may be useful in the standard of care clinical diagnosis of pulmonary insufficiency.

5.9 Limitations

This proof of concept pilot study is limited by several factors. Firstly, the sample size of the subject population was too small to draw any general conclusion regarding the values of the energy-based endpoints for the two groups: rTOF and normal. Despite such limitations, our study does indicate that the values of stroke work, energy transfer ratio ($e_{mpa}$) and energy loss in branch PA are significantly different for the two groups. Therefore, these endpoints can assess the RV inefficiency for these two groups. Further studies, utilizing a larger statistical sample of patients have confirmed to validate this assessment [204,205].

Secondly, the use of pressure data obtained from cardiac catheterization to calculate the energy-based endpoints is a limiting factor in applying this method in clinical settings. Cardiac catheterization is invasive and is no longer routinely performed for typical rTOF patients as a part of standard of care practice. The cardiac catheterization data was used in this proof of concept pilot study only to validate the energy-based approach. In the following chapter, methodol-
ogy based on patient-specific image-based hemodynamic computation will be developed, that can provide the endpoints noninvasively.

Thirdly, the catheterization and MR imaging data for the subjects were not acquired simultaneously. Simultaneous and synchronized MRI and pressure measurements are preferred options. Unfortunately, this scenario is not attainable in any clinical setting. Therefore, the ECG wave form was used to synchronize the pressure and the flow or the pressure and RV volume pulse of the subjects. This inherently required the cardiac MRI and catheterization to be performed within a reasonable duration of time so that the ventricular characteristics were not affected by remodeling. Therefore, for this pilot study the subjects were selected so that they matched in age and size, and had MRI and catheterization performed as close as possible under comparable physiologic conditions (intubation and general anesthesia for both the procedures). The fact that heart rates were comparable for both procedures in each subject (Table 5.1) attests to the statement that the physiologic conditions for the subjects were comparable.

Fourth, the application of Womersley velocity profile as a boundary condition for hemodynamic computation, and rigid wall modeling are simplistic idealizations of the in-vivo conditions. Womersley velocity profile is an idealized profile representing a developed flow condition. For pulmonary arterial flow in the proximity of PV, the length of the artery between the PV to our measurement site in the MPA, is inadequate for the flow profile to develop into a developed flow profile. Specifically, Grigoni et al., 2006[206] found fairly substantial variation in energy loss at low flow rate depending on which flow profile was used (plug versus parabolic) in total-cavo-pulmonary-connection physiology. The use of a spatially as well as temporally varying velocity profiles and patient specific geometric data incorporating arterial wall compliance effects [150,207] may provide more realistic energy result.
Lastly, this study did not focus on developing appropriate dimensionless expressions for the energy-based endpoints. This may in the future be required to statistically compare their values among subjects with differing physiological characteristics (age, weight, BSA, etc.).

5.10 Conclusions

The energy-based endpoints for the normal and rTOF subject were obtained using their clinically measured pressure and imaging data. These results constitute the outcome of the research tasks for Specific Aims 1 and 2, mentioned in Chapter 1.

The energy-based endpoints were found to be distinctly different in values for the normal subject and the subject with pulmonary insufficiency. For example, the stroke work for the normal subject was 47% higher than that of the subject with PI. Similarly, the energy transfer ratio for the normal subject was 47% higher than the one obtained for the subject with PI. The energy loss in the branch PA of the normal subject was significantly lower (by 65%) than that of the subject with PI. These results clearly demonstrate that the energy-based hemodynamic endpoints proposed in this research can delineate the pulmonary arterial flow characteristics of normal subject from that of a subject with PI.

So far in our research, the methodologies for calculating the energy-based endpoint require pressure measurement that can only be obtained through invasive catheterization. This limits the clinical applicability of these methods. Development of non-invasive methodologies to obtain these endpoints will require patient-specific hemodynamic computation without using any pressure boundary conditions. However, the velocity boundary conditions that are most often used in literatures, such as uniform plug profile, parabolic or Womersley profile do not re-
reflect the true profiles observed in the artery. Therefore, for accurate computational results, velocity boundary conditions that are truly observed in the artery will have to be used as boundary conditions. These velocity profiles typically vary both: 1) spatially over the arterial cross-section, as well as, 2) the shape of the profile changes over the cardiac cycle. In other words, this will require hemodynamic computations with time and spatially varying velocity profiles.

In the next chapter, methodology will be developed to perform the hemodynamic computation with time and spatially varying velocity data obtained from phase-contrast MRI. This patient-specific velocity data will be used with patient-specific geometry of the branch pulmonary artery.
Chapter 6

Patient-Specific Hemodynamics using Time- and Spatially-Varying Velocity Profiles

6.1 Introduction

In the previous chapter, a methodology for patient-specific (PS) hemodynamic computation using Womersley type velocity profile as boundary condition was developed. Although the calculation of the velocity boundary condition utilized PS phase-contrast MRI (PC-MRI) data, it nevertheless was an idealized profile and not an actual velocity profile observed in the pulmonary artery (PA). The in-vivo velocity profiles observed in the PA, using phase-contrast MRI (PC-MRI) show a high degree of spatial and temporal variation unlike any of the idealized developed flow profiles, e.g., a uniform plug profile, parabolic profile or a Womersley profile [190,194,208]. In addition to that, pulmonary arterial flow in patients with pulmonary insufficiency has an additional complexity due to significant flow regurgitation resulting from dysfunctional and often nonexistent pulmonary valve.

Pulmonary arterial flow is also a developing flow; which implies that the velocity profiles at different cross-section along the length of the artery vary. The short length of the main PA
distal to the pulmonary valve is insufficient for the flow to become a fully developed flow. The results of hemodynamic computation are questionable, when the developed velocity profiles are used as boundary condition for flow near heart valves [14]. Therefore, for performing an accurate hemodynamic computation, the complex velocity profile must be applied as boundary condition at the precise location of its measurement, while simultaneously capturing its spatial and temporal variation over the non-circular arterial cross-section under \textit{in-vivo} conditions. Most of the published researches apply velocity boundary condition at the outlet of long artificial extensions that can cause inaccuracies in the computed flow field for developing flows [14,124-126,131].

In this chapter a methodology for hemodynamic analysis of complex flows that \textit{directly incorporates temporal and spatially varying PS velocity data} from PC-MRI, with PS arterial geometry, obtained from angiographic MRI is presented. In this proposed methodology, there is no subjectivity in determining the location of inlet and outlets, which are determined by the location of PC-MRI measurement planes. Therefore it is suitable for modeling developing flows in the proximity of valves. This methodology is applied to model PA flow in two different subjects: one normal and the other with pulmonary insufficiency; as the subject with pulmonary insufficiency has highly regurgitant PA flow field.

\subsection{Method}

The patient characteristics, the parameters for MRI protocols and the mathematical details of the proposed methodology are described in the sections below.
6.2.1 Patient Selection

Two subjects, one normal (Age: 14 years, Sex: male, Wt.: 55 Kg) and the other rTOF (Age: 8.5 years, Sex: male, Wt.: 40 Kg) who had undergone clinical cine PC-MRI and cardiac MRI were selected for this study. The “normal” subject had a functioning pulmonary valve as confirmed by exam and echocardiography. The rTOF subject had been diagnosed with tetralogy of Fallot and had undergone repair surgery in his infancy and had essentially a non-functional pulmonary valve with large flow regurgitation as assessed by echocardiography. The study protocol was approved by the Institutional Review Board at CCHMC.

6.2.2 Cardiac and Flow MRI

MR images were acquired using a 1.5T, 8-channel cardiac coil GE Signa Excite scanner (GE Medical, Milwaukee). Each subject underwent their MRI via general endotracheal anesthesia with breath holding technique. For the normal subject, the typical scan settings for the angiographic cardiac MRI (Fig. 6.1A) were: acquisition type = 3D, slice thickness = 2.5 mm, TR/TE = 3.0/0.9 sec, flip angle = 20 Deg., image resolution 256 x 256, slice spacing 2.5 mm and the pixel resolution 1.33 mm x 1.33 mm. Similarly, the settings for the rTOF subject were: acquisition type = 3D, slice thickness = 5 mm, TR/TE = 3.3 sec/1.26 sec, flip angle = 30 Deg., image resolution 256 x 256, slice spacing 2.5 mm and the pixel resolution 1.48 mm x 1.48 mm.

PA flow imaging was performed using retrospective ECG-gating, through-plane velocity-encoded PC-MRI at the branch PA inlet, i.e., at the main-PA (MPA) and the two outlets at the left-PA (LPA) and the right-PA (RPA), respectively (Fig. 6.1B). Velocity encoding limits were adjusted as needed for minimal peak to avoid aliasing of the phase signal. For each of the subjects, a total of 30 magnitude and 30 phase images were acquired at PA inlet and outlets. For the
normal subject, the typical scan parameters for PC-MRI were: acquisition type = 2D, slice thickness = 5 mm, TR/TE = 12.03 sec/4.5 sec, flip angle = 20 Deg., image resolution 256 x 256, single slice and pixel resolution 1.25 mm x 1.25 mm. Similarly, the parameters for the rTOF subject were: acquisition type = 2D, slice thickness = 6 mm, TR/TE = 14.18 sec/6.7 sec, flip angle = 30 Deg., image resolution 256 x 256, single slice and pixel resolution 1.4 mm x 1.4 mm.

**Fig. 6.1:** A) A typical stack of $R$ ($R=48$) spatial angiographic MRI that were used for PA geometry reconstruction. The images represent a series of sagittal slices at a different spatial location along the $z$ axis as indicated by different $z$ values. B) A typical velocity encoded PC-MRI phase image (30 phases over a cardiac cycle).
6.2.3 Sequential block diagram of the overall methodology

A sequential block diagram of the overall methodology is shown in Fig. 6.2A. The individual steps of our methodology are:

1. Construct the branch PA geometry from angiographic MRI by applying automatic image segmentation algorithm.

2. Locate the PC-MRI velocity measurement planes in the reconstructed geometry from Step 1 to create planar inlet and outlets (Fig. 6.2B).

3. Construct the 3D geometry for hemodynamic computation that has planar inlet and outlets defined by the PC-MRI velocity measurement planes.

4. Compute the time- and spatially-varying PS velocity profiles from the PC-MRI data at each of the inlet and outlets (Fig. 6.2C).

5. Perform hemodynamic computation using the velocity profiles developed in Step 4 as boundary conditions at the inlet and outlets.

These steps are described in details in the following sections.
Fig. 6.2: Sequential block diagram: A) of the proposed methodology; B) for calculating PC-MRI plane location for each inlet and outlet in the domain of reconstructed geometry; C) to develop interpolation function for patient-specific velocity profiles from PC-MRI phase values.
6.2.4  **PA geometry from Angiographic MRI**

The 3D geometry of the branch PA was created using the angiographic MRI of the subject (Step 1, Fig. 6.2A). The branch PA was delineated on the angiographic MRI from the rest of the surrounding tissues by applying the automatic image segmentation algorithm in MIMICS (Materialise Inc., Leuven, Belgium) with a range of intensity threshold as input. Details of this process are given in our previous study (Das et al., 2010). Instead of MIMICS, any other image reconstruction algorithm can also be implemented. The surface of this reconstructed geometry was then exported as a stereolithographic (STL) file of surface triangles. At this stage, the reconstructed geometry did not have any well-defined inlet and outlet planes (Fig. 6.3).

![Branch PA geometry (STL surface triangles)](image)

Fig. 6.3: Reconstructed geometry of branch PA from angiographic MR images in form of STL surface triangles (for rTOF subject).

6.2.5  **Locate inlet and outlet from PC-MRI**

To accurately model the developing flow in PA, where the flow profile at different arterial cross-section along the length of the artery vary, the inlet and outlet sections must coincide
with the planes of PC-MRI velocity measurement. Therefore, inlet and outlet planes were created in the reconstructed geometry from the PC-MRI data at MPA, LPA and RPA. The PC-MRI velocity measurement plane was located using the top left corner point (O) of one of its images and a vector, normal to the image plane. The individual PC-MRI stores the direction cosines of two in-plane vectors representing the x and y axes of the PC-MRI image coordinate system (Fig. 6.4A). The x-axis of this image coordinate system is defined by a unit vector $e_1$, parallel to the top edge of the image from the top left corner point O to the top right corner point of the image (Fig. 6.4A). Similarly, the y-axis is represented by a unit vector $e_2$, parallel to the vertical edge of the image from the point O to the bottom left corner of the image (Fig. 6.4A). Therefore, the plane normal $e_3$ is defined by their cross-product, i.e., $e_3 = e_1 \times e_2$, where ‘x’ denotes cross product of vectors.

However, the data for direction cosines of $e_1$, $e_2$, and the coordinates of the point O, are all recorded in the PC-MRI header with respect to a coordinate system called patient coordinate system. In Fig. 6.4A, this coordinate system is denoted by $a_1$, $a_2$, $a_3$, where, $a_1 = (1, 0, 0)$, $a_2 = (0, 1, 0)$ and $a_3 = (0, 0, 1)$. This coordinate system is different from the coordinate system of the reconstructed geometry. The points on the reconstructed geometry have coordinates with respect to the unit vectors $g_1$, $g_2$, $g_3$ which represent the unit vectors of the geometry reconstruction space (Fig. 6.4A). This coordinate system is specific to the 3D geometry reconstruction algorithm but is related to the image coordinate system of the angiographic MRI (e.g. either translated or rotated). Therefore, a plane created with the coordinate data of the point O, stored with the image and the plane normal $e_3$, calculated from the direction cosines of $e_1$, $e_2$, stored with the image, will be wrongly positioned in the reconstructed geometry. To correctly position the PC-MRI
plane in the reconstructed geometry, transformation from the patient coordinate system to the coordinate system of the geometry reconstruction space is required.

**Fig. 6.4:** A) Reconstructed geometry along with the different image coordinate systems (Patient: $a_1$, $a_2$, $a_3$; PA Geometry reconstruction: $g_1$, $g_2$, $g_3$ and PC-MRI: $e_1$, $e_2$, $e_3$). B) Velocity measurement planes from PC-MRI located in the space of geometry reconstruction. C) Geometry for computation with planar inlet and outlets (truncated with the PC-MRI planes at the inlet and outlets); arrows showing the blood flow direction.
The transformation matrix \( (T_{ag}) \) for transforming the coordinates of a point from patient coordinate system \((a_1, a_2, a_3)\) to the geometry reconstruction coordinate system \((g_1, g_2, g_3)\) is:

\[
T_{ag} = (g_i \cdot a_j)
\]

(6.1)

where, an element of \( T_{ag} \) at row \( i \) and column \( j \) is obtained by dot product \((\cdot)\) of the unit vector \( g_i \) with the unit vector \( a_j \). The coordinates of the PC-MRI top left corner point \( O \) in the reconstructed geometry \((g_1, g_2, g_3)\) were calculated by \( T_{ag}O \) and the direction cosines of the plane normal by \( T_{ag}e_3 \).

Using the transformed coordinates of the corner point \( (T_{ag}O) \) and the direction cosines of the plane normal \( (T_{ag}e_3) \) with respect to \( g_1, g_2, g_3 \), the PC-MRI planes were correctly positioned in the reconstructed geometry. The procedure was applied to each set of PC-MRI, at the inlet (MPA) and the outlets (LPA and RPA). The resulting PC-MRI planes at MPA, LPA and RPA (Fig. 6.4B) were used to partition the 3D branch PA geometry from step 1 to construct the geometry for hemodynamic computation. As shown in Fig. 6.4C, this geometry has planar inlet and outlets at the location of PC-MRI velocity measurement.

6.2.6 Patient-specific velocity profile from PC-MRI

The velocity value associated with each image pixel was calculated from the pixel phase value by applying the appropriate scale stored in the PC-MRI header (which is MRI machine specific). This calculation was performed for each of the \( N \) phase images in the PC-MRI series. For both of our subjects, the number of phase images, \( N \) was 30. The velocity encoding number (VENC) for all PC-MRI was appropriately selected to be larger than the minimum and maximum value of velocity magnitude in the artery. This ensured that the PC-MRI did not require correction for phase wrapping.
The calculated pixel velocity is denoted by $V^p(\alpha, \beta)$, where, the superscript $p$, with $p=1, \ldots, N$, represents the phase, and the image pixel itself is designated by its unique coordinate location, $(\alpha, \beta)$ with respect to the unit vectors $e_1$ and $e_2$ of PC-MRI image coordinate system (Fig. 6.4A). It may be noted that for each image pixel, $\alpha$ and $\beta$ are discrete values in multiples of image pixel spacing in the $e_1$ and $e_2$ directions, respectively. A two step process was implemented (Step 4, Fig. 6.2C) to construct the PS velocity profiles using the pixel velocity, $V^p(\alpha, \beta)$. This involved: a) background noise correction for pixel velocity $V^p(\alpha, \beta)$ and b) the construction of the piece-wise continuous velocity function using the noise-corrected velocity values.

**Background noise correction.** The image pixels in the region of static tissue on PC-MRI with little blood flow except perfusion, also records some spurious velocity values resulting from eddy currents in the magnets. These anomalous velocity contents in image pixel velocity $V^p(\alpha, \beta)$, are termed as background noise and need to be corrected [209]. The region of static tissue $\Omega_s$, was identified by finding the image pixels $(\alpha, \beta)$ that had low temporal variation in pixel velocity, $V^p(\alpha, \beta)$ over the cardiac cycle. First, an index $h(\alpha, \beta)$ was calculated at each image pixel $(\alpha, \beta)$ by:

$$h(\alpha, \beta) = \frac{|\mathbf{\Omega}_s(\alpha, \beta)|^2}{\sum_{k=1}^{N} |f_k(\alpha, \beta)|^2} \quad (6.2)$$

where, $f_0(\alpha, \beta)$, $f_1(\alpha, \beta)$, $\ldots$, $f_N(\alpha, \beta)$ are the Fourier transforms of the $N$ pixel velocity values $V^p(\alpha, \beta)$, for phase $p=1$ to $N$. Second, mean velocity, $\bar{V}(\alpha, \beta)$ and standard deviation $\sigma(\alpha, \beta)$ of the $N$ velocity values, $V^1(\alpha, \beta), \ldots, V^N(\alpha, \beta)$ over $N$ phases were calculated at each pixel.
The static region $\Omega_s$ was calculated by identifying the image pixels $(\alpha, \beta)$, which met the condition:

$$\Omega_s = \{(\alpha, \beta) | \sigma(\alpha, \beta) < \sigma_L \text{ or } h(\alpha, \beta) < k\}.$$  \hfill (6.3)

Where, parameters $K$ and $\sigma_L$ are the threshold values to determine the static region. To calculate the threshold limit $\sigma_L$ in Eq. 6.3, the minimum and maximum value of $\sigma(\alpha, \beta)$, i.e.,

$$\sigma_m = Min\{\sigma(\alpha, \beta)\} \quad \text{and} \quad \sigma_M = Max\{\sigma(\alpha, \beta)\}$$

respectively, was calculated. The value $\sigma_L$ was obtained using $\sigma_L = L(\sigma_M - \sigma_m) + \sigma_m$ by specifying a value of $L$. The range of value of $L$ for our subjects was typically from 0.01 to 0.013 and that of $K$ was from 0.9 to 0.95.

**Fig. 6.5:** Calculation of the velocity profiles from PC-MRI data. Figures 5A-5C show the result for background noise correction. A) Distribution of standard deviation $\sigma(\alpha, \beta)$ of velocity (red<1%; 1.5<Green<3%; 3%<Blue<5%; 5%<Yellow<10% of the min to max range). B) Static region ($\Omega_s$) shown in blue on the phase image. C) Anatomical image showing tissues.

The static region $\Omega_s$ was plotted on the PC-MRI phase image (Fig. 6.5A, 6.5B) for visual inspection. The magnitude image (Fig. 6.5C) was used as a guide to identify the regions of tissue. The plotting of the static region on both the PC-MRI and the corresponding magnitude image (Fig. 6.5A, 6.5B, 6.5C) provided a visual check to ensure that no point from the lumen area was accidentally used for background noise calculation. The values of the parameters $K$ and
were adjusted to ensure that no image pixel points from the regions of significant blood flow were included in the static region (Fig. 6.5B, 6.5C).

The background noise \( E^p(\alpha, \beta) \) at each phase \( p \) was assumed to be a first order polynomial in \( \alpha \) and \( \beta \) of the form:

\[
E^p(\alpha, \beta) = A^p \alpha + B^p \beta + D^p. \quad (6.4)
\]

The parameters \( A^p, B^p, \) and \( D^p \) at each phase \( p \) were calculated by least square minimization of the error norm \( \varepsilon \),

\[
\varepsilon = \sum_{i=1}^{S} \left[ V^p(\alpha_i, \beta_i) - \left( A^p \alpha_i + B^p \beta_i + D^p \right) \right]^2 \quad (6.5)
\]

over the \( S \) pixels of the static region \( \Omega_x \). The solution for the parameters \( A^p, B^p, \) and \( D^p \) is given by:

\[
\frac{\partial \varepsilon}{\partial A^p} = 0; \quad \frac{\partial \varepsilon}{\partial B^p} = 0; \quad \frac{\partial \varepsilon}{\partial D^p} = 0. \quad (6.6)
\]

For each \( p \), equation 6.6 can be simplified to a system of linear equations:

\[
\begin{align*}
\left( \sum_{i=1}^{S} \alpha_i^2 \right) A^p + \left( \sum_{i=1}^{S} \alpha_i \beta_i \right) B^p + \left( \sum_{i=1}^{S} \alpha_i \right) D^p &= \sum_{i=1}^{S} \alpha_i V^p(\alpha_i, \beta_i), \\
\left( \sum_{i=1}^{S} \alpha_i \beta_i \right) A^p + \left( \sum_{i=1}^{S} \beta_i^2 \right) B^p + \left( \sum_{i=1}^{S} \beta_i \right) D^p &= \sum_{i=1}^{S} \beta_i V^p(\alpha_i, \beta_i), \\
\left( \sum_{i=1}^{S} \alpha_i \right) A^p + \left( \sum_{i=1}^{S} \beta_i \right) B^p + (S) D^p &= \sum_{i=1}^{S} V^p(\alpha_i, \beta_i). \quad (6.7a, 6.7b, 6.7c)
\end{align*}
\]

which can be solved for \( A^p, B^p, \) and \( D^p \). The background-noise-corrected phase velocity \( W^p(\alpha, \beta) \) was calculated by:

\[
W^p(\alpha, \beta) = V^p(\alpha, \beta) - E^p(\alpha, \beta). \quad (6.8)
\]
The values of $W^p(\alpha, \beta)$ at each pixel ($\alpha, \beta$) and for each phase $p$ was used to construct the time- and spatially-varying PS velocity profile at each of the inlet and outlets.

*Construction of piece-wise continuous velocity function.* A closed-loop of points was generated on the artery boundary (Fig. 6.6A) of the reconstructed geometry at a spacing of 0.5 mm. This boundary-loop of points was mapped on to the corresponding PC-MRI plane to identify the PC-MRI pixels inside the artery boundary. Since the boundary points are located on the reconstructed geometry, their coordinates are in terms of the unit vectors, $g_1, g_2, g_3$ of the geometry reconstruction space. Therefore, in order to map the boundary correctly on the PC-MRI, these coordinates have to be transformed to the PC-MRI image coordinate system, $e_1, e_2, e_3$ (Fig. 6.4A). Following the derivation of Eq. 6.1, the 3x3 transformation matrix ($T_{ae}$) for transforming a point from the patient coordinate system ($a_1, a_2, a_3$) to PC-MRI image plane ($e_1, e_2, e_3$) was obtained by:

$$T_{ae} = \{e_1 \cdot a_j \}.$$  \hspace{1cm} (6.9)

An artery point $P_g$ on an inlet or an outlet (interior or on the artery boundary point) can be positioned on the corresponding PC-MRI plane by calculating its transformed coordinates $P_e$ by:

$$P_e = (T_{ae})^{-1}T_{ag}(P_g - O).$$  \hspace{1cm} (6.10)

It may be noted that the coordinates of $P_g$ ($\hat{x}, \hat{y}, \hat{z}$) are with respect to the unit vectors $g_1, g_2, g_3$; whereas, $P_e$ has coordinates ($x, y, z=0$) with respect to the coordinate system ($e_1, e_2, e_3$) with $z = 0$, as it is located on the plane itself. Result of locating artery boundary on the PC-MRI using Eq. 6.10 for one case is shown in Fig. 6.6. Following this procedure, artery boundary of each of the inlet and outlets were plotted on their respective PC-MRI.
The plotting of the arterial boundary on the respective PC-MRI (Fig. 6.6B) provided an important visual check to ensure that the artery was correctly identified on the PC-MRI. This ensured that the correct image pixel points within the lumen region were used for velocity interpolation. The grid of regularly spaced image pixel points inside this arterial boundary was identified by point-in-polygon test [210]. These set of PC-MRI pixel points form a mesh of rectangular elements as shown in Fig. 6.7A. The annular zone between the actual artery boundary that was mapped on the PC-MRI and the outer boundary of the zone of rectangular elements was meshed with triangular elements generated by constrained-Delaunay [211] triangulation (Fig. 6.7A). These triangular elements bridge the boundary points with the interior PC-MRI pixel points.

Fig. 6.6: A) Points generated on the artery boundary of each of the inlet and outlets of the computational domain. B) Result of mapping the boundary points on to the corresponding PC-MRI.

The velocity interpolation function was developed using a piece-wise continuous function defined over the individual elements using canonical basis functions. The bilinear canonical ba-
sis functions \( \psi_i \) associated with the nodes \( i=1, 2, 3 \) and 4 of a typical rectangular element (Fig. 6.7B) in terms of the normalized local coordinates \( (\xi, \eta) \) of a point \( P \) are obtained from:

\[
\psi_1 = \frac{1}{4} (l - \xi)(l - \eta),
\]

\[
\psi_2 = \frac{1}{4} (l + \xi)(l - \eta),
\]

\[
\psi_3 = \frac{1}{4} (l - \xi)(l + \eta),
\]

\[
\psi_4 = \frac{1}{4} (l + \xi)(l + \eta).
\]

The normalized local element coordinates \( (\xi, \eta) \) of a point \( P= (x, y) \) are given by:

\[
\xi = \frac{2(x - a_1) - l}{l},
\]

and

\[
\eta = \frac{2(y - b_1) - h}{h},
\]

where, \( (x, y) \) and \( (a_1, b_1) \) are the coordinates of the point \( P \) and the element node at \( i=1 \) with respect to the image coordinate system \( (e_1, e_2) \); \( l \) and \( h \) are the lengths of the sides of the rectangular element as shown in Fig. 6.7B. Similarly, the canonical basis functions \( \psi_i \) associated with the nodes \( i=1, 2 \) and 3 of a triangular element (Fig. 6.7B) in terms of the local barycentric coordinate system are given by:

\[
\psi_i = \frac{A_i}{A}
\]

with,

\[
A = \sum_{i=1}^{2} A_i
\]
where, $A_i = 1, 2, 3$ are the areas of triangles shown in Fig. 6.7B; and $P$ is the point inside the triangle (Fig. 6.7B).

**Fig. 6.7:** A) A hybrid mesh of triangular and rectangular elements in the arterial domain to construct velocity profile. B) Rectangular and triangular element with their respective local coordinate systems.

To calculate velocity $w(\hat{x}, \hat{y}, \hat{z}, t)$ at a point $P_g = (\hat{x}, \hat{y}, \hat{z})$ on an inlet or outlet at an instant $t$, two consecutive phases $p$ and $p+1$ (out of the $N$ phases of PC-MRI) were identified, such that the time instants of the two phases, $t^p$ and $t^{p+1}$, satisfied $t^p \leq t < t^{p+1}$. The point $P_g$ was mapped to the PC-MRI image at phase $p$ using Eq. 6.10 and the artery element that contained the mapped point, which may be a rectangle or a triangle, (Fig. 6.7A) was identified. At each of the corner node $i$ of the element ($i=1,2,3$ for triangle and $i=1,2,3,4$ for rectangle; Fig. 6.7B), nodal velocity $w_i(t)$ at time $t$ was interpolated from the background-noise-corrected velocity values $w_i^p$ and $w_i^{p+1}$ at PC-MRI phases $t^p$ and $t^{p+1}$, respectively, by:
\[
    w_i(t) = w_i^p + \frac{w_i^{p+1} - w_i^p}{t^{p+1} - t^p} (t - t^p); \quad t^p \leq t < t^{p+1}.
\]

If the node \(i\) corresponded to a PC-MRI pixel, \(w_i^p\) and \(w_i^{p+1}\) in Eq. 6.14, were assigned the background noise corrected velocity values provided by Eq. 6.8 at the phases \(p\) and \(p+1\), respectively.

On the other hand, if the node \(i\) was found to be located on the arterial boundary, \(w_i^p\) and \(w_i^{p+1}\) were assigned a value 0 to impose the no-slip condition at the arterial wall. The velocity \(w(x, y, z, t)\) at point \(P_G\) at the time instant \(t\) was calculated using:

\[
    w(x, y, z, t) = \sum_{i=1}^{K} \psi_i w_i(t)
\]

where, \(K\) is the number of corner nodes of the element (\(K = 4\) for rectangle and \(K = 3\) for triangles). If the element that contained the map of the point \(P_G\) was a rectangle, the nodal shape functions \(\psi_i\) were evaluated using Eq. 6.11a-6.11d; and if the element was a triangle, Eq. 6.13a was used instead.

In general, velocity at a point on the inlet or outlet plane will have both in-plane component called transverse component and a component normal to the plane called the axial component. PC-MRI measurement can capture both the components. Therefore, in our formulation, \(w(x, y, z, t)\) in Eq. 6.15 can be a combination of the transverse component and the axial component. However, for this research work, for simplicity, only the axial velocity component, normal to the PC-MRI plane, was measured, at each of the inlet (MPA) and outlets (LPA and RPA). It must be emphasized that the method presented in this paper can incorporate both axial as well as transverse velocity components simultaneously. A typical set of velocity profiles at different time points observed in a rTOF subject that has flow reversal due to dysfunctional pulmonary valve is presented in Fig. 6.8.
Fig. 6.8: A) Flow rate versus time graph from PC-MRI data showing different phases (for our rTOF subject at LPA). B)-G) Velocity profile at phases: 2, 4, 7, 11, 17, 20 as marked in Fig. A (units: z-axis is velocity in cm/sec; x and y axes distances on LPA PC-MRI plane are in mm).
6.2.7 Flow rate measurement

In the absence of any gold standard for evaluating image based hemodynamic models [108,114], flow rate was used as a measure to assess the accuracy of our methodology. In our method, the flow rate at each inlet and outlets was calculated numerically by integrating the velocity profile calculated by using Eq. 6.15, over the respective arterial cross-section from the reconstructed geometry. This flow rate is referred to as PCMR-Direct, since the PC-MRI data was directly converted to spatial and temporal velocity profiles without any assumption.

For independent verification, the flow rate was also obtained by the standard of care method using QFlow software (Medis Inc., Leiden, The Netherlands). The inlet and outlet artery boundaries were drawn manually in QFlow on each of the phase images (Total of 30 phases for each subject). Care was taken to ensure that velocity close to the arterial boundary was minimal. The data for flow rates were obtained from QFlow software at the 30 phases. These flow rates are referred to as ‘QFlow’.
**Fig. 6.9:** A) Artery boundary drawn on PC-MR magnitude image at different phases $N$ (total 30). B) A line segment drawn across the boundary. C) Velocity profile along the line segment drawn in B, showing velocity close to walls to be almost 0.0 cm/sec.
6.2.8 Hemodynamic model

Mathematical formulation. The branch PA hemodynamics was modeled using unsteady, laminar, incompressible flow of non-Newtonian Carreau fluid [186] with rigid arterial wall assumption. Following the standard tensorial notation, where, \( u_i, \ i=1, 2, 3 \) are the velocity components in the direction of the unit vectors \( g_1, g_2, g_3 \) (Fig. 6.4A), the continuity equation:

\[
\sum_{i=1}^{3} u_{i,i} = 0 \tag{6.16}
\]

and the mass-momentum equations (with body force neglected):

\[
\rho \left( \frac{\partial u_i}{\partial t} + u_j u_{i,j} \right) = -p_{,i} + \left[ \mu (u_{i,j} + u_{j,i}) \right]_j \tag{6.17}
\]

were numerically solved using finite-volume method. In Eq. 6.17, \( \rho \) is the density of blood taken to be 1.05 gm/cc, \( p \) is the static pressure and \( \mu \) is the shear rate (\( \dot{\gamma} \)) dependent non-Newtonian blood viscosity:

\[
\mu (\dot{\gamma}) = \mu_\infty + (\mu_0 - \mu_\infty)(1 + A \dot{\gamma}^2)^n \tag{6.18}
\]

with the parameters, \( \mu_\infty = 0.0345 \) poise, \( \mu_0 = 0.56 \) poise, \( A = 10.975 \) sec\(^2\), \( n = 0.3568 \), and the shear rate \( \dot{\gamma} \) (in sec\(^{-1}\)) is,

\[
\dot{\gamma} = \sqrt{\frac{1}{2} \sum_{i} \sum_{j} \dot{\gamma}_{ij} \dot{\gamma}_{ji}} \tag{6.19}
\]

The Reynolds number (Re) at the inlet (MPA) and the outlets (LPA and RPA) was calculated using the spatial and time averaged velocity, obtained from PC-MRI measurements. For the normal subject, the Re at the MPA, LPA and RPA was 1422, 1192 and 827 respectively; whereas, for the rTOF subject, it was 750 at MPA, 328 at LPA and 364 at RPA. Therefore, it
was reasonable to assume that the Re within the branch PA would be in the unsteady laminar regime. However, we do not rule out possible organized local shear layer instabilities and organized larger vortical cells, rather than a turbulent flow, which typically signifies random fluctuations.

**Boundary conditions.** Velocity boundary conditions were applied at MPA and LPA (Fig. 6.10) as axial component of the velocity vector normal to the surface. The strategy was to compute the RPA velocity profile and validate it with RPA measurement, whereas, the MPA and LPA velocity were implemented as input condition. The transverse velocity components were neglected, considering the axial velocity component to be of orders of magnitude higher than the transverse components. Time and spatially varying velocity profiles were computed from PC-MRI data using Eq. 6.15. A stress-free outflow boundary condition was applied at the end of the extended RPA conduit of length 20 times the mean RPA diameter (Fig. 6.10). The extension was needed to ensure that there was no boundary effect on the upstream velocity profiles at the location where experimental validation with numerical data was sought for. Since the goal of this research was to develop a methodology for applying non-invasive PS blood velocity measurements for numerical computation with a rigid arterial domain, pressure boundary condition was not needed.

**Numerical formulation.** The main segment of the branch PA domain (between the MPA inlet and the two outlets at LPA and RPA) was meshed with linear tetrahedral elements (476K elements for normal; 425K elements for rTOF) in a pre-processor (GAMBIT, ANSYS, Canonsburg, PA). The extension at the RPA was meshed with linear triangular prism elements (846K elements for normal; 971K elements for rTOF; Fig. 6.10). The flow equations (Eq. 6.16 and 6.17) were solved using finite volume solver (FLUENT, ANSYS, Canonsburg, PA) with the velocity
boundary conditions obtained from PC-MRI measurements implemented using user defined functions (UDF). SIMPLE method with second order velocity and first order pressure correction with time step of 0.001 sec and a tolerance of 1e-4 for both velocity and flow-rate residuals was used. Mesh independence of the computed solution was verified by reducing the mesh size by half and also reducing the time step to 0.0005 sec. The numerically computed RPA flow rate was compared with the flow rates obtained from PC-MRI measurement (Fig. 6.10).

**Fig. 6.10:** Finite volume mesh used for numerical computation (shown here for the rTOF subject). Time and spatially varying velocity profiles from PC-MRI measurement was applied as boundary condition at the MPA inlet and RPA outlet. A stress free out-flow boundary condition was applied at the end of the RPA extension. Numerically computed flow rate and velocity profiles at RPA (interior) were validated with PC-MRI measurements at the same location.

### 6.3 Results

The time- and spatially- varying velocity profiles were computed from PC-MRI data by the proposed methodology. Flow rate was calculated at the inlet (MPA) and the outlets (LPA
and RPA) by numerically integrating the respective velocity profiles over the arterial cross-section. This flow rate is referred to as ‘PCMR-Direct’. The accuracy of these computed velocity profiles were evaluated in terms of the time averaged flow rate obtained from the profiles. Flow rates were independently quantified by the standard of care technique using the QFlow software. These are designated as ‘QFlow’. In this study, the flow rates obtained from QFlow were used as benchmark to assess the flow rates obtained from the proposed methodology (PCMR-Direct). Finally, numerical computation was performed by applying the computed velocity profiles (from PCMR-Direct) as boundary conditions. The flow rates obtained from the numerical computation are designated as ‘Numerical’.

The results are presented in four parts. First, the flow rates from the proposed methodology (PCMR-Direct) are compared with those obtained from QFlow. This provides an independent verification of the proposed methodology by the standard of care technique. Second, the verification of the transfer of time- and spatially- varying PC-MRI data to boundary conditions is presented. For this, the flow rate from the numerical computation at the MPA and LPA, which are the locations of applied boundary conditions, is compared with those from PCMR-Direct. Third, the analysis of flow balance between the inlet (MPA) flow rate and outlet (LPA and RPA) flow rate are presented. Finally, the numerically computed flow rate at RPA is validated with the flow rate from PC-MRI measurement.

6.3.1 Comparison of flow rate: QFlow versus PCMR-Direct

The time variation of the flow rates obtained from QFlow and PCMR-Direct are presented in Fig. 6.11. The flow rates obtained from QFlow at MPA, LPA and RPA are designated as \( F_{QM} \), \( F_{QL} \) and \( F_{QR} \), respectively. The corresponding flow rates obtained from PCMR-Direct are designated as \( F_{PM} \), \( F_{PL} \) and \( F_{PR} \), respectively. The flow rates for the normal subject are pre-
sented in Fig. 6.11A, 6.11B and 6.11C. The flow rates for the rTOF subject are presented in Fig. 6.11D, 6.11E and 6.11F. The time averaged values of FQM, FQL, FQR, FPM, FP and FR for the normal subject are presented in Table 6.1. The corresponding values for the rTOF subject are presented in Table 6.2.

Table 6.1: Time averaged flow rate at the inlet (MPA) and the outlets (LPA and RPA) for the normal subject (where bar denotes average and the subscript j denotes the inlet or outlet). The last row gives the absolute value of flow imbalance between inlet and outlets (|MPA-(LPA+RPA)|) and the % value w.r.t MPA baseline is given in brackets.

<table>
<thead>
<tr>
<th>Inlet/Outlet (j)</th>
<th>QFlow (FQj) (ml/sec)</th>
<th>PCMR-Direct (FPj) (ml/sec)</th>
<th>%Difference (FQj and FPj)</th>
<th>Numerical (FNj) (ml/sec)</th>
<th>%Difference (FPj and FNj)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA (j=M)</td>
<td>93.2</td>
<td>92.4</td>
<td>0.9%</td>
<td>91.5</td>
<td>1%</td>
</tr>
<tr>
<td>LPA (j=L)</td>
<td>58.6</td>
<td>60.6</td>
<td>3.4%</td>
<td>60.9</td>
<td>0.5%</td>
</tr>
<tr>
<td>RPA (j=R)</td>
<td>39.8</td>
<td>38.4</td>
<td>3.5%</td>
<td>30.7</td>
<td>20%</td>
</tr>
<tr>
<td>LPA+RPA(j=LR)</td>
<td>98.4</td>
<td>99.0</td>
<td>0.6%</td>
<td>91.6</td>
<td>7.5%</td>
</tr>
<tr>
<td>Flow Imbalance</td>
<td>5.2</td>
<td>6.6</td>
<td>-</td>
<td>0.1</td>
<td>-</td>
</tr>
</tbody>
</table>

For the normal subject, the time averaged MPA flow rate obtained from QFlow, FQM was 93.2 ml/sec (Table 6.1). The time averaged flow rate from PCMR-Direct, FPM was 92.4 ml/sec. The difference between the time averaged FQM and FPM was 0.8 ml/sec (0.9%). At LPA, the time averaged, FQL was 58.6 ml/sec (Table 6.1). The time averaged, FPL was 60.6 ml/sec. The difference between the time averaged FQL and FPL was 2.0 ml/sec (3.4%). Likewise, at RPA, the time averaged, FQR was 39.8 ml/sec. The time averaged, FPR was 38.4 ml/sec. The difference between the time averaged FQR and FPR was 1.4 ml/sec (3.5%). Therefore, for the normal
subject, the flow rates obtained by our methodology (PCMR-Direct) were within 2.0 ml/sec of the value obtained by the standard of care technique (QFlow).

Table 6.2: Time averaged flow rate at the inlet (MPA) and the outlets (LPA and RPA) for the rTOF subject (where bar denotes average and the subscript j denotes the inlet or outlet). The last row gives the absolute value of flow imbalance between inlet and outlets (|MPA - (LPA + RPA)|) and the % value w.r.t MPA baseline is given in brackets.

<table>
<thead>
<tr>
<th>Inlet/Outlet (j)</th>
<th>QFlow (FQj) (ml/sec)</th>
<th>PCMR-Direct (FPj) (ml/sec)</th>
<th>%Difference (FQj and FPj)</th>
<th>Numerical (FNj) (ml/sec)</th>
<th>%Difference (FPj and FNj)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA (j=M)</td>
<td>56.3</td>
<td>49.3</td>
<td>12.4%</td>
<td>49.7</td>
<td>0.8%</td>
</tr>
<tr>
<td>LPA (j=L)</td>
<td>24.3</td>
<td>29.8</td>
<td>22.6%</td>
<td>29.6</td>
<td>0.7%</td>
</tr>
<tr>
<td>RPA (j=R)</td>
<td>27.2</td>
<td>22.3</td>
<td>18.0%</td>
<td>20.2</td>
<td>9.4%</td>
</tr>
<tr>
<td>LPA+RPA (j=LR)</td>
<td>51.5</td>
<td>52.1</td>
<td>1.2%</td>
<td>49.8</td>
<td>4.4%</td>
</tr>
<tr>
<td>Flow Imbalance</td>
<td>4.8</td>
<td>2.8</td>
<td>-</td>
<td>0.1</td>
<td>-</td>
</tr>
</tbody>
</table>

For the rTOF subject, the time averaged MPA flow rate obtained from QFlow, FQM was 56.3 ml/sec (Table 6.2). The time averaged flow rate from PCMR-Direct, FPM was 49.3 ml/sec. The difference between the time averaged FQM and FPM was 7.0 ml/sec (12.4%). At LPA, the time averaged, FQL was 24.3 ml/sec (Table 6.2). The time averaged, FPL was 29.8 ml/sec. The difference between the time averaged FQL and FPL was 5.5 ml/sec (22.6%). Likewise, at RPA, the time averaged, FQR was 27.2 ml/sec. The time averaged, FPR was 22.3 ml/sec. The difference between the time averaged FQR and FPR was 4.9 ml/sec (18.0%). Therefore, for the rTOF subject, the maximum difference between the time averaged flow rate obtained by our methodology (PCMR-Direct) and those obtained by the standard of care technique (QFlow) was 7.0
ml/sec (12.4%). The overall flow rate for the rTOF patient is significantly lower as compared to the normal subject. The higher values of percentage difference for the rTOF subject are the result of reduced core flow rate due to the flow regurgitation at the dysfunctional pulmonary valve and abnormal downstream PA.

6.3.2 Verification of the implementation: Boundary condition from PC-MRI data

For the numerical computation, velocity profiles obtained from PCMR-direct were applied as boundary condition at MPA and LPA by implementing user-defined functions (UDF) in the finite-volume solver. Therefore, the application of the time- and spatially- varying PC-MRI velocity data as boundary condition was verified by comparing the numerically computed flow rate at MPA and LPA with the corresponding PCMR-Direct flow rates (Fig. 6.12).

The plots for the time variation of the numerically computed flow rates at MPA, LPA and RPA are shown by FNM, FNL and FNR, respectively (Fig. 6.12). The time variation of PCMR-Direct flow rates, FPM, FPL and FPR are replotted in the Fig. 6.12 for comparison with FNM, FNL and FNR, respectively. The results for the normal subject are presented in Fig. 6.12A, 6.12B and 6.12C. The corresponding flow rates for the rTOF subject are presented in Fig. 6.12D, 6.12E and 6.12F, respectively.

For both the normal as well as the rTOF subject, time averaged MPA flow rate from the numerical computation, FNM, was within 1% of the flow rate, FPM from PCMR-Direct (Table 6.1 and 6.2). Likewise, for both the subjects, the percentage difference between FNL and FPL, at LPA was also within 1%. This shows that the boundary conditions for the numerical computation were indeed implemented accurately from the time- and spatially- varying PC-MRI velocity data.
6.3.3 Flow balance between inlet and outlet of branch PA

The time variation of the combined outlet flow rate (LPA+RPA) from PCMR-Direct, FP_L+FP_R, for the normal and the rTOF subject is shown in Fig. 6.12A and 6.12D, respectively. The flow imbalance in flow rates from PCMR-Direct is the difference between the outlet flow rate, FP_L+FP_R and the inlet flow rate FP_M (Fig. 6.12A and 6.12D). The flow imbalance in terms of the time-averaged value, for the normal and the rTOF subject is presented in Table 6.1 and Table 6.2, respectively. For the normal subject, the time averaged combined outlet flow rates from PCMR-Direct, FP_L+FP_R was 99.0 ml/sec. The time averaged inlet flow rate at MPA, FP_M was 92.4 ml/sec. Therefore, the flow imbalance between the inlet, FP_L+FP_R, and the outlet, FP_M was 6.6 ml/sec (7.1%; Table 6.1). For the rTOF subject, the time averaged outlet flow rate, FP_L+FP_R was 52.1 ml/sec. The time averaged inlet flow rate at MPA, FP_M was 49.3 ml/sec. The imbalance between the time averaged inlet and outlet flow rate was 2.8 ml/sec (5.7%; Table 6.2). Therefore, for both the subjects, the flow imbalance from the proposed methodology (PCMR-Direct) was within 7.1%.

The imbalance between inlet and outlets was also observed for flow rates obtained from the standard of care method, QFlow. The time variation of the combined outlet flow rates from QFlow, FQ_L+FQ_R, for the normal and the rTOF subject are shown in Fig. 6.11A and 6.11D, respectively. The flow imbalance in flow rates from Qflow is the difference between the outlet flow rate, FQ_L+FQ_R and the inlet flow rate FQ_M (Fig. 6.11A and 6.11D). The corresponding time-averaged values for the normal and the rTOF subject are presented in Table 6.1 and Table 6.2, respectively. For the normal subject, the combined outlet flow rates from QFlow, FQ_L+FQ_R was 98.4 ml/sec. The inlet flow rate at MPA, FQ_M was 93.2 ml/sec. The flow imbalance between the time averaged FQ_M and FQ_L+FQ_R was 5.2 ml/sec (5.6%; Table 6.1). For the rTOF
subject, the time averaged combined outlet flow rate, $F_{QL} + F_{QR}$ was 51.5 ml/sec. The time averaged inlet flow rate, $F_{QM}$ was 56.3 ml/sec. The time averaged value of the flow imbalance was 4.8 ml/sec (8.5%; Table 6.2). Therefore, for both the subjects, the flow imbalance from the standard of care methodology (QFlow), was within 8.5%.

### 6.3.4 Validation of computed RPA flow rate with PC-MRI measurement

Numerical computation was performed by specifying the PS velocity boundary condition at MPA and LPA and an outflow boundary condition, applied at the end of a straight extension at RPA (Fig. 6.10). The velocity profiles for the boundary conditions were obtained from PCMR-Direct. Therefore, the numerically computed flow rate, $F_{NR}$ at the RPA plane was validated with the corresponding PCMR-Direct flow rate, $F_{PR}$ (Fig. 6.10). The comparison of $F_{NR}$ with $F_{PR}$ is presented in Fig. 6.12C for the normal subject and in Fig. 6.12F for the rTOF subject. The time averaged values for the normal and the rTOF subject are presented in Table 6.1 and Table 6.2, respectively. For the normal subject, the numerically computed RPA flow rate, $F_{NR}$ was 30.7 ml/sec (Table 6.1; Fig. 6.12C). This was within 7.7 ml/sec (20%) of the PCMR-Direct flow rate, $F_{PR}$ (38.4 ml/sec). For the rTOF subject, the numerically computed RPA flow rate, $F_{NR}$ was 20.2 ml/sec (Table 6.2; Fig. 6.12F). The difference between time averaged $F_{NR}$ and that obtained from PCMR-Direct, $F_{PR}$ (22.3 ml/sec), was 2.1 ml/sec (9.4%).
Fig. 6.11: Comparison of flow rate from QFlow with those from PCMR-Direct: A) at MPA, B) at LPA and C) at RPA of the normal subject. D) For rTOF subject at MPA, E) at LPA and F) at RPA. Graphs designated “LPA+RPA” are sum of the LPA and RPA flow rates.
Fig. 6.12: Comparison of flow rate from PCMR-Direct with those from numerical computation: A) at MPA, B) at LPA and C) at RPA of the normal subject. D) For rTOF subject at MPA, E) at LPA and F) at RPA. Graphs designated “LPA+RPA” are sum of the LPA and RPA flow rates. Note that the flow rate graphs for PCMR-Direct are same as Fig. 5.11; and the velocity profiles from PCMR-Direct were applied as boundary condition at LPA and MPA for numerical computation.
6.3.5 Comparison of computed RPA velocity profiles with PC-MRI measurement

Comparison of RPA axial velocity contours from PC-MRI measurements with those obtained from numerical computations for the normal subject is shown in Fig. 6.13. It may be noted that the velocity contour results presented here are calculated without the in-plane transverse velocity component in the applied boundary conditions. This was due to the fact that the flow images of the transverse flow component were not available as they are not part of standard of care practice.

Four time points were selected during the systolic phase to compare the out of plane axial velocity contours (dot product of velocity vector with outward RPA plane normal). The negative contour values represents region of flow reversal. The time point, t=0.04 sec was during accelerating flow, whereas, t=0.102 sec, t=0.133 sec and t=0.256 sec were during the deccelerating phase of the systolic flow. The ratio of spatial average velocity at a given time instant to the peak spatial average velocity over the entire cardiac cycle was 0.67 at t=0.04 sec, 0.93 at t=0.102 sec, 0.8 at t=0.133 and 0.3 at t=0.256 sec for numerical computation. Whereas, the same ratio for the PC-MRI measurement was found to be was 0.68 at t=0.04 sec, 1.0 at t=0.102 sec, 0.96 at t=0.133 and 0.32 at t=0.256.

Comparison of RPA axial velocity contours from PC-MRI measurements with those obtained from numerical computations for the rTOF subject are shown in Fig. 6.14. Points t=0.06 sec, t=0.08 sec and t=0.15 sec were during the accelerating phase of the systolic flow; whereas the one at 0.22 sec was during decelerating systolic phase. The ratio of spatial average velocity at a given time instant to the peak spatial average velocity over the entire cardiac cycle was 0.63 at t=0.06 sec, 0.74 at t=0.08 sec, 0.89 at t=0.15 and 0.79 at t=0.22 sec for numerical computation.
Fig. 6.13: Comparison of out of plane velocity contours at RPA from PC-MRI data with those from numerical computation at: Times, $t=0.04$ sec (accelerating flow), $t=0.102$ sec (accelerating flow), $t=0.133$ sec (decelerating flow) and $t=0.256$ sec (decelerating flow). Units are in m/sec.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>PCMR-Direct</th>
<th>Numerical</th>
</tr>
</thead>
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<td>0.04</td>
<td><img src="image1" alt="PCMR-Direct 0.04" /></td>
<td><img src="image2" alt="Numerical 0.04" /></td>
</tr>
<tr>
<td>0.102</td>
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<td><img src="image4" alt="Numerical 0.102" /></td>
</tr>
<tr>
<td>0.133</td>
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<td><img src="image6" alt="Numerical 0.133" /></td>
</tr>
<tr>
<td>0.256</td>
<td><img src="image7" alt="PCMR-Direct 0.256" /></td>
<td><img src="image8" alt="Numerical 0.256" /></td>
</tr>
</tbody>
</table>

Velocity (m/sec)

- 0.8
- 0.7
- 0.6
- 0.5
- 0.4
- 0.3
- 0.2
- 0.1
- 0.05
- -0.05
- -0.1

154
$t = 0.22$ sec (decelerating flow). Units are in m/sec.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>PCMR-Direct</th>
<th>Numerical</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>0.08</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>0.15</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>0.22</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

**Fig. 6.14:** Comparison of out of plane velocity contours of the rTOF subject at RPA from PC-MRI data with those from numerical computation. Times are, $t=0.06$ sec, $t=0.08$ sec and $t=0.15$ sec (accelerating flow) and $t=0.22$ sec (decelerating flow). Units are m/sec.
Whereas, the same ratio for the PC-MRI measurement was found to be was 0.67 at t=0.06 sec, 0.85 at t=0.08 sec, 0.92 at t=0.15 and 1.0 at t=0.22 sec.

6.4 Discussion

Obtaining accurate and realistic geometry from imaging in order to perform PS hemodynamics has been the focus of past researches [108,114,119,122]. The boundary conditions in these researches have been simplistic; namely idealized developed flow profiles. There is a gap in the research on incorporating PS boundary conditions for hemodynamic computations. Therefore, the focus of this research has been to obtain the PS velocity boundary conditions from PC-MRI measurements and integrate it with the PS geometry obtained from angiographic MRI. The methodology developed here, directly incorporates the time- and spatially- varying PS velocity data as boundary conditions for hemodynamic computation.

The in-vivo hemodynamic conditions in an artery are simulated, more accurately by using time- and spatially- varying PS velocity data as boundary conditions. Moreover, in the proposed methodology, the planes defining the inlet and outlets of the flow domain were also determined from the PC-MRI data itself. This eliminates the ambiguity in locating the inlet and outlet planes where the boundary conditions are applied. As a result, the velocity profiles are applied as boundary conditions at the exact location of the PC-MRI measurement. This is particularly useful for modeling developing flows, where the velocity profiles change from cross-section to cross-section along the length of the artery.

The accuracy of the velocity profiles obtained from our methodology were assessed in terms of flow rates. The calculated flow rates were compared with flow rates obtained independently by processing the PC-MRI data in Qflow software. It is possible to have some inaccu-
racies in flow rate calculation in QFlow, since the arterial boundary at each time point was incorporated in QFlow using semi-automatic means. Even though the manually drawn artery boundaries in QFlow were carefully constructed by ensuring that the velocity magnitude close to the boundary was near 0.0 cm/sec, the manually drawn boundary may not coincide with the true arterial boundary. This is because the PC-MRI phase values regions of low velocity close to the arterial walls may not be recorded accurately on the image. This could have contributed to the flow imbalance between the inlet flow rate, $F_{QM}$ at MPA and outlet flow rate, $F_{QL}+F_{QR}$ at LPA and RPA (Fig. 6.11A and 6.11D).

In the proposed methodology (PCMR-Direct), the fixed artery boundary from the reconstructed geometry was mapped on the PC-MRI phase image to calculate velocity profiles. Since the artery boundary in the reconstructed geometry could be somewhat different from the manually constructed boundary in QFlow, a mismatch between the flow rates from QFlow and PCMR-direct is expected (Fig 7). At the same time it is physically impossible to attain a perfect flow balance in PCMR-Direct either (Fig 8A and 8D). The numerically computed RPA flow rate is constrained by the continuity equation. The inlet flow rate at MPA and the outlet flow rate at LPA are determined by the applied velocity boundary conditions obtained from PCMR-Direct. Therefore, the flow imbalance inherent in the PC-MRI data affected the results of the numerical computation. For example, for the normal subject, the 7.7 ml/sec (20%) difference between the numerically computed RPA flow rate and that from PCMR-Direct was primarily the result of the flow imbalance of 6.6 ml/sec (Table 6.1). Likewise, the 2.1 ml/sec (9.4%) difference for the rTOF subject was also the result of the flow imbalance in the PCMR-Direct data (Table 6.2).

PC-MRI with higher resolution and MR with improved image contrast are expected to improve the flow balance.
6.4.1 Future work

The results of hemodynamic computation reported in this research can be improved by the following modifications to the computational model. These modifications could not be implemented in this study due to the unavailability of the requisite PS data. It should be noted that these modifications do not alter the proposed methodology.

The pulmonary arterial flow in the proximity of pulmonary valve has both axial (out-of-plane) and transverse (in-plane) component of the velocity vector. Currently, as a part of the standard of care clinical practice, PC-MRI is used to image only the axial component of the velocity vector. Therefore, this study was performed with the PC-MRI of only the axial component of the blood velocity at each of the inlet and outlets. However, PC-MRI can also image the transverse component of the velocity vector. The proposed methodology has an advantage that it can include both these velocity components simultaneously as boundary condition. In other words, it can also incorporate 3D velocity field obtained from 4D MRI data. Therefore, as a future work, the results for the numerical computation can be improved by including the transverse component of the velocity vector along with the axial component.

In the absence of the knowledge of the downstream arterial architecture of the RPA vasculature, an outflow boundary condition was applied at the end of the straight extension (Fig. 6.10). The flow resistance from the downstream RPA vasculature is expected to have an effect on the RPA velocity profiles [212-214]. Therefore, if the information of the downstream RPA vasculature is known for the patients, it is possible to incorporate a lumped parameter model based on the vasculature resistance with this methodology [106,135,137,138].
6.4.2 Limitations of fixed arterial wall geometry

One of the limitations of the proposed computational model is the assumption of rigid arterial wall. Our results for the flow rate data obtained from PC-MRI show an inherent flow imbalance of the order of 10% between inlet (MPA) and outlets (LPA and RPA). Therefore, hemodynamic computation based on a rigid wall model and a PS boundary condition may be adequate for obtaining time averaged flow rate (or mean velocity). However, existence of arterial wall compliance may also influence the flow balance. Fluid accumulation or discharge within compliant arterial wall was ignored as a result of the rigid arterial wall assumption. For a compliant artery, the geometry will also need to vary in time and space, in addition to the boundary condition being space and time varying. Capturing and implementing the time varying geometry accurately at different time points coupled with imaging of transient flow will require a significant enhancement in the field of imaging. In the future, a hemodynamic analysis with compliant arterial wall with PS material property and boundary condition could be investigated.

The arterial cross-section on the PC-MRI can possibly shift somewhat, from one phase image to another due to rigid body motion of the heart. This motion was small for pulmonary artery and was neglected for this study.

6.5 Conclusion

A novel methodology was developed to perform hemodynamic computation of the developing flow in branch PA distal to the pulmonary valve using PC-MRI based velocity measurement. One of the novelties of this methodology was combining the time- and spatially- varying \textit{in-vivo} velocity data obtained from PC-MRI as boundary conditions with PS arterial geometry. The other novelty was in the determination of the location of inlet or outlets, where the
boundary conditions were applied from the PC-MRI measurement planes itself. Therefore, for a developing flow near a valve, where the velocity profiles vary from cross-section to cross-section along the artery, this method provides a realistic computational model where the boundary conditions are applied unambiguously.

The computational results were obtained for a normal and rTOF subject. The accuracy of these velocity profiles was assessed using time averaged flow rate. The results for flow rates obtained from these profiles were in good agreement with the independently obtained flow rates by standard of care method using QFlow software. Specifically, for the normal subject, the difference between the computed flow rate and that obtained using QFlow was 0.8 ml/sec (0.9%) at the MPA, 2 ml/sec (3.4%) at the LPA and 1.4 ml/sec (3.8%) at the RPA. For the rTOF subject, the difference was 7 ml/sec (12.4%) at the MPA, 5.5 ml/sec (22.6%) at the LPA and 4.9 ml/sec (18.0%) at the RPA. The higher percentage differences for the subject with pulmonary insufficiency, was the result of overall lower values of the forward mean flow rate caused by excessive flow regurgitation.

We conclude that the methodology presented here is particularly suitable for modeling developing flows near valves. It has clinical relevance, being fully non-invasive in its data requirements. Although, the focus of this research was to model a developing flow, this methodology is applicable to any arterial flow. It also provides a non-invasive method for obtaining other hemodynamic endpoints such as pressure drop and wall-shear stresses. Therefore, it can be useful for design and analysis of medical devices such as valves, stents and grafts and for PS surgical planning and interventions.

Since the pulmonary artery is known to be distensible, for more accurate simulation of the PA flow, the arterial wall compliance needs to be incorporated in the mathematical model. In
the next chapter, methodology is developed for compliant wall blood flow interaction model with patient-specific PA geometry.
Chapter 7

Patient-Specific Hemodynamics with Compliant Arterial Wall

7.1 Introduction

In the previous chapter hemodynamic computation was performed with a rigid arterial wall model of a pulmonary artery. Arteries are known to be distensible [39,130]. Therefore, improved calculation of the energy exchange between the blood flow and distensible arterial wall under pulsatile pressure requires computational model with a compliant arterial wall.

The challenge in performing hemodynamic computation with compliant arterial wall is that it requires more data than simply the in-vivo arterial geometry and boundary conditions. Arteries are embedded in the surrounding tissues and are constrained by the adventitia and microvessels. These surrounding tissues and the arterial branches tether the artery motion in its in-vivo state. The tethering along with the mean arterial blood pressure and flow causes physiologic stresses in the arterial wall. This causes the in-vivo arterial wall to be pre-stressed. While, the arterial geometry are routinely developed from imaging data, the physiologic stresses present in
the *in-vivo* state are difficult to determine. Any hemodynamic computation with a rigid wall does lead to inaccurate results as it does not incorporate arterial wall pre-stress.

It is not trivial to measure *in-vivo* stresses in the arterial walls. In other words, the *in-vivo* stresses in the arterial wall are difficult to determine, and therefore these cannot be easily specified as initial condition in a numerical computation. An excised artery, when removed from the surrounding tissues, shrinks radially and longitudinally. Applying the *in-vivo* mean arterial pressure, and the longitudinal stretch to the un-loaded and un-tethered arterial geometry, and matching the *in-vivo* arterial geometry, results in a pre-stressed arterial geometry. Such computation requires: arterial wall thickness, its material properties, and the data for arterial shrinkage observed in an excised sample of the artery (please refer to Chapter 2). Therefore, performing hemodynamic computations with compliant arterial wall is a significantly more challenging task than one with the rigid wall assumption.

The computations with compliant arterial wall and blood flow were performed in three steps. First, the un-loaded and un-tethered arterial configuration was computed from the *in-vivo* configuration. A new *shrink-and-fit inverse* algorithm based on nonlinear least square optimization was developed to obtain the un-loaded, and un-tethered arterial geometry from the unstressed *in-vivo* geometry. In the second step, the *in-vivo* pre-stressed configuration was computed by applying mean *in-vivo* pressure and longitudinal stretch to the un-loaded and un-tethered arterial configuration. Finally, the pulsatile pressure-flow computation was conducted by applying the time varying pressure loads on the pre-stressed *in-vivo* arterial configuration obtained in the second step.

As was mentioned above, incorporating arterial wall compliance in hemodynamic computation requires a significant amount of physiological data. This data is less readily available
for a human pulmonary artery [130]. Therefore, the method and results presented in this chapter will be limited to using an idealized arterial geometry from our group’s previous research for demonstration of the proof-of-concept. A straight uniform diameter model of the femoral artery of a dog, based on the investigation by Sinha Roy et al., 2008 [152], was assessed for this research. Although the artery geometry for this study is axisymmetric, a 3D patient-specific geometry can be used in future.

7.2 Mathematical Model

Basic equations of motion for arterial wall and blood flow along with boundary conditions and additional compatibility constraints are presented below [98,147,152,153].

7.2.1 Blood Flow in Compliant Artery

Blood flow through compliant arteries involves flow in an arterial conduit with elastic wall. The pulsatile flow exerts forces on the arterial wall in the longitudinal (along the axis) and transverse (in direction normal to the axis) directions. The longitudinal forces result from the arterial wall shear stresses, whereas the transverse forces result from the pulsatile pressure exerted on the inner wall surface as normal traction [140,142]. Arteries are generally embedded in surrounding wall tissues called adventitia. Observations of in-vivo arteries show that the surrounding tissues significantly constrain the longitudinal wall motion. However, the wall motion in the transverse direction is constrained less significantly by the surrounding tissues [215,216]. The transverse wall motion of the arterial wall is typically in the form of dilation and contraction of the wall due to normal pressure on the wall. Therefore, the arterial wall is modeled as a deformable body that accounts for fluid-arterial wall (structure) interaction between blood flow and the arterial wall.
Fluid-structure-interaction (FSI) computation involves solution of the equation of motion for the fluid flow and arterial wall (solid) as a coupled system. The pressure load from the blood flow on the arterial wall results in radial wall movement. The equation of motion of the arterial wall is solved for wall deformation field, \( d = (d_j), j=1,2,3 \), whereas those for blood flow are solved for velocity distribution, \( u =(u_j), j=1,2,3 \), and pressure, \( p \). Additional compatibility constraints on flow velocity, \( u \), and wall displacements, \( d \), are imposed at the common surface between the arterial wall and blood flow. The basic equations for FSI in arterial flow are described below.

### 7.2.2 Fluid Model: Blood Flow

**Flow equations.** The blood flow was modeled with assumptions of unsteady, laminar, incompressible flow. The governing equations are:

\[
u_{i,j} = 0 \quad \text{(Continuity equation)} \tag{7.1}
\]

and

\[
\rho \left( \frac{\partial u_j}{\partial t} + u_j u_{i,j} \right) = -p_{,i} + \left[ \mu (u_{i,j} + u_{j,i}) \right], \quad i,j=1,2,3 \quad \text{(Momentum equation)} \tag{7.2}
\]

where, \( \rho \) is the density of blood (1.05 gm/cc), \( p \) is the static pressure, \( \mu \) the blood viscosity and \( u_i, i=1,2,3 \) are the components of velocity field.

**Blood material model.** The blood was modeled as non-Newtonian Carreau fluid [186] with shear rate (\( \dot{\gamma} \)) dependent blood viscosity, \( \mu \), given by:

\[
\mu (\dot{\gamma}) = \mu_\infty + (\mu_0 - \mu_\infty) \left(1 + A \dot{\gamma}^2 \right)^n \tag{7.3}
\]

The parameters are: \( \mu_\infty = 0.0345 \) poise, \( \mu_0 = 0.56 \) poise, \( A = 10.975 \) sec\(^2\), \( n = 0.3568 \), and the shear rate \( \dot{\gamma} \) (in sec\(^{-1}\)) is,
\[
\dot{\gamma} = \sqrt{\frac{1}{2} \left[ \sum_i \sum_j \dot{\gamma}_{ij} \dot{\gamma}_{ji} \right]}. \\
\] (7.4)

Fluid domain boundary conditions. Pulsatile pressure pulse, \( p_{\text{in}}(t) \) and \( p_{\text{out}}(t) \) was applied as pressure (normal traction) on the planar inlet and outlet surfaces of the flow domain. Therefore:

\[
p|_{\text{inlet}} = p_{\text{in}}(t) \tag{7.5a}
\]

and

\[
p|_{\text{outlet}} = p_{\text{out}}(t). \tag{7.5b}
\]

The inlet and outlet velocity profiles were assumed to be developed profiles by imposing:

\[
\frac{\partial u}{\partial n}|_{\text{inlet,outlet}} = 0 \tag{7.6}
\]

where, \( u \) and \( n \) are the velocity vector and unit normal at each of the inlet and outlet surfaces [147,152,153].

7.2.3 Solid Model: Arterial Wall

Governing equations. The governing equations for the solid model are the equations of motion:

\[
\rho \ddot{d}_i = \sigma^S_{ij} \tag{7.7}
\]

where, \( \ddot{d}_i, i=1,2,3 \) are the component of acceleration vector, and \( \sigma^S_{ij} \) are the components of the Cauchy stress tensor representing arterial wall stresses (superscript \( S \) stands for solid).

Arterial wall material model. Arterial wall material was modeled as isotropic, incompressible, hyperelastic material. The strain energy density function, \( W \), was assumed to be of generalized Mooney-Rivlin type of form:
\begin{equation}
W = \sum_{p+q=1}^{N} C_{pq} (I_1 - 3)^p (I_2 - 3)^q \tag{7.8}
\end{equation}

of order \( N=2 \), in terms of the invariants \( I_1 \) and \( I_2 \) \([2,158,167,169]\). The material constants \( C_{pq}, p, q = 0, 1, 2 \) were obtained by nonlinear least square fit between calculated Cauchy stresses based on the strain energy function \( W \) and the corresponding experimentally obtained values. The Cauchy stresses are obtained from \( W \) by:

\begin{equation}
\sigma_1^S = 2\left(\lambda_1^2 - \lambda_1^{-2}\lambda_2^{-2}\right)\left(\frac{\partial W}{\partial I_1} + \lambda_1^2 \frac{\partial W}{\partial I_2}\right) \tag{7.9a}
\end{equation}

and

\begin{equation}
\sigma_2^S = 2\left(\lambda_2^2 - \lambda_1^{-2}\lambda_2^{-2}\right)\left(\frac{\partial W}{\partial I_1} + \lambda_2^2 \frac{\partial W}{\partial I_2}\right) \tag{7.9b}
\end{equation}

where, \( \lambda_l \ (l=1,2) \) are the principal stretches in direction \( l \) determined by the deformation imposed by material testing process on the sample. The principal stretches \( \lambda_l \ (l=1,2,3) \) are related to engineering strains, \( \varepsilon_{ll} \) by:

\begin{equation}
\varepsilon_{ll} = \lambda_l - 1 \tag{7.10}
\end{equation}

The strains \( \varepsilon_{ij} \) in the arterial wall are also related to wall deformation field \( d \) by:

\begin{equation}
\varepsilon_{ij} = \frac{1}{2} \left( d_{i,j} + d_{j,i} + d_{ki}d_{kj} \right) \tag{7.11}
\end{equation}

where, the repeated index in \( k \) represents a summation over \( k=1,2,3 \).

**Boundary conditions.** On the outer wall surface of the artery, a no traction boundary condition:

\begin{equation}
\sigma_{ij}^S n_j = 0 \tag{7.12}
\end{equation}
was applied, where $\sigma_{ij}^S$, $i,j=1,2,3$ are the components of the stress tensors in solid domain and $n=(n_j), j=1,2,3$ is a unit vector normal at a point on the outer surface of the wall [147,152,153].

7.2.4 Fluid-Solid Boundary

Conditions for displacement, velocity and traction compatibility are imposed on the inner arterial wall surface which is the surface of contact between the arterial wall and blood [147,152,153]. It is assumed that arterial wall does not collapse and there is no separation between blood and wall surface at any time during the cardiac cycle.

The displacement compatibility due to no separation contact at the inner arterial wall is:

$$d^S = d^F \quad (7.13)$$

where, $d^S$ and $d^F$ are the displacement of the same point at the solid and fluid contact surface, respectively. The compatibility of normal traction is given by:

$$\sigma_{ij}^S \cdot n_j = \sigma_{ij}^F \cdot n_j \quad (7.14)$$

where, $\sigma_{ij}^S$ and $\sigma_{ij}^F$, $i,j=1,2,3$ are the components of the stress tensor in the solid and fluid domain respectively, and $n=(n_j), j=1,2,3$ is a unit vector normal at a point on the inner surface.

No slip velocity boundary condition was applied on the inner arterial wall $S_i$ as:

$$u|_{S_i} = \bar{d}|_{S_i} \quad (7.15)$$

7.2.5 Numerical Solution

Arbitrary-Lagrangian-Eulerian (ALE) formulation was used to solve the FSI equations. ALE formulation is a numerical technique that is implemented as a combination of Lagrangian
and Eulerian formulation for solving boundary value problems. Typically, Lagrangian formulation is adopted for structural deformation problems where the structural mesh undergoes large deformation under the applied loads. In contrast, Eulerian formulation is adopted for fluid flow problems where the computational mesh remains static in space but incorporates convection and advection of physical quantities in the mathematical formulation. ALE formulation combines the two methods by allowing the fluid domain computational mesh to be Eulerian but at the same time “deform or move” with the distortion of the Lagrangian mesh for the structural domain [217]. However, since the amount of structural deformation is not known a-priori in any FSI problem, an arbitrary velocity known as mesh velocity, \( u_m = (u_{mj}), j=1,2,3 \) is incorporated in the computational equations for fluid flow. The modified N-S equations for the ALE formulation are:

\[
\rho \left[ \frac{\partial u_i}{\partial t} + (u_j - u_{mj})u_{ij} \right] = -p_i + \left[ \mu (u_{i,j} + u_{j,i}) \right]_j
\]  

(7.16)

This mesh velocity, \( u_m \), is based on heuristics of the ALE algorithm and gives the qualifier “arbitrary” to the name of ALE method [218].

7.3 In-vivo Pre-stress in Arterial Wall

Different stress states of an arterial segment are described in details in Chapter 2. As was explained in Chapter 2, an excised artery shrinks longitudinally as well as radially in the absence of in-vivo loading and tethering from the surrounding tissues and arterial branches. This implies that in-vivo arteries in the body are in a state of physiologic pre-stress. The untethered and unloaded artery, excised from the body and without the surrounding tissues, will be referred to as load-free artery. The arterial geometry obtained from imaging without physiologic stresses will
be referred to as *in-vivo* unstressed geometry. The loaded and tethered state of arteries *in-vivo* will be referred to as the *in-vivo* pre-stressed artery or simply the *pre-stressed* artery (see Chapter 2).

Application of physiologic pulsatile *in-vivo* pressure directly to the reconstructed geometry, which does not have any *in-vivo* stresses, will result in excessive radial deformation. In concept, the load-free geometry is obtained from the *in-vivo* geometry by radially and longitudinally shrinking the *in-vivo* arterial geometry. The load-free geometry, when imposed with *in-vivo* loads, must deform to the *in-vivo* geometry. Therefore, improved hemodynamic computation with compliant arterial wall requires wall pre-stress in the *in-vivo* geometry.

To obtain the pre-stressed state of the artery, first the load-free geometry was calculated from the *in-vivo* geometry. A new computational algorithm was developed to calculate the load-free arterial geometry from patient-specific *in-vivo* geometry. The proposed algorithm is referred to as the *shrink-and-fit inverse* algorithm. The pre-stressed arterial geometry was calculated by applying the *in-vivo* mean pressure and axial extension to the load-free geometry.

### 7.4 Computation of Load-free Arterial Geometry

The shrink-and-fit inverse algorithm is an optimization based elastostatic inverse method for calculating the load-free geometry from the *in-vivo* geometry. It computes the load-free arterial wall geometry, by using a nonlinear least square technique to minimize the deviation between the points of the *in-vivo* arterial wall, and those of the *pre-stressed* arterial wall, obtained by the application of *in-vivo* pressure and longitudinal stretch to the load-free wall.

The *in-vivo* data that is required as input for the algorithm consists of: *in-vivo* mean pressure, $p_f$, the longitudinal shrinkage of the artery from *in-vivo* length, and the *in-vivo* arterial wall geometry. The algorithm is implemented using two basic operators: a *shrink operator*, $S$, and a
fit operator, $F$. Both shrink ($S$) and fit ($F$) apply a combination of longitudinal and radial deformation to the given arterial geometry. The longitudinal deformation, $\chi_{LS}$, deforms the arterial wall longitudinally. It shrinks or stretches the arterial geometry longitudinally and at the same time maintains its in-vivo shape. The radial deformation, $\chi_{RS}$, deforms the artery radially. It stretches (expands) or shrinks (contracts) the arterial geometry in the radial direction.

Notation. To describe the working of the algorithm the following notation is adopted.

$x_I$: A point in the unstressed in-vivo arterial wall geometry obtained from image reconstruction.

$x_L$: A point in the load-free wall.

$x$: A point in the pre-stressed wall.

An arterial configuration $A$, in a state of stress $\sigma$ is represented by $A(X, \sigma)$, where,

$X$: is a point in the wall (used for indicating the geometry being referred to).

$\sigma$: is used to denote $A$ to be in the state of stress tensor.

A zero stress state will be designated by $\hat{0}$ (null) tensor. It may be noted that $x_L$ and $x$ will also be used to refer to points of the trial load-free and trial pre-stressed geometry, respectively, which are generated in the computational iterations of the shrink-and-fit inverse algorithm. Using the above notation:

$A(x_I, \hat{0})$: represents an in-vivo wall reconstructed from imaging in $\hat{0}$ stress state.

$A(x_L, \sigma)$: represents a load-free artery in a state of stress state, $\sigma$.

$A(x_L, \hat{0})$: represents a load-free artery in a stress-free state, i.e., in the state of stress $\hat{0}$.

$A(x, \sigma)$: represents pre-stressed artery.

The load-free arterial state, $A(x_L, \hat{0})$, without stresses is obtained from, $A(x_I, \sigma)$, by deleting the stresses from the $A(x_I, \sigma)$, so that only the load-free geometry is retained.
Fig. 7.1: Block diagram of the shrink-and-fit algorithm to compute the load-free and pre-stressed geometry from the in-vivo geometry, load, and longitudinal shrinkage.
Fig. 7.2: Pictorial representation of the shrink-and-fit algorithm.
**Shrink-and-fit inverse algorithm.** Mathematically, the algorithm can be stated as: given the unstressed in-vivo geometry \( A(x_I, 0) \), mean in-vivo pressure \( p_I \) and in-vivo axial stretch \( \delta_I \), calculate the load-free configuration \( A(x_L, 0) \) and the in-vivo pre-stresses configuration \( A(x, \sigma) \), by using nonlinear least square technique by minimizing \( \| x - x_L \| \) over all points of \( A \).

The block diagram of the shrink-and-fit inverse algorithm is presented in Fig. 7.1. A pictorial description of the process starting with the construction of the input in-vivo wall geometry is presented in Fig. 7.2 in form of a flow chart.

The key steps of the shrink-and-fit process are shown in Fig. 7.3, using a patient specific PA wall geometry. The computation of the load-free wall geometry and the pre-stressed geometry for this case will be performed in future study, after obtaining the material properties and the in-vivo longitudinal shrinkage data of a PA wall.

### 7.4.1 In-vivo Wall Geometry

In a patient specific scenario, the in-vivo arterial wall geometry can be constructed from in-vivo lumen surface geometry (Fig. 7.2). The in-vivo lumen surface geometry is obtained by image reconstruction using angiographic MRI.

Thus, for patient specific PA, the lumen surface of the blood flow domain was obtained by image reconstruction using the patient’s angiographic MRI (Fig. 7.3A). This surface forms the shape of the inner wall surface of the in-vivo PA. The surface is represented by a mesh of STL triangles.

The 3D geometry of the PA wall was constructed by offsetting the lumen surface in the outward normal direction by in-vivo wall thickness (Fig. 7.3B). The offsetted surface forms the outer surface of the arterial wall. The outward normal direction was computed for each node of
the STL mesh by the following procedure (Fig. 7.4). A set of all triangles, \( T = \{ T_1, T_2, \ldots \} \), connected at the particular node was determined. The local normal \( N \) at the particular node was calculated by:

\[
N = \frac{\sum k \alpha_k e_k}{\sum k \alpha_k},
\]  

(7.17)

where, \( e_1, e_2, \ldots \) are the unit normals of the individual triangles, \( T_1, T_2, \ldots \) and \( \alpha_1, \alpha_2, \ldots \) are the included angle at the node for these triangles. The position of the node on the outer wall surface \( R \), was calculated from the position of the inner wall node \( r \), by:

\[
R = r - t\hat{n}.
\]  

(7.18)

where, \( r \) is the in-vivo wall thickness and \( \hat{n} = N/\|N\| \) is the unit normal vector at the node (Fig. 7.4).

In general the patient-specific wall thickness is difficult to obtain under physiologic condition. For the subject in this study, the resolution of MRI acquired as a part of standard of care, was inadequate to capture the PA wall thickness. Therefore, wall thickness equal to 10% the mean lumen diameter was adopted for PA based on published data [219]. The surface of the 3D artery was also formed using an STL mesh of surface triangles (Fig. 7.3B). This 3D arterial geometry was used for constructing the finite element model of the radial deformation operator, \( \mathcal{X}_{RS} \), and longitudinal deformation operator, \( \mathcal{X}_{LS} \).

The arterial wall geometry was meshed with 51,230, 8-noded linear hexahedral elements (Fig. 7.3C) for the finite element model of the deformation operators. A total of 5 elements were generated across the wall thickness. It may be noted that the finite element mesh can be finer (or coarser) than STL triangles depending on the desired numerical accuracy. The boundary condi-
tions, constraints and loads required by the deformation operators $\chi_{RS}$ and $\chi_{LS}$ were specified to this finite element mesh (Fig. 7.3D).
Fig. 7.3: Intermediate steps of the shrink-and-fit algorithm. A) Lumen surface in form of triangular mesh of STL triangles obtained by geometry reconstruction. B) Arterial wall geometry in form of STL-mesh of surface triangles. C) Finite element mesh of the wall geometry using 8 node hexahedral elements. D) Constraints imposed on the arterial wall motion in each shrink and fit iteration. Rigid contact surface superimposed on the outer arterial wall surface and extended at the ends, to maintain arterial shape during the longitudinal (axial) shrink or stretch operation. Contact surface meshed with 4-noded quadrilateral elements. Only in-plane radial motion in $d_r$-$d_\theta$ plane allowed for the nodes of the inlet and outlet surfaces. Additionally, nodes of the outlets are allowed to move in $d_z$ direction during longitudinal stretch or shrink operation.
7.4.2 Radial and Longitudinal Wall Deformations

The shrink-and-fit inverse algorithm (Fig. 7.1) performs two basic deformation operations on the arterial wall: 1) longitudinal deformation, $\chi_{LS}$, and 2) radial deformation, $\chi_{RS}$. As mentioned above, both these operations are part of shrink ($S$) as well as fit ($F$) operators (Fig. 7.1). This section describes these deformation operations along with their boundary conditions and constraints.

**Longitudinal deformations, $\chi_{LS}$**. The longitudinal deformation operator performs a longitudinal shrinking or stretch of the artery, maintaining its *in-vivo* shape. It is denoted by:

$\chi_{LS}(X, \delta_l)$ and its inputs are the arterial configuration represented by, $X$ and a real number, $\delta_l$.

The parameter $\delta_l$ is the incremental longitudinal deformation applied at the outlets of the arterial wall in the direction $d_z$ for extending or shrinking the wall geometry (Fig. 7.3D). If $\delta_l > 0$, $\chi_{LS}$ stretches the artery whereas, for $\delta_l < 0$, it shrinks the artery. Therefore, $\chi_{LS}$ performs a longitu-
dinal shrink or stretch, respectively, depending on negative or positive value of $\delta_1$. The boundary conditions and constraints used by $\chi_{LS}$ to maintain the in-vivo arterial shape are described below.

*Maintaining in-vivo shape during longitudinal deformation, $\chi_{LS}$.* A rigid contact surface coinciding with the outer surface of the arterial wall was created to maintain the in-vivo arterial shape (Fig. 7.3D). The contact between the rigid contact surface and the arterial wall was modeled as a frictionless sliding contact with no separation constraint. The surface was extended at the inlet as well as outlet for robustness of the contact algorithm. At the outlets, displacement $d_3$ was applied to longitudinally shrink or stretch the artery. Therefore, the sign of displacement $d_3$ determines the type of deformation operation: shrink ($d_3 < 0$) or stretch ($d_3 > 0$).

*Radial deformations, $\chi_{RS}$.* The radial deformation operator performs radial expansion (stretch) or contraction (shrink) of the artery. The radial deformation can be performed in two ways: 1) a geometrical scaling by offsetting the nodes in the normal direction, and 2) by expanding the arterial wall by applying a mean arterial pressure, $p_r$. In the process of radial deformation by geometrical scaling, no wall stresses are produced. However, in the process of radial expansion under pressure load, stresses are generated. Like $\chi_{LS}$, the radial deformation is denoted by: $\chi_{RS}(X, a)$ and its inputs are the arterial configuration represented by $X$ and a real number $a$. The parameter $a$ can be pressure in the case of pressure induced deformation, or it can be a real number $\delta_r$ for the geometric scaling operation. The pressure induced radial deformation can only result in a radial expansion of the arterial wall. A negative value of inner wall pressure is not allowed as it will lead to material instability. For geometric deformation by scaling, $\chi_{RS}$ can radially expand the artery by applying a radial stretch $\delta_r$, $\delta_r > 0$, or it can radially shrink the
artery by applying $\delta_r < 0$. Therefore, for simplicity of notation, the second input of $\chi_{RS}$, the parameter $a$, will be used interchangeably to specify pressure, $p_I$, or radial stretch, $\delta_r > 0$, or radial shrink, $\delta_r < 0$.

**Boundary conditions and constraints for radial shrink or stretch, $\chi_{RS}$**: The radial deformation by geometric scaling, i.e., $\chi_{RS}(X, a)$ with the parameter $a$ being $\delta_r$, does not require any boundary condition. The process of application of $\delta_r > 0$ or $\delta_r < 0$ is a geometrical operation involving modification of nodal coordinates. The coordinates of the new point, $X$, is calculated from the position of the old point $x$ on the surface of the STL mesh of the arterial wall (Fig. 7.3B) by using the normal vector calculated by Eq. 7.17. The nodal positions are modified according to:

$$X = x + \delta_r \hat{n};$$  \hspace{1cm} (7.19)

where, similar to Eq. 7.18, $\delta_r$ is the parameter controlling stretch or shrink and $\hat{n} = N/\|N\|$ is the unit normal vector at the node (Fig. 7.4).

When mean *in-vivo* pressure, $p_p$ is applied to expand the artery, the deformation is the result of arterial wall expansion subjected to pressure load. As the first step in this deformation process, the rigid contact surface is deactivated and internal stresses are allowed to equilibrate with applied loads and reaction forces. Thus the artery expands radially in an outward direction.

**Inlet and outlet constraints**. The arterial wall is known to predominantly deform in the radial direction due to the pulsatile pressure induced by the flow. For patient-specific arterial geometry, this radial direction is the local normal vector at the individual point on the inner wall surface. To obtain finite element solution, the wall was constrained to prevent rigid body motion. A local reference node was created at the centroid of each of the inlet and outlets (Fig. 180).
7.3D). A local cylindrical coordinate system, \((r, \theta, z)\), was created at the location of the reference node at each inlet and outlet. The reference node at the centroid of each inlet and outlet, served as the origin of the coordinate system and the coordinate \(z\) points in the direction normal to the cross-sectional plane. The nodal constraints for the nodes on the inlet and outlet cross-sectional plane of the arterial wall were defined with respect to this local cylindrical coordinate system. Deformation of all nodes on a particular inlet or outlet was constrained with respect to the reference node. All the nodes on the inlet and outlet were allowed to move in the radial direction from the reference node at the origin of the local coordinate system, \((r, \theta, z)\), in the \(r-\theta\) plane. Motion of those nodes in the \(z\) direction was prevented at the inlet. At the outlets, motion in \(z\) direction was allowed in order to apply longitudinal shrink or stretch. These inlet and outlet nodal constraints were specified for both the radial shrink (or stretch) as well as the longitudinal shrink (or stretch) operator, \(\chi_{RS}\) and \(\chi_{LS}\), respectively.

7.4.3 Shrink and Fit Operators

*Shrink operator (S).* The shrink operator, \(S\), contracts (shrinks) the *in-vivo* geometry, \(A(x_1, 0)\) to a trial load-free geometry, \(A(x_L, 0)\). It consists of a sequence of radial deformation, \(\chi_{RS}\) and a longitudinal deformation, \(\chi_{LS}\). It requires two arguments to control the longitudinal and radial deformations: a parameter for longitudinal shrinkage, \(\delta_\ell\), and a parameter for radial shrinkage, \(\delta_r\). The value of the longitudinal shrinkage has to be less than zero \((\delta_\ell<0)\), for shrinking the artery length wise. Likewise, the value of the radial shrinkage \(\delta_r\) is also less than zero for contracting the artery radially. The shrink deformation is applied in two stages: radial
shrink, $\chi_{RS}$ followed by longitudinal shrink, $\chi_{LS}$. The radial deformation operator, radially shrinks the in-vivo geometry by $\delta_r$, $\delta_r<0$:

$$x_{RS} = \chi_{RS}(x, \delta_r).$$  \hfill (7.20)

The point, $x_{RS}$, is a point on the radially shrunk geometry resulting from the operation. It may be noted that the radial shrink operation performed on $S$ is geometrical shrinking and it does not result in stresses in the wall. The operation of longitudinal shrinking, shrinks the radially shrunk geometry by $\delta_l$, $\delta_l<0$ is:

$$x_{L} = \chi_{LS}(x_{RS}, \delta_l).$$  \hfill (7.21)

The point, $x_{L}$, is a point on the load-free arterial geometry. Therefore, shrink operator $S$ is a composition of $\chi_{RS}$ and $\chi_{LS}$, i.e.,

$$S = \chi_{RS} \circ \chi_{LS},$$ \hfill (7.22)

where, $\circ$ represents the composition of two functions, defined as: $f_2 \circ f_1 = f_1(f_2(x))$.

The boundary conditions and constraints for $\chi_{RS}$ and $\chi_{LS}$ have been described in the last section. The arterial wall resulting from shrink operator has stresses. These stresses are deleted to obtain the load-free geometry (Fig. 7.1 and 7.2).

**Fit operator ($F$).** The fit operator applies the in-vivo mean pressure, $p_I$ and the longitudinal stretch, $\delta_l$ to the load-free geometry, $A(x_L, 0)$, produced by shrink operator. It requires two input parameters, the in-vivo axial stretch, $+\delta_l$, for longitudinal stretch, and mean arterial pressure, $p_I$ for radial stretch. Both shrink and fit are implemented using the same two basic deformation operators: radial shrink or stretch, $\chi_{RS}$ and longitudinal shrink or stretch, $\chi_{LS}$. 

182
Deformation for fit is applied in two stages: longitudinal stretch, $\chi_{LS}$ followed by radial stretch, $\chi_{RS}$. Longitudinal stretch, stretches the trial load-free geometry by in-vivo stretch, $\delta_l$:

$$x_1 = \chi_{LS} (x_L, +\delta_l). \quad (7.23)$$

The point, $x_1$, is a point on the resulting geometry. Radial stretch, expands the geometry resulting from longitudinal stretch by applying in-vivo mean pressure, $p_I$:

$$x = \chi_{RS} (x_1, p_I). \quad (7.24)$$

Therefore, fit operator $F$ is a composition of $\chi_{LS}$ and $\chi_{RS}$, i.e.,

$$F = \chi_{LS} \circ \chi_{RS}. \quad (7.25)$$

The end result of the fit operator is a trial pre-stressed geometry, $A(x, \sigma)$.

### 7.4.4 Optimization Method

The optimization loop in the shrink-and-fit inverse algorithm, starts with an initial guess of $\delta_r$, and $\delta_l$. It applies the shrink operator $S$ on the in-vivo geometry, followed by the fit operator, $F$, to calculate a trial pre-stressed geometry, $A(x, \sigma)$. A trial load-free geometry, $A(x_L, \emptyset)$ is also generated in each iteration (Fig. 7.1, 7.2). At the end of each optimization loop, the trial pre-stressed geometry is compared with the in-vivo geometry by evaluating the least square objective function:

$$\mathcal{E} = \|x - x_I\|_\Omega = \sqrt{\sum_\Omega \|x - x_I\|^2}, \quad (7.26)$$

which represents the sum of deviation between points of the in-vivo artery and the deformed artery obtained by application of in-vivo pressure and longitudinal stretch to the load-free arterial geometry. Therefore, in $x$ in Eq. 7.26 is the coordinate of a point on the deformed geometry.
obtained by application of *in-vivo* pressure and longitudinal stretch to the load-free artery, and \( \mathbf{x}_i \) is the coordinate of the corresponding point on the *in-vivo* geometry obtained by image reconstruction. In the optimization loop, the “trial” pre-stressed artery, i.e., the artery obtained by application of *in-vivo* pressure and longitudinal stretch to the “trial” load-free arterial geometry is updated in each iteration. The values of the optimization variables, \( \delta_r \), and \( \delta_l \) are updated by the Nelder-Mead optimization algorithm based on the value of the objective function \( \varepsilon \). The next iteration repeats with those new values of \( \delta_r \), and \( \delta_l \). In general, the set of points \( \Omega \) for the summation in Eq. 7.26 contains all points of the artery. However, in the actual implementation, the minimization of \( \varepsilon \) was carried over the set of points of the outer surface only (and not the whole artery). This enhanced the performance of the optimization algorithm. If points on the outer surface of the *in-vivo* and pre-stressed artery are near to each other, due to incompressibility, the points of the inner wall surface are also expected to be close to the *in-vivo* inner diameter.

Gradient free Nelder-Mead optimization was used to iterate on the values of \( \delta_l \) and \( \delta_r \) until minimization was attained. A predetermined parameter \( \varepsilon \) was used for termination of the algorithm. The objective function value (Eq. 7.26), \( \varepsilon \), represents the square-root of the sum of squares of nodal deviations. The value of \( \varepsilon < 0.5 \) was found to be adequate in practice. A normalized \( \varepsilon \) weighted by total number of nodes used for summation may also be used in future.

*Convergence of the shrink-and-fit inverse algorithm.* The convergence of the shrink-and-fit inverse algorithm is shown in Fig 7.5. The rate of convergence is depicted in terms of the value of the least-square objective function at the \( i \)-th evaluation from the beginning of the shrink-and-fit process. The \( x \)-axis shows the number of objective function evaluations from the start of the process and the \( y \)-axis shows its corresponding value at that evaluation. It may be noted for clarification, that the shrink-and-fit process is driven by the Nelder-Mead optimization
algorithm (Fig. 7.1). A single Nelder-Mead iteration consists of multiple objective function evaluations. Therefore, the $x$-axis value shows the cumulative number of objective function evaluations as part of the Nelder-Mead optimization loop (Fig. 7.1).

The test for convergence was conducted with a 3-D idealized geometry of the femoral artery of a dog presented below. The arterial wall material for the test was assumed to be linearly elastic with Young’s modulus, $E=0.77$ $N/mm^2$ and Poisson’s ratio, $\nu=0.49$.

![Fig. 7.5: Convergence of the shrink-and-fit optimization algorithm in terms of the objective function value and the number of function evaluation.](image)

Nelder-Mead is a gradient-free optimization algorithm. Therefore, unlike a gradient-based or a Hessian matrix evaluation based optimization algorithm, an initial guess with objective function value closer to optimal solution does not necessarily guarantee a faster convergence. However, with a better initial guess the shrink and fit algorithm was found to converge
within 20 to 30 evaluations of the objective function. In practice, the objective function values from the first few function evaluations provided a reasonable initial guess for $\delta_i$ and $\delta_r$. For the present methodology, an objective function value of 0.5 or less was found to provide an acceptable optimal solution. The maximum nodal deviation was found to be only 0.0015 mm with the objective function value of 0.5.

7.4.5 Implementation Details

The complete methodology presented above has been implemented using python scripting language in ABAQUS CAE (Dassault Systems, Paris, France) application. The program was implemented in two modules: 1) model building module and 2) optimization module. The model building module was implemented to construct the finite element model by taking an input of the in-vivo lumen surface STL mesh, in-vivo thickness, wall material properties and mean arterial pressure. The optimization module performed the iterations of shrink and fit operations within the Nelder-Mead algorithm. The optimization module was implemented using Nelder-Mead subroutines from python Numpy and Scipy libraries.

7.5 Application of Inverse Algorithm: Canine Femoral Artery

The methodology presented in this chapter was developed specifically for performing a patient-specific hemodynamic computation with compliant arterial wall. Before conducting computations for a patient-specific pulmonary arterial flow, the method was tested for a simple arterial geometry from our previous publication [152]. This consisted of a uniform diameter idealized straight cylindrical model of a canine femoral artery adopted from Sinha-Roy et al., 2008.
The results of pre-stress and load-free geometry computation, and the stresses and deformations under pulsatile pressure were obtained by applying the proposed methodology.

Sinha-Roy et al., 2008, used an axisymmetric geometry and blood flow in the idealized dog femoral artery. Therefore, this study adopted an axisymmetric computational model for arterial wall-flow interaction. To demonstrate the proposed inverse methodology which was specifically developed for calculating load-free geometry in a patient-specific case, a 3D arterial wall geometry was constructed. Thus, the results presented here mimic the exact steps as in the case of a patient-specific scenario.

**Arterial geometry.** The idealized geometry of dog-femoral artery adopted here consists of a straight arterial segment of uniform cross-section with a length of 52 mm, inner radius of 1.8 mm and thickness of 0.27 mm (Fig. 7.6). The arterial geometry used by Sinha-Roy et al., 2008, was straight tapered artery. The inner wall radius of 1.8 mm (Fig. 7.6) in this study corresponds to the inner wall radius at the outlet of the tapered artery used by Sinha-Roy et al., 2008. Comparison of arterial dimensions adopted here with those of Sinha-Roy et al., 2008, are also presented in Table 1.

**Fig. 7.6:** Geometry used for the compliant arterial wall-blood flow interaction with arterial pre-stress. The arterial dimensions of this straight, uniform diameter, canine femoral artery were adopted from Sinha-Roy et al., 2008.
Arterial wall material property. The arterial wall material was modeled as homogeneous, incompressible, isotropic, hyperelastic material. The constitutive equations for wall material was derived using the generalized Mooney-Rivlin strain energy density function (Eq. 7.8) of order N=2. The material constants: $C_{10} = 11570.53 \text{ dynes/cm}^2$, $C_{01} = -3137.05 \text{ dynes/cm}^2$, $C_{20} = 136893.47 \text{ dynes/cm}^2$, $C_{11} = 79420.13 \text{ dynes/cm}^2$, and $C_{02} = 4430.36 \text{ dynes/cm}^2$ were obtained by nonlinear least square curve fitting technique using the circumferential stress-strain data for dog femoral artery [220]. The result of the curve fitting is shown in Fig. 7.7A, where the $x$-axis values are principal stretch ratios and the $y$-axis values represent Cauchy stresses. The continuous curve is the plot of Cauchy stresses in the circumferential direction obtained from the curve fitting of the experimental stress-stretch data of the arterial wall. The experimentally obtained longitudinal stresses and longitudinal stretches are also plotted in the same figure for comparison. Since the material testing was performed with an excised sample of the femoral artery, the stress-strain data obtained from testing [220] can be directly adopted for cylindrical arterial geometry for the present study.

The contour plot of the strain energy density, $W$ (Eq. 7.8) as a function of the axial and circumferential stretch ratios, $\lambda_z$ and $\lambda_\theta$, respectively, is presented in Fig. 7.7B. The magnitude of strain energy density, $W$, at $\lambda_z = \lambda_\theta = 1$ is 0.0. The contours of the strain energy density function, $W$, are convex in shape. This implies that the material model obtained by curve fitting is stable and a positive value of energy is required for finite deformation of the material.

Load-free and pre-stressed wall. The load-free arterial wall geometry was obtained by the shrink-and-fit inverse algorithm described in the previous section. The algorithm also calculates the pre-stressed arterial geometry. The results for stresses, strains and wall deformations under mean arterial pressure and in-vivo longitudinal stretch were obtained from the pre-stress
model. The mean in-vivo arterial pressure, \( p_I \) was assumed to be 104.1 mmHg and the in-vivo axial stretch for the femoral artery was assumed to be 48% of the load-free artery length.
Fig. 7.7: (A) Experimental data and curve-fit of the circumferential Cauchy stress and stretch data of dog femoral artery from Attinger et al., 1968. The curve-fit generated using generalized Mooney-Rivlin model with $N=2$. (B) Contour plot of the corresponding strain energy density function.
Analytical and computed stresses in linear-elastic arterial wall: a validation step. The material model of the load-free arterial geometry calculated by the shrink-and-fit inverse algorithm was set to a linear elastic material with elastic modulus, $E=0.767$ N/mm$^2$, and Poisson’s ratio, $\nu=0.49999$. The geometry was longitudinally stretched with in-vivo longitudinal stretch, and pressurized with the mean in-vivo arterial pressure. Stresses, strains and deformations in the arterial wall in $r$, $\theta$ and $z$ directions were calculated using the numerical model. These results were compared with the ones calculated using the analytical solution obtained from the theory of elasticity for a thick cylinder of linear elastic material subjected to internal pressure and axial elongation. This procedure was performed to test the accuracy of the boundary conditions and constraints imposed on the finite element models for radial ($\chi_{rs}$) and longitudinal deformation ($\chi_{ls}$) operators.

Pre-stressed wall. Pre-stressed wall was obtained from the load-free arterial wall by applying the in-vivo longitudinal stretch and the mean in-vivo arterial pressure. The arterial wall material property used in the computation was the hyperelastic model presented above. The material constants for the arterial wall were obtained from curve-fitting of the actual test data for canine femoral artery [220]. The actual computation of the pre-stressed arterial wall was performed by the shrink-and-fit inverse algorithm following computation of the load-free arterial geometry.

Pulsatile pressure-flow response. The pulsatile pressure-flow response on the arterial wall was computed by solving the coupled equations of wall deformation (Eq. 7.7) and the hemodynamic equations of blood flow (Eq. 7.1-7.2). The blood was modeled as a Carreau fluid (Eq. 7.3).
An axisymmetric finite element model of the fluid and the structure was used for the pulsatile flow analysis (Fig. 7.8). Analysis was performed in two steps. In the first step, the load-free artery was pre-stressed by applying *in-vivo* longitudinal stretched, δ̂, and the mean *in-vivo* arterial pressure. In the second step, the pulsatile pressure was applied to the pre-stressed artery from the previous step. The pressure pulses, \( p_{\text{in}}(t) \) and \( p_{\text{out}}(t) \) were applied at the inlet and outlet, respectively (Fig. 7.9), as normal surface traction [152].

![Finite element model for transient blood-flow-arterial wall interaction computation](image)

**Fig. 7.8:** Finite element model for transient blood-flow-arterial wall interaction computation. The geometry is the load-free geometry obtained from the shrink-and-fit algorithm.

The load-free geometry was the starting geometry for the pulsatile arterial wall-blood flow interaction calculations. The dimensions \( r_o, r_i \) and \( L_0 \) were obtained from the load-free geometry (Fig. 7.8) computed by the shrink-and-fit inverse algorithm.
7.6 Results

The results presented in this section demonstrate the steps of the shrink-and-fit inverse algorithm through the use of a simple idealized arterial geometry of the femoral artery of a dog (Fig. 7.6). In addition to that, results for stresses, strains and wall deformations are presented for the pre-stressed artery as well as for the *in-vivo* artery under pulsatile physiologic pressure loading.
### 7.6.1 Application of Shrink-and-Fit Inverse Algorithm

The basic steps of the shrink-and-fit inverse algorithm are demonstrated in Fig. 7.10 using the idealized dog-femoral artery geometry. These steps are the intermediate geometrical constructions and finite element model construction steps for the shrink-and-fit inverse algorithm.

To mimic the geometry reconstruction step as in the patient-specific scenario, a 3D-geometry of the inner lumen surface was constructed based on the arterial dimensions (Fig. 7.10A). The lumen surface geometry is represented in the form of a surface mesh of disjointed STL triangles. This lumen surface mesh is used to construct the 3D arterial wall geometry by offsetting the STL mesh of the lumen surface by wall thickness in the direction of the local normal (Fig. 7.10B). As seen in Fig. 7.10B, the 3D arterial wall geometry is still in the form of a surface mesh of STL triangles (not volume mesh). It is to be noted that during the radial shrinking process, \( \chi_{RS} \), this wall thickness \( t \) is calculated by solving the incompressibility constraint, \( V(t) = V_0 \), where \( V(t) \) is the volume of the arterial wall as a function of wall thickness, and \( V_0 \) is the volume of the in-vivo wall.

The arterial wall geometry shown in Fig. 7.10B was meshed with 8-noded linear hexahedral elements to develop a finite element model for shrink and fit deformation operators (Fig. 7.10C). As shown in Fig. 7.10C, the finite element mesh is much finer than the STL surface mesh.
**Fig. 7.10:** Application of the shrink-and-fit algorithm to a straight artery. A) *In-vivo* lumen surface of STL triangles for idealized geometry of dog femoral artery (Sinha-Roy et al., 2008). B) Arterial wall geometry in form of STL mesh. C) Arterial wall mesh with 8 node hexahedral element. D) Finite element model with boundary conditions.
The finite element model for the longitudinal shrink (or stretch) $\chi_{LS}$ and radial shrink (or stretch) $\chi_{RS}$ is shown in Fig. 7.10D. Loads, constraints and boundary conditions for $\chi_{LS}$ and $\chi_{RS}$ are specified on the nodes of the finite element mesh in Fig. 7.10C. The figure shows the rigid contact surface is constructed on the outer wall for longitudinal shrink or stretch, $\chi_{LS}$.

The extensions at the inlet and outlet are for numerical stability of the contact computations. The nodal constraints at inlet and outlet are specified with respect to the local cylindrical coordinate system, $(r, \theta, z)$, located at the reference node created at the centroid of the inlet and outlet. The nodes on the inlet and outlet cross-section are constrained to move only in the radial direction on the $r-\theta$ plane. The construction of the 3D arterial geometry and the finite element model is executed within each of the optimization iterations as a part of the shrink-and-fit inverse algorithm. The 3D arterial geometry construction and finite element model building is fully automated by implementing a python program in ABAQUS CAE (Dassault Systems, Paris, France).

### 7.6.2 Load-Free and Pre-Stressed Arterial Geometry

The results of the shrink-and-fit inverse algorithm applied to the idealized straight geometry of dog femoral artery are presented in Fig. 7.11. The \textit{in-vivo} artery dimensions are shown in Fig. 7.11A. The dimensions of the load-free artery computed by the shrink-and-fit inverse algorithm are shown in Fig. 7.11B. The dimensions of the pre-stressed artery obtained by applying \textit{in-vivo} longitudinal stretch and mean arterial pressure to the load-free geometry are shown in Fig. 7.11C. For comparison, an image of the load-free geometry is also superimposed on the image of the pre-stressed artery. Arterial cross-sections of different stress-configurations are compared in Fig. 7.11D and 7.11E. The pre-stressed and load-free cross-sectional details are shown in Fig. 7.11D, whereas Fig. 7.11F shows the details of \textit{in-vivo} and pre-stressed cross-
sections. Some dimensions are shown in 3 to 4 decimal places to emphasize the accuracy in matching the pre-stressed and the *in-vivo* geometry.

The length, inner diameter and the thickness of the load-free arterial geometry calculated by the shrink-and-fit inverse algorithm are: 35.14 mm, 3.1 mm and 0.435 mm, respectively. The *in-vivo* and the load-free artery dimensions for the present case are compared in Table 7.1 under the column “*Straight uniform diameter.*” The load-free artery length of 35.14 mm represents shrinkage of 32.4% from the *in-vivo* length of 52 mm. It also represents an axial stretch of 48% from the load-free length to the *in-vivo* length. The diameter change from the inner arterial wall, between the load-free artery (3.1 mm) and the *in-vivo* artery (3.6 mm) was 16.2%, whereas that for the outer arterial wall was 4.3%. The thickness of the load-free artery was 0.435 mm, which was 61% thicker than the *in-vivo* artery with thickness 0.27 mm.

**Table 7.1:** The dimensions of load-free geometry calculated by the shrink-and-fit inverse algorithm and those obtained by the direct method used by Sinha-Roy et al., 2008.

<table>
<thead>
<tr>
<th></th>
<th>Straight uniform diameter</th>
<th>Straight tapered (Sinha-Roy et al., 2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>In-vivo</em></td>
<td>Load-free (inverse)</td>
</tr>
<tr>
<td>Inner radius (mm)</td>
<td>Inlet</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Outlet</td>
<td>1.8</td>
</tr>
<tr>
<td>Outer radius (mm)</td>
<td>Inlet</td>
<td>2.07</td>
</tr>
<tr>
<td></td>
<td>Outlet</td>
<td>2.07</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0.270</td>
<td>0.435</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>52.0</td>
<td>35.13</td>
</tr>
<tr>
<td>Volume (mm³)</td>
<td>170.69</td>
<td>169.90</td>
</tr>
</tbody>
</table>
Fig. 7.11: Results from the shrink-and-fit inverse algorithm to compute the load-free and the pre-stressed geometry for the idealized, straight, uniform diameter dog femoral artery model. Dimensions of: A) *in-vivo* wall; B) load-free wall; C) pre-stressed arterial wall with load-free wall superimposed on it. D) Details of the load-free and the pre-stressed cross-section. E) Shows the match between the pre-stressed artery and the *in-vivo* artery to be within 0.0015 mm deviation (the two almost superimpose on one another).
The length, inner diameter and the thickness of the pre-stressed artery obtained by applying a mean arterial pressure and axial stretch of 48% to the load-free geometry were: 51.99 mm, 3.603 mm and 0.2685 mm, respectively. The agreement between the in-vivo and the pre-stressed artery is shown in Fig. 7.11E. The difference in length between the in-vivo artery and the pre-stressed artery was 0.01 mm (0.019%). The inner wall diameter of the pre-stressed artery was within 0.003 mm (0.08%) of the in-vivo inner wall diameter of 3.6 mm. The difference in wall thickness between the in-vivo artery and pre-stressed artery was 0.0015 mm.

The comparison of the in-vivo and load-free artery dimensions of the tapered artery analyzed by Sinha-Roy et al., 2008 is also presented in Table 7.1. Sinha-Roy et al., 2008, adopted a direct method involving a manual trial and error procedure to obtain the load-free arterial geometry [152]. The changes in the inner diameter between the load-free artery and the in-vivo artery at the inlet and outlet are 48% and 48.3%, respectively. The changes in the outer wall diameter between the load-free and the in-vivo artery are 24.8% and 23.6% at the inlet and outlet, respectively.

### 7.6.3 Stresses in Arterial Wall with Linear-Elastic Material

The results from numerical computations with finite element model of arterial wall with linearly-elastic (E=0.767 N/mm²), incompressible material (v=0.4999) were compared with the analytical solution from theory of elasticity. The analytical solutions were obtained for a thick cylinder of linear elastic material subjected to internal pressure and axial elongation obtained from the theory of elasticity.
Table 7.2: Stresses, strains and radial deformation on the inner and outer arterial wall. Results for arterial model with linear-elastic material and those for the pre-stressed artery with hyperelastic material for canine femoral artery. Strains under the column of linear elastic artery are engineering strains; those under the hyperelastic materials are logarithmic strains. For small deformations, logarithmic strains are close to engineering strains in magnitude. Units for deformations are in mm and stresses in N/mm².

<table>
<thead>
<tr>
<th></th>
<th>Linear-elastic: E=0.767 N/mm²</th>
<th></th>
<th>Pre-stressed Wall (Hyperelastic material)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Analytical solution</td>
<td>Numerical solution</td>
<td>% Difference</td>
</tr>
<tr>
<td>$r = r_i$ (Inner wall)</td>
<td>$\sigma_{rr}$</td>
<td>-0.01388</td>
<td>-0.01333</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{\theta\theta}$</td>
<td>0.05728</td>
<td>0.05752</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{zz}$</td>
<td>0.39007</td>
<td>0.039017</td>
</tr>
<tr>
<td></td>
<td>$\varepsilon_{rr}$</td>
<td>-0.30963</td>
<td>-0.30898</td>
</tr>
<tr>
<td></td>
<td>$\varepsilon_{\theta\theta}$</td>
<td>-0.17051</td>
<td>-0.17048</td>
</tr>
<tr>
<td></td>
<td>$\varepsilon_{zz}$</td>
<td>0.4801</td>
<td>0.4802</td>
</tr>
<tr>
<td></td>
<td>$d_r$</td>
<td>-0.26407</td>
<td>-0.2652</td>
</tr>
<tr>
<td>$r = r_0$ (Outer wall)</td>
<td>$\sigma_{rr}$</td>
<td>0.0</td>
<td>-0.205 x 10⁻³</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{\theta\theta}$</td>
<td>0.04339</td>
<td>0.04376</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{zz}$</td>
<td>0.39007</td>
<td>0.39017</td>
</tr>
<tr>
<td></td>
<td>$\varepsilon_{rr}$</td>
<td>-0.28249</td>
<td>-0.28270</td>
</tr>
<tr>
<td></td>
<td>$\varepsilon_{\theta\theta}$</td>
<td>-0.19764</td>
<td>-0.19761</td>
</tr>
<tr>
<td></td>
<td>$\varepsilon_{zz}$</td>
<td>0.4801</td>
<td>0.4802</td>
</tr>
<tr>
<td></td>
<td>$d_r$</td>
<td>-0.3929</td>
<td>-0.3923</td>
</tr>
</tbody>
</table>

The distribution of circumferential stress and strain obtained from numerical computation is shown in Fig. 7.12A and 7.12B, respectively. The distribution of the longitudinal stress and strain is shown in Fig. 7.12C and 7.12D, respectively. The stresses are Cauchy stresses in...
N/mm² and the strains are engineering strains. For small deformations, engineering strains are numerically close to logarithmic strains. The results are presented in the local cylindrical coordinate system at the outlet reference node (Fig. 7.10D). As expected, the distribution of longitudinal stress and strain is uniform throughout the cylinder (Fig. 7.12C and 7.12D). The different color-bands for $\sigma_{zz}$, in Fig. 7.12C, are within 0.5% between the maximum and minimum value signifying a constant distribution. The circumferential stress and strain distributions are a function of the radius only (Fig. 7.12A and 7.12B).

The comparison of the stresses, strains, and radial displacement at the inner and outer wall from numerical computations and analytical solutions are presented in Table 7.2 under the column of “linear-elastic artery.” The results are tabulated for: 1) radial ($\sigma_{rr}$), circumferential ($\sigma_{\theta\theta}$) and axial ($\sigma_{zz}$) stresses; 2) radial ($\varepsilon_{rr}$), circumferential ($\varepsilon_{\theta\theta}$) and axial ($\varepsilon_{zz}$) strains; and 3) wall deformation in the radial direction, $d_r$.

The maximum difference between the analytical and numerical results is 4% for the radial stress $\sigma_{rr}$ on the inner wall. All other stresses, strains, and radial deflections $d_r$ are within 1% of the analytical results. The radial stress $\sigma_{rr}$ on the inner wall surface is -0.013333 N/mm² and is equal to the mean arterial pressure of 100 mmHg. The close agreement between the analytical and numerical solutions for the linear elastic case shows that the nodal constraints imposed at the inlet and outlet are within acceptable limits.
Fig. 7.12: Cauchy stresses (in N/mm²) and engineering strains in pre-stressed artery with linear elastic material: A) and B) in the circumferential direction; C) and D) in the longitudinal direction. The different color bands for $\sigma_{zz}$ are within 0.5% between the maximum and minimum value.
7.6.4 Stresses and Strains in Pre-Stressed Artery (Hyperelastic Material)

The stress, strain and deformation results for the pre-stressed artery under the mean in-vivo pressure of 104.1 mmHg and in-vivo longitudinal stretch of 48% from the load-free length are presented in this section. The distribution of the circumferential stresses and strains are shown in Fig. 7.13A and 7.13B, respectively. The distribution of the longitudinal stresses and strains are shown in Fig. 7.13C and 7.13D, respectively. The deformations of the pre-stressed wall from the load-free configuration in the radial and longitudinal directions are shown in Fig. 7.14A and 7.14B, respectively. The value of the stresses, strains and deformations at the inner and the outer wall are tabulated in Table 7.2.

As was expected, the radial stress ($\sigma_{rr}$) varies from the value of 0.0136 N/mm$^2$, equal to the applied pressure, at the inner wall, to 0.0 N/mm$^2$ on the outer wall surface (Table 7.2). The change in circumferential stress from the inner wall surface (0.127 N/mm$^2$) to the outer wall surface (0.071 N/mm$^2$) was 44%. Due to the nonlinear material property, the longitudinal stress also varied across the vessel thickness. The difference in the longitudinal stress between the inner (0.193 N/mm$^2$) and the outer wall (0.140 N/mm$^2$) was 27.8%. In the pre-stressed configuration, the circumferential stresses are lower in magnitude than the longitudinal stresses. At the inner wall, the circumferential stress (0.127 N/mm$^2$) was 34% lower than the longitudinal stress (0.193 N/mm$^2$). Similarly, at the outer wall, the circumferential stress (0.071 N/mm$^2$) was 49% lower than the longitudinal stress (0.140 N/mm$^2$).

The strains and wall deformation in the radial direction, $d_r$, for the actual arterial model with hyperelastic material has opposite sign compared with the corresponding values for linear elastic material (Table 7.2). This is the result of the combined effect of material property and in-vivo longitudinal stretch on the wall deformation under in-vivo pressure.
Fig. 7.13: Cauchy stresses (in N/mm$^2$) and logarithmic strains in pre-stressed artery with hyperelastic material: A) and B) in the circumferential direction; C) and D) in the longitudinal direction.
7.6.5 Wall Stresses under Transient Load

The variation of the longitudinal and circumferential Cauchy stress over the cardiac cycle under pulsatile inlet and outlet pressure is presented in Fig. 7.15. The time averaged value of Cauchy stress in the longitudinal direction was 0.148 N/mm², and that in the circumferential direction was 0.104 N/mm². In other words, the time averaged longitudinal stress was 42.5% higher than the circumferential stress. The stress variation between the inlet and outlet was insignificant.

Fig. 7.14: Radial and axial deformations in mm from load-free configuration for wall with hyperelastic material.
Fig. 7.15: Cauchy stresses at the mid-wall location in the circumferential and longitudinal direction at the inlet and outlet.

7.7 Discussion

The main contribution of this section of the study was the development of the shrink-and-fit inverse algorithm to calculate the *in-vivo* arterial pre-stress for a patient-specific artery. The algorithm was tested using an idealized arterial wall geometry of a cylindrical shape. Even though this idealized geometry was axisymmetric, the algorithm was tested using a 3D cylindrical geometry. This was done as a test-case to mimic the steps of a patient-specific case. Nevertheless, it is important to test the performance and robustness of the algorithm for patient-specific case by adopting the steps developed for the present 3D cylindrical geometry. For example, the
algorithm employs a longitudinal wall deformation operator, $\chi_{LS}$, to shrink or stretch the arterial wall. The operator uses sliding contact on a rigid contact surface without contact separation to deform the wall while not altering its \textit{in-vivo} arterial shape. The complex and tortuous 3D wall shape in the patient-specific case is expected to influence the accuracy and performance of the contact algorithm.

In the implementation of the shrink-and-fit inverse method, the Nelder-Mead optimization algorithm was utilized for solving the non-linear least square minimization problem. One of the drawbacks of the Nelder-Mead algorithm is its slow convergence near the optimal solution. Moreover, the convergence of Nelder-Mead to an optimal solution has not been proven mathematically. Other researchers have typically used the Levenberg-Marquardt (LM) algorithm to implement a similar inverse method. The LM algorithm is a preferred method for solving the nonlinear least square problem. However, the advantage of Nelder-Mead is that it is a derivative free algorithm. In other words, it does not require computation of gradient or second order derivatives of the objective function. In the present study, the optimization iterations involve a finite element solution of the longitudinal and radial deformation of the artery. Therefore, numerical computations of the derivatives of the objective function can become expensive and unstable.

In the test with the idealized straight arterial geometry, the shrink-and-fit inverse algorithm was found to be close to an acceptable solution within 20 to 25 evaluations of the objective function. However, as stated above for the case of robustness, the convergence of the algorithm for a real patient-specific case needs to be tested.

The validity of the load-free geometry computed by the shrink-and-fit inverse algorithm was assessed by two criteria: 1) based on the geometrical match between the dimensions of the pre-stressed artery and the \textit{in-vivo} artery, and 2) the change in diameter between the load-free
artery and the pre-stressed artery. The first criterion is the necessary condition for a valid inverse solution. However, numerical experimentation performed by changing the arterial material property from softer to stiffer material, with the idealized straight cylindrical geometry revealed that a solution of the inverse problem satisfying the first criteria was always obtained. For the softer material, the deformation of the artery from the load-free to the pre-stressed configuration was large. This illustrates that specifying correct material property for the vessel material is important. Excessive diameter changes between the calculated load-free geometry and the pre-stressed geometry signifies inaccurate results. Ideally, the diameter change should match with the *in-vivo* measurements. The outer diameter change for the femoral artery in the present study was 4.3% between the load-free (3.97 mm) and pre-stressed artery (4.14 mm), and the inner diameter change was 14%. This was similar to the 5% outer diameter change as reported by Huang et al., 2009 [94], for a human carotid artery using a direct method (based on trial and error procedure), and a decrease of 19% in the inner diameter of a porcine LAD as reported by Hamza et al., 2003 [163].

The magnitude of the average circumferential and longitudinal stress in the artery has been reported to depend on value of longitudinal stretch applied to an un-tethered and unloaded, *ex-vivo* artery. Zhang et al., 2005 [164], have reported lower magnitude of average stress in the longitudinal direction compared to the circumferential direction for porcine LAD, when axial stretch is less than 40%. They report that longitudinal stresses exceed circumferential stresses for axial stretch ratios greater than 1.4 (i.e., 40% stretch from load-free length). However, the present result for the femoral artery subjected to an *in-vivo* longitudinal stretch of 48% from its load-free length show development of higher stresses in the longitudinal direction than circum-
ferential. Specifically, under pulsatile pressure, the mean stress in the longitudinal direction was 42.5% higher than the stress in the circumferential direction.

Without the availability of an in-vivo arterial stress data for the present study, the arterial stresses are obtained by computation. The factors involved in the computation are: a) wall deformations, and b) wall material properties. Present results for the dog femoral artery can be affected by any of those factors. Zhang et al., 2005 [164] have reported that use of an isotropic Mooney-Rivlin material model, instead of an anisotropic model, can result in a lower value of the computed circumferential stresses. Similarly, considerable variation in the in-vivo axial stretch along the arterial vasculature has been reported by many studies. These include, Guo et al., 2003 [160] for mouse aorta, Algranti et al., 2011 [161], for coronary arteries and Guo et al., 2012 [162], coronary arteries as well as veins. Guo et al., 2012 [162] have also shown the dependence of in-vivo axial stretch on the vessel diameter. For the present study, it is possible that the axial stretch of 48% may need further investigation for the diameter of the femoral artery evaluated for this study.

7.8 Conclusions

A method for performing hemodynamic computation with compliant vessel wall was developed and tested. Arterial wall pre-stresses that are known to exist in the in-vivo conditions were incorporated into the computation using a novel shrink-and-fit inverse method. This method was developed specifically for computing the load-free geometry for a patient-specific arterial geometry. Due to the unavailability of complete patient-specific data, an idealized straight arterial geometry was tested. The optimization based inverse algorithm was able to calculate the load-free geometry for the idealized arterial model. It is important to note that modifi-
cation to the algorithm was not needed for the idealized geometry, considering the nonlinearity of the wall material and the existence of large deformations as well as strains. The calculated load-free geometry, when subjected to in-vivo pressure and longitudinal stretch, was within 0.0015 mm of the in-vivo geometry. However, further testing is required to assess the performance and robustness of the inverse algorithm for a patient-specific case.

For the particular arterial model tested, the *in-vivo* axial stretch of 48% from the load-free length was found to induce higher stress in longitudinal direction than the circumferential direction as opposed to stress equalization in the two directions as reported by Kassab’s group [160,162,164]. This could be the result of either somewhat higher *in-vivo* stretch (48% of load-free length) assumed in our computation or use of an isotropic material model, instead of incorporating anisotropic wall material formulation.

The results presented in this chapter demonstrate possible application of the proposed methodology for any compliant artery modeling. Further testing is required for a patient-specific case with: a) the realistic material property, and b) an accurate measurement of *in-vivo* longitudinal stretch.
Chapter 8

Conclusions and Future Work

8.1 Summary

In this research, energy-based hemodynamic endpoints were assessed to determine the inefficiencies in the pulmonary arterial flow. These endpoints were developed from fundamental fluid mechanics principles. The motivation for this research was to apply these endpoints for the clinical diagnosis of pulmonary insufficiency (PI). Methodologies were developed to calculate these endpoints from patient-specific data. First, the proof-of-concept was established by demonstrating the applicability of these endpoints to analyze pulmonary flow under physiologic and patho-physiologic conditions. Subsequently, non-invasive methodologies were developed such that the endpoints could be obtained under clinical settings.

Specifically, right ventricular (RV) stroke work, energy loss in the branch PA and a new endpoint, energy transfer ratio were tested in a normal subject and a patient. Patient-specific data for right ventricular volume, in conjunction with pressure and flow rate at the inlet and outlets of the branch pulmonary artery were utilized for calculating the diagnostic endpoints. A method based on ECG-gating was developed to determine these endpoints from data acquired
under clinical setting for individual subjects. This enabled calculation of the endpoints from non-simultaneously acquired catheter and MRI data.

This study has demonstrated that the values of the energy-based endpoints distinctly differentiated a normal pulmonary flow physiology from one with pulmonary insufficiency. For example, between the normal and the diseased subject, the difference in RV stroke work was 32%. Similarly, the variation in energy loss between the two was 64% and the energy transfer ratio was nearly two times for the normal subject as compared to that of the subject with PI. Based on this outcome, it is evident that the energy-based endpoints could be helpful in longitudinal assessment of PI. Therefore, these endpoints have the potential to improve the clinical diagnosis of pulmonary insufficiency and determine the optimum window for performing pulmonary valve replacement surgery. A study with a larger sample size of patients is required to further assess the outcome of this study.

The proposed energy-based endpoints combine pressure-based and volume-based measures into a single parameter. This resolves the quandary that clinicians currently face in selecting either pressure-based or volume-based endpoint for the diagnosis of PI. Therefore, it eliminates the potential ambiguity and conflicting outcomes when one type of endpoint is selected over the other during decision making. However, one drawback of these endpoints was the requirement of simultaneous measurements of pressure and volume or flow rate. The ECG-gating resolved this problem by enabling the use of non-simultaneously acquired pressure from catheterization, and flow rate or ventricular volume from cardiac MRI. With the development of non-invasive methodology, the requirement of pressure measurement by invasive cardiac catheterization can be eliminated. On-going development in 4D-MRI based non-invasive pressure calculation will allow these endpoints to be clinically more relevant.
The flow field in the main pulmonary artery, downstream of the pulmonary valve, is complex as it a developing flow. Such flow poses computational challenge as the inlet spatial velocity boundary conditions are difficult to measure and specify for numerical computation. The image-based methodology, developed for non-invasive computation of the endpoints, was specifically developed for such developing flows. The use of time- and spatial-varying velocity data by the present method allows direct use of MRI and PC-MRI data. The maximum difference between the computed flow rate from image data and the one from standard of care measurement was 7 ml/sec at the main PA of the diseased subject. This validates the proposed computational method presented in this study.

The computation of the PA flow and wall interaction using pulsatile pressure pulse was outside the scope of this study. The inverse (shrink-and-fit) algorithm developed for calculating \textit{in-vivo} pre-stress in patient-specific arterial wall geometry was only tested with an idealized straight conduit model of a canine femoral artery. Testing with a patient specific arterial geometry is required in future.

Finally, the applicability and relevance of this research to other bio-medical problems are discussed here. Although the focus of this research was pulmonary insufficiency, many of the methodologies developed here can be applied to multiple cardiovascular areas. For instance, the methodology for patient-specific hemodynamic computation using actual time- and spatially-varying PC-MRI data is applicable to any arterial flow. In particular, this method has an advantage in modeling the complex developing flow in the proximity of valves where the velocity field is too complex to resemble a simplistic profile, such as parabolic or Womersley. Although the computation of the energy-based endpoints was the focus of this research, using this methodology, researchers can determine pressure drop and wall-shear stresses non-invasively. Therefore,
it can be useful for design and analysis of medical devices such as valves, stents, and grafts and for patient-specific surgical planning and interventions. Likewise, the optimization based inverse-elastostatics method was developed here for obtaining the load free arterial geometry. However, it has many applications in orthopedics for determining in-vivo loads in muscles, bones and joints. Another significant application is in obtaining in-vivo mechanical properties of tissues from imaging data.

8.2 Future Work

As part of future work, a statistical study with a sufficiently large sample size is required to validate the results of this research. A set of threshold values for the proposed energy-based endpoints are necessary to determine the optimum window for PV replacement surgery. Additionally, variability in endpoints need to be compared between subjects with dissimilar physical and hemodynamic characteristics (e.g., age, weight, height, heart rate, body-surface-area, cardiac-output, blood-pressure, etc.).

Hemodynamic computational methods developed in this research can be improved by utilizing lump parameter outlet boundary conditions by incorporating the flow resistance from the downstream pulmonary arterial vasculature. Further development of the non-invasive methods for obtaining the endpoints using 4D-MRI is needed.

The computations with compliant arterial wall model were performed with a simplistic idealized arterial geometry due to the unavailability of necessary patient-specific data for pulmonary artery. The newly developed shrink-and-fit inverse algorithm and the methodology for transient blood-flow arterial wall simulation have to be tested with a patient-specific pulmonary arterial geometry.
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