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Assessment on Pulmonary Insufficiency using Energy-Based Endpoints and

4D Phase Contrast MR Imaging

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ABSTRACT

A congenital heart disease (CHD), such as tetralogy of Fallot (TOF) and aortic valve disease requiring the Ross procedure (pulmonary autograft), causes fatal right heart dysfunction over time and often sudden death for a patient. Patients who have undergone the repair surgery often confront pulmonary insufficiency (PI) which is the main life-threatening postoperative dysfunction. PI, which is caused mainly due to the dysfunctional pulmonary valve, results severe pulmonary regurgitation, right ventricular (RV) dilatation, and elevated RV and pulmonic pressure over time. Therefore, reoperation, such as pulmonary valve replacement surgery in patients, has to be performed at the right time to correct PI.

Since the appropriate time for intervention is critical for patients with right heart dysfunction, the hemodynamics of the RV and pulmonary arteries (PAs) has to be carefully monitored throughout the lifetime of the patient. However, due to the complexity of symptoms, it is sometimes difficult to diagnose the progress of the diseases accurately using existing cardiac indices, such as RV volume and pressure. Recently, energy-based endpoints that couple RV volume, RV pressure data, and PA flow conditions, such as RV stroke work indexed to BSA (SW\textsubscript{i}), energy transfer ratio (\textit{e}_{\text{MPA}}) between the RV and the main PA, and energy loss in the branch PAs, were investigated by our group. In this research the proposed endpoints were calculated and compared between a group of patients with abnormal RV-PA physiology and normal subjects.
Energy-based endpoints require accurate measurement of cardiac blood flow and pressure data in a current clinical setting. Consequently, invasive cardiac catheterization, which is not a standard of care procedure for repaired CHD patients, is often required for those measurements. To circumvent this issue, in this research we developed a methodology to calculate the pressure information non-invasively using 4D phase contrast magnetic resonance imaging (PC MRI). The time varying pressure and flow data obtained from 4D PC MRI enabled us to calculate energy loss in the branch PAs non-invasively. As a result, it can eliminate the need for invasive cardiac catheterization procedure; thus, further extending the applicability of energy-based endpoints.

Our results showed that RV SW1 of the patient group (0.176 ± 0.055 J/m²) was significantly higher by 93.4 % (p<0.01) than that of the control group (0.091± 0.030 J/m²). The mean $e_{MPA}$ of the patient group (0.56 ± 0.33) was significantly lower than that of the control group (1.56 ± 0.85) with p<0.01, despite the fact that the patient group had a significantly higher RV SW1 than the control group (0.21 ± 0.10 J/m² vs. 0.09 ± 0.04 J/m²; p<0.02). Further, the non-invasively computed energy loss in the branch PAs using 4D PC MRI for the patient group was order of magnitude larger than the control group.

Based on our results, we believe that energy-based endpoints we proposed, RV SW1, $e_{MPA}$, and energy loss in the branch PAs, can distinguish the RV-PA abnormal physiology from the normal physiology. These can be useful clinical measures to evaluate the PA hemodynamics for longitudinal clinical assessment of patients.
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List of Nomenclatures

AP - anterior to posterior
A - area (cm²)
bpm - heart rate (beats/min)
BSA - body surface area (m²)
CCHMC - Cincinnati Children’s Hospital Medical Center
CFD - computational fluid mechanics
CHD - congenital heart disease
CMR - cardiac magnetic resonance imaging
cp - centipoise [g/(cm·s)]
ECG - electrocardiogram (electrocardiographic)
EDV - end-diastolic volume (ml)
EDP - end-diastolic pressure (mmHg)
EF - ejection fraction (%)
ESP - end-systolic pressure (mmHg)
\dot{E} - rate of energy transferred at the PA (J/s)
FH - foot to head
FOV - field of view
ESV - end-systolic volume (ml)
\epsilon_{MPA} - energy transfer ratio (=E_{net}/RV SW)
E_{net} - the net energy transferred by RV over T
LV - left ventricle
n - unit normal vector to a plane
MRA - magnetic resonance angiography

P - pressure (mmHg)

p - probability value

PI - pulmonary insufficiency

PA - pulmonary artery (main, right, and left PA for M-, R- and LPA, respectively)

PC - phase contrast

PVR - pulmonary valve replacement

\( \mathcal{V} \)P - pressure gradient field

Q - volumetric flow rate (ml/s)

r - Pearson’s correlation coefficient

RF - regurgitation fraction (%)

RL - right to left

RV - right ventricle

RVOT - right ventricular outflow track

SSFP - steady state free precession

SW - stroke work (J)

STL - stereo-lithographic

t - time (sec)

T - cardiac cycle

TOF - tetralogy of Fallot

rTOF - repaired TOF

u - axial velocity (cm/s)

V - volume (ml)

VENC - velocity encoding (cm/s)

VSD - ventricular septal defect
WSS - wall shear stress

Greek

\( \rho \) - density (kg/m\(^3\))

\( \zeta \) - flow resistance coefficient

Subscripts

\( i \) - indexed by body surface area (BSA)

\( \text{Loss} \) - energy loss

\( m \) - MPA

\( x \) - velocity component in anterior to posterior (AP)

\( y \) - velocity component in right to left (RL)

\( z \) - velocity component in foot to head (FH)
Chapter 1  Introduction

1.1 Congenital Heart Disease Associated with the Right Heart

Approximately two million children of the United States were born with congenital heart disease (CHD) between 1940 and 2002 (Hoffman et al., 2004). Specifically, CHD associated with the right heart, such as tetralogy of Fallot (TOF) and aortic valve disease requiring the Ross procedure, account for 25% ~ 35% of total congenital heart disease (Roger et al., 2011). Especially, TOF is the most complicated cyanotic congenital heart diseases. Most infants born with TOF have repair surgeries within a couple of weeks to several months after their births, depending on the severity of lesions. Despite the excellent early survival rate after the repair (Ooi et al., 2006), the main postoperative issue for a patient who underwent the repair surgery is pulmonary insufficiency (PI) due to a dysfunctional pulmonary valve, resulting in pulmonary regurgitation, i.e., the reverse flow in the right ventricle (RV) from the main pulmonary artery (MPA) (Geva, 2011). The pulmonary regurgitation is also the major issue for patients who have the Ross procedure from aortic valve disease.

Patients with chronic pulmonary regurgitation are often left with RV dilatation associated with progressive RV myocardial dysfunction. This is because pulmonary regurgitation abnormally alters RV loading conditions that results in the increase in the RV size, leading to stiffening myocardium of RV over time, which is called RV hypertrophy (Fig. 1.1).
Figure 1.1. Comparison of representative right ventricle cardiac MR images. A) Heart of a normal subject and B) abnormally enlarged RV and altered RVOT of a rTOF patient with RV hypertrophy. RVOT: right ventricular outflow track, RV: right ventricle, and LV: left ventricle
1.2 Motivation and Objective

With recent advances in diagnosing CHD and its repair surgery, the lives of infants and young children born with CHD have significantly been extended. However, a risk of late postoperative mortality still exists, resulting in sudden death from congestive heart failure (Murphy et al., 1993, Pigula et al., 1999, Yang et al., 2011). Specifically, pulmonary insufficiency (PI) is one of the main long term life-threatening ailments confronting adult CHD patients. PI causes pulmonary regurgitation and results in RV myocardial dysfunction, including RV hypertrophy, over time. Progressive RV myocardial dysfunction often leads to fatal arrhythmias and even RV failure resulting in sudden death (Miyazaki et al., 2009, Hazekamp et al., 2001, Therrien et al., 2000, Davlouros et al., 2006, Harrild et al., 2009, d'Udekem et al., 2000).

Surgical repair, such as pulmonary valve replacement (PVR) surgery, is required to alleviate the RV regurgitation for patients before the onset of irreversible RV myocardial dysfunction. However, PVR has to be performed at the right time because there is a potential risk of additional surgery if it is performed too early. This is because the prosthetic pulmonary valve does not grow along with the patient’s somatic growth. On the other hand, if PVR is delayed for too long, RV myocardial dysfunction can turn into an irreversible condition (Fiore et al., 2008, Burkhoff et al., 2005, Schamberger et al., 2000, Caldarone et al., 2000) which does not rectify even after PVR. Thus, the pathophysiology of the RV and the pulmonary arteries (PA) has to be carefully monitored throughout the patient’s lifetime to determine the right timing for PVR for patients. However, due to the complexity of symptoms, it is sometimes difficult to
diagnose the progress of the diseases properly with current clinical indices alone, such as RV volumes (RV end-diastolic and end-systolic volumes indexed to body surface area) and RV pressures (RV end-diastolic and end-systolic pressure), from cardiac magnetic resonance imaging (CMR) and catheterization, respectively.

Therefore, in this research we have confirmed the clinical usefulness of newly proposed energy-based endpoints, such as RV stroke work index (RV SWI), energy transfer ratio between the RV and the main PA (MPA), $e_{MPA}$. We have evaluated and compared these endpoints between a cohort of patients having RV-PA pathophysiology and control subjects having normal RV-PA physiology. We believe that an energy-based approach would better characterize the RV-PA hemodynamics since it incorporates RV volume and pressure, as well as PA blood flow conditions. It may enable us to predict the onset of RV dysfunction. Further, we have developed a non-invasive methodology to calculate the pressure drop and energy loss in the branch PAs using 4D phase contrast magnetic resonance image (PC MRI) data, i.e. three directional and dimensional velocity data over the cardiac cycle. This enables to extend the applicability of energy-based endpoints in practice, eliminating a need for invasive cardiac catheterization.

1.3 Hypothesis

The central hypothesis of the dissertation is that energy-based endpoints RV SWI, energy transfer ratio between the RV and the MPA ($e_{MPA}$), and energy loss in the branch PAs (RPA and LPA), will differentiate the pulmonary insufficiency in the RV-PA pathophysiology from a normal RV-PA physiology.
1.4 Specific Aims

Specific aims for this research are summarized as:

Specific Aim 1: To compare energy-based endpoints, RV SW₁ and $e_{MPA}$, computed from combination of cardiac MRI and catheterization between CHD patients with abnormal RV physiology and control subjects with normal RV physiology.

   Task 1-1: To compute and compare RV SW₁ between CHD patients and control subjects.
   Task 1-2: To calculate and compare $e_{MPA}$ between CHD patients and control subjects.

Specific Aim 2: To compare a new energy-based endpoint, energy loss in the branch PAs, obtained from non-invasive 4D phase contrast (PC) MRI between CHD patients and control subjects.

   Task 2-1: To compute pressure drop and energy loss in the branch PAs using 4D PC MRI data and compare them between CHD patients and control subjects.
   Task 2-2: To investigate a methodology for numerical computation using 4D PC MRI data to calculate energy loss in the branch PAs.

The brief description for each task is given below:
In the task 1 of specific aim 1, RV SW₁ was calculated from the pressure-volume curve for each subject. The time varying RV volume and RV pressure were obtained by CMR and cardiac catheterization, respectively. The co-registration procedure, to synchronize individually measured RV volume and pressure, was performed by using electrocardiogram (ECG) gating for each subject in this research.

In the task 2 of specific aim 1, \( e_{MPA} \), defined as the ratio between the energy that RV produces (RV SW) and the energy transferred at the MPA, was calculated for each subject. To compute the energy transferred at the PAs, the PA pressure was measured by cardiac catheterization and PA blood flow rate and velocity were obtained using current 2D cardiac MRI.

In the task 1 of specific aim 2, the pressure drop and energy loss in the branch PAs were computed non-invasively using 4D PC MRI data. In order to confirm the clinical significance, the pressure drop and energy loss between a group of patients and control subjects were statistically compared.

In the task 2 of specific aim 2, a methodology for the numerical computation using 4D PC MRI data, including 3D PA reconstruction and image enhancement techniques, was investigated with data of a control subject with normal RV-PA physiology. The PA hemodynamics and energy loss at the PAs calculated from the numerical computation was compared to those directly computed by 4D PC MRI data.
1.5 Outline of the Dissertation

This dissertation consisted of two main parts: 1) to determine the applicability of energy-based endpoints, RV SW\textsubscript{1} and \( e_{MPA} \), calculated using a combination of MRI (non-invasive) and catheterization (invasive) data as a useful clinical diagnostic indices for CHD patients (task 1 and 2 of specific aims 1, respectively); and 2) to extend the applicability of energy-based endpoints with a new endpoint, energy loss in the branch PAs computed from non-invasive 4D PC MRI data (task 1 and 2 of specific aim 2)

The chapters in this dissertation follow the sequence of the specific aims listed above which are the research steps being undertaken.

1) In chapter 2, a brief background and literature review for topics in the subsequent chapters, such as tetralogy of Fallot, aortic valve disease, Ross procedure, energy-based endpoints, cardiac MRI, 4D PC MRI, are presented.

2) In chapter 3, methodologies to compute energy-based endpoints presented in this dissertation, RV SW\textsubscript{1}, \( e_{MPA} \), and energy loss in the branch PAs, are introduced.

3) In chapter 4 through 7 the results of the research are presented. Chapter 4 and 5 describe the clinical usefulness of RV SW\textsubscript{1} and \( e_{MPA} \), respectively. Co-registered non-simultaneously measured RV cardiac volume and pressure data are used to compute RV SW\textsubscript{1} and \( e_{MPA} \). Current RV cardiac indices, such as RV end-systolic/diastolic volumes and pressures, ejection fraction, and regurgitation fraction, are also investigated for a cohort of TOF patients and
control subjects. Chapter 6 describes the comparison of non-invasively obtained pressure drop and energy loss in the branch PAs using 4D PC MRI data between a group of CHD patients and normal subjects. Chapter 7 demonstrates an approach for the numerical computation to compute the hemodynamics and energy loss in the branch PAs using 4D PC MRI.

4) In chapter 8, the summary of the research and the recommendations for the future work are outlined.
Chapter 2  Background and Literature Review

2.1  Congenital Heart Disease Associated with the Right Heart

2.1.1  Tetralogy of Fallot

Normal Heart. The heart consists of four chambers, right/left atria and right/left ventricles as shown in Fig. 2.1. In a normal heart, deoxygenated blood flows from right ventricle towards the lungs via the pulmonary arteries for oxygenation, i.e., pulmonary circulation, which is the main focus of the dissertation. Oxygenated blood in the lungs comes back to the left ventricle through the pulmonary veins, i.e., pulmonary venous return. Then, the left ventricle contracts to pump the oxygenated blood to all organs and tissues, i.e., systemic circulation. The right atrium receives deoxygenated blood from the organs and tissues through the superior and inferior vena cava, i.e., systemic venous return. The simple schematic of the blood circulation systems explained above is given in Fig. 2.2.
Figure 2.1 Schematic of the normal heart. Blue and red arrows indicate the direction of deoxygenated and oxygenated blood, respectively. (http://www.nhlbi.nih.gov/health/health-topics/images/tetralogy_fallot.jpg)

Figure 2.2. Schematic of the human blood circulation system. (http://www.mpoullis.net/bsphysiol/physio/Lecture%20Notes-15.htm)
**Right Heart with Tetralogy of Fallot.** Tetralogy of Fallot (TOF) is one of the main heart defects and leads to cyanosis and shortness of breath for a patient due to low oxygen levels in the blood. It consists of four abnormalities associated with the right heart (Taussig 1947) (Fig. 2.3):

1) **right ventricular outflow track (RVOT) obstruction**, a narrowed or stenosed RVOT or pulmonary valve that causes the reduction in blood flow towards the lungs; 2) **ventricular septal defect** (VSD), a hole in the ventricular septum between the right and left ventricles that causes the mixing of oxygen-poor blood with oxygen-rich blood; 3) **overriding aorta**, shifting of the aorta towards the right side of the heart so that it sits over the ventricular septal defect; and 4) **RV hypertrophy**, abnormal thickening and stiffening of the muscular wall of the right ventricle (Taussig 1947).

The hemodynamic of the heart with TOF is significantly altered by the presence of VSD. As shown in Fig. 2.3, the bluish oxygen-poor blood is mixed with the oxygen-rich blood through the hole between the ventricular septum, and then back to the systemic circulation. This causes oxygen deficiency in the blood, resulting in the poor organs and tissues function that leads to the characteristic bluish skin and lips for an infant born with TOF. The symptoms as manifested are also associated with other abnormalities, such as RVOT obstruction and hypertrophied RV. In TOF patients, due to blood leaking and obstruction, the RV is forced to contract harder to push more blood to the lungs for oxygenation, resulting in deteriorating RV hypertrophy, abnormal thickening and stiffening of the RV muscles over time. Furthermore, since most of the mixed blood flows into the aorta, the aorta gets enlarged, known as overriding aorta.
Figure 2.3. Schematic of the heart with tetralogy of Fallot. It involves RVOT obstruction, ventricular septal defect, overriding aorta, and RV hypertrophy. (http://www.nhlbi.nih.gov/health/health-topics/images/tetralogy_fallot.jpg)
Tetralogy of Fallot Repair Surgery. To repair the defects of tetralogy of Fallot before the onset of irreversible RV-PA dysfunction, surgical intervention has to be performed. Fortunately, after the first surgery, performed by Dr. Lillehei and Varco in 1954 (Lillehei et al., 1955a, Lillehei et al., 1955b), tetralogy repair has advanced rapidly and now has an excellent survival rate (Pigula 1999, Bacha et al., 2001).

Surgical repair involves: 1) closing the VSD with a patch, made of homograft or synthetic material, to remove the shunt from the RV to left ventricle (LV); 2) widening the RVOT and main pulmonary artery to alleviate RVOT obstruction; 3) closing the incision on the RVOT and PA with a transannular patch as shown in Fig. 2.4. After the repair, the flow volume in the pulmonary artery increases, and the flow volume in the aorta decreases, resulting in a relief of the overriding aorta.
Figure 2.4. The details of the repair for normalizing the blood flow in tetralogy of Fallot: 1) closing ventricular septal defect (VSD) with a patch, 2) removing an obstruction in the RVOT and PA, and then applying a patch. The repair results in increased PA flow and alleviating overriding aorta.

(http://www.chw.org/display/displayFile.asp?filename=/images/TetralogyofFallot_TN.gif)
2.1.2 Aortic Valve Disease Requiring the Ross Procedure

*Aortic Valve Stenosis.* In the normal heart the aortic valve controls the oxygenated blood flow from the left ventricle (LV) to the aorta. It helps the LV pump the blood into the aorta leading to the rest of the body. However, when the aortic valve is stenosed (Fig. 2.5), i.e., abnormally narrowed, the LV has to work harder for an equivalent amount of blood to be pumped. It leads to the LV volume and pressure overloading causing a thickening of cardiac muscle wall, i.e., hypertrophy, over time (Bonow et al., 2006, Roberts et al., 2005). The LV volume and pressure overloading will be manifested as aortic stenosis occurs together with aortic regurgitation. A repair surgery, such as the Ross procedure, is necessary to alleviate the symptoms, including LV volume and pressure overloading, so the LV function can be normalized. In the course of the Ross procedure, a diseased aortic valve is removed and replaced by the pulmonary valve (autograft). Then the pulmonary valve is replaced with a conduit or a cadaveric pulmonary valve (homograft). As a result, the pulmonary regurgitation often gets severe over time.
Figure 2.5. A representative figure of the heart showing aortic stenosis. Due to narrowed aortic valve, blood from the LV is unable to flow freely to the aorta, causing a large pressure gradient.
Ross Procedure. The Ross procedure, named after English surgeon Dr. Donald Ross, conducted in 1967, is the surgical repair for a patient with aortic valve disease, aortic stenosis and aortic regurgitation (Ross 1962). It is the aortic valve replacement using the pulmonary autograft and is performed in infants and children in particular. As shown in Fig. 2.6, the stenosed aortic valve and the pulmonary valve are removed and coronary arteries are detached (Fig. 2.6a), then the pulmonary autograft is attached to the aortic position and coronary arteries are reattached (Fig. 2.6b). In turn, the pulmonary valve is replaced with a conduit or pulmonary homograft (Fig. 2.6c). The main advantage of the use of the pulmonary autograft in the Ross procedure, compared to the mechanical valve as the replacement of the aortic valve, is that the patient doesn’t require blood thinning medication for life. Further, the pulmonary autograft will grow as the patient grows; as a result of, the patient will have a lesser chance of the reoperation. However, due to the absence of the pulmonary valve, RV-PA hemodynamics becomes abnormally altered, such as pulmonary regurgitation, that leads to RV volume and pressure overloading, and PA dilation and hypertension.
Figure 2.6. The Ross procedure: (a) the stenosed aortic valve and the pulmonary valve (autograft) are removed, (b) the pulmonary autograft is attached to the place where the aortic valve is taken out, and (c) the pulmonary homograft (or a conduit) is placed at the right ventricular outflow track (http://www.chw.org/applications/PPF/DocID/21359/image/RossProcedure/image.asp)
2.1.3 Post-operative Issue: Pulmonary Regurgitation

The repair surgery, such as RVOT obstruction repair for TOF and a conduit replacement during the Ross procedure, for patients often causes a dysfunctional pulmonary valve and RVOT remodeling that leads to pulmonary regurgitation during the diastole phase as has been observed in many cases (Murphy 1993, Pigula 1999, Frigiola et al., 2008, Oosterhof et al., 2007). Over time, severe pulmonary regurgitation can develop, as described in the following paragraphs (Fig. 2.7) (Kuehne et al., 2003, Kuehne et al., 2001, Siwek et al., 1985).

This is because the repair surgery, such as the TOF repair and the Ross procedure, is usually required for infants born with CHD. Thus, at the time of the first repair, the heart rate is relatively high and the diameters of the PA are small and also the RV is already hypertrophied for infants. These conditions lead to a shorter duration of the diastole phase. Therefore, pulmonary regurgitation does not reduce the volume of blood flowing into the PA significantly.

However, over time, chronic pulmonary regurgitation can cause the progressive RV dilatation with the increase of RV compliance. This leads to increase in the RV diastole phase. As the patient grows the heart rate progressively decreases. Thus, the degree of pulmonary regurgitation increases because of a combination of factors, such as RV dilatation, increase in RV compliance, and decrease in the heart rate. The severe pulmonary regurgitation causes chronic RV volume overloading and even RV myocardial dysfunction, which often leads to sudden death. Surgical reintervention, such as pulmonary valve replacement (PVR), is required to alleviate RV volume overloading before the onset of irreversible RV dysfunction (Fiore et al., 2008, Burkhoff et al., 2005, Schamberger et al., 2000).
Figure 2.7. Typical processes in developing severe pulmonary regurgitation after the repair surgery for a rTOF patient (Geva, JCMR, 2011, 13:9).
2.2 **Current Clinical RV Indices: RV End-diastolic Volume Index, RV End-systolic Pressure, and RV Ejection Fraction.**

Surgical reintervention, such as PVR and the Ross procedure, often left for a CHD patient with severe PI. Pulmonary regurgitation, resulting from PI, increases the risk of irreversible RV myocardial dysfunction as the patient grows (Rosenthal 1993, Walsh et al., 1988). Therefore, continuous monitoring of patient’s RV pathophysiology, such as RV dilatation, RV pressure overload, and the increase in the degree of pulmonary regurgitation, is crucial to extend the patient’s life. Currently, cardiac MRI (CMR) is routinely performed as a standard care of procedure for patients, to monitor the changes in RV pathophysiology via measured cardiac indices, RV end-diastolic volume index and pulmonary regurgitation. Cardiac catheterization is also carried out when a patient has elevated RV pressure due to severe obstruction in RVOT and PA, or hypertrophied RV.

Many clinicians reported that the severity of pulmonary regurgitation directly affects RV pathophysiology in rTOF patients (Knauth et al., 2008, Lytrivi et al., 2004, Samyn et al., 2007). They observed that RV end-diastolic volume (largest RV volume over the cardiac cycle) indexed to body surface area (BSA), EDV\textsubscript{I}, increases, RV ejection fraction (\(=\) stroke volume/EDV) decreases, and RV end-systolic pressure (highest RV pressure over the cardiac cycle) decreases as the degree of pulmonary regurgitation increases. Further, several researchers have suggested cutoff values for RV EDV\textsubscript{I} and RV end-systolic pressure to help determine the right timing for an intervention. Therrien et al. suggested a cutoff value of 170 ml/m\textsuperscript{2} for RV EDV\textsubscript{I} based on their human study with 17 patients. Also, Warnes et al. have recommended a cutoff value of 0.7
for RV/LV end-systolic pressure ratio (Warnes et al., 2008). They found that if those indices, RV EDV\(_1\) and RV end-systolic pressure exceeded their cutoff values, RV myocardial function was not renormalized even after the surgical repair. Other factors that can adversely affect RV pathophysiology involve akinesis, contraction of heart muscle, or dyskinesis, abnormal movement of heart muscle such as bulging, of the patched RVOT and residual stenosis in the pulmonary valve and pulmonary arteries.

However, it is sometimes difficult to assess the progress of RV dysfunction with current individual cardiac indices alone. This is because of the complexity of RV-PA interaction and interdependence of the current indices. Therefore, an energy-based endpoint that couples RV volume and pressure, as well as flow conditions in the PA may be useful as a quantitative measure of RV-PA pathophysiology in the monitoring of the patient’s clinical status.

### 2.3 Energy-based Endpoints

Energy-based endpoints such as RV stroke work indexed to BSA (RV SW\(_1\)), energy transfer ratio (= net energy transferred at the MPA/ RV stroke work, \(e_{MPA}\)) and energy loss in the branch PAs, in our study, are motivated by the fact that RV myocardial dysfunction affects the performance of the RV. Energy-based endpoints have been applied to analyze other pathophysiology such as Fontan (Whitehead et al., 2007, Dasi et al., 2009, Dasi et al., 2008), but have not been applied to abnormal RV-PA physiology. The key issue in computing energy-based quantities, such as RV SW and \(e_{MPA}\), is that they require simultaneous measurements of RV pressure and volume (Akins et al., 2008).
The MRI based RV volumetry is a standard clinical care of procedure for a CHD patient associated with the RV. However, reliable pressure measurement in RV requires cardiac catheterization. Clinically, it is difficult to perform cardiac MRI and catheterization simultaneously. In a pilot study of our group Das et al., 2010 have proposed a methodology to synchronize non-simultaneously measured RV volume and pressure using electrocardiographic (ECG) gating. Using their approach it is possible to use non-simultaneously acquired RV pressure and volume, to compute RV SW_l.

The \( e_{MPA} \) incorporates RV SW and flow conditions in the MPA into a single index which provides more comprehensive RV-PA hemodynamics for patients with abnormal RV-PA physiology. Further, the calculation of energy loss in the branch PAs involves the pressure drop between the MPA and the branch PAs, RPA and LPA, as well as flow rate and blood velocity information at the PAs. Therefore, these energy-based endpoints would enable us to better characterize RV and PA hemodynamics. This may help clinicians in predicting the right timing for intervention for patients.

The details of current clinical indices and energy-based endpoints introduced in this dissertation are shown in following Table 2.1 and 2.2, respectively.
<table>
<thead>
<tr>
<th>Current parameter</th>
<th>Unit</th>
<th>Equation</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume index, EDV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>ml/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>EDV/BSA</td>
<td>EDV indexed to BSA</td>
</tr>
<tr>
<td>End-systolic volume index, ESV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>ml/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ESV/BSA</td>
<td>ESV indexed to BSA</td>
</tr>
<tr>
<td>End-systolic pressure, ESP</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>End-diastolic pressure, EDP</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ejection fraction, EF</td>
<td>%</td>
<td>(\frac{\text{Stroke volume}}{\text{EDV}} \times 100)</td>
<td>Stroke volume = EDV-ESV</td>
</tr>
<tr>
<td>Regurgitation fraction</td>
<td>%</td>
<td>(\frac{\text{Backward flow}}{\text{Forward flow}} \times 100)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy-based endpoint</th>
<th>Unit</th>
<th>Equation</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV stroke work, SW</td>
<td>J/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>(\int PdV)</td>
<td>(P=\text{pressure, } V=\text{volume})</td>
</tr>
<tr>
<td>Energy transfer ratio, (e_{MPA})</td>
<td>-</td>
<td>(\frac{SW}{E_{\text{net}}})</td>
<td>(E_{\text{net}} = \text{net energy transferred to the PA over cardiac cycle})</td>
</tr>
<tr>
<td>Energy loss in the branch PA, (E_{\text{Loss}})</td>
<td>mJ/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>refer Eq. 3.17</td>
<td>-</td>
</tr>
</tbody>
</table>
2.4 Cardiac Magnetic Resonance Imaging (MRI)

Cardiac magnetic resonance imaging (MRI), or known as CMR, uses radio frequency energy pulses to misalign positively charged hydrogen protons in water molecules in the body. A radio frequency energy pulse from the external magnet changes the direction of the magnetic vector field of protons that have the same frequency as the radio frequency pulse. When the radio frequency pulse is stopped, the protons relax back to the original alignment releasing a radio frequency energy pulse. MR image reconstruction can be done capturing the radio frequency energy pulse from the protons.

As described above, cardiac MRI uses the same basic principles as MRI, but it includes optimizations for use in the cardiovascular system, such as the use of ECG gating and rapid pulse sequence (steady state free precession, SSFP). Cardiac MRI is now a standard care of procedure for diagnosing and evaluating the structure and function of the cardiovascular system (Geva 2011, Kilner et al., 2010). Current issues regarding CMR are cardiac movement and respiratory motion that cause artifacts during MRI acquisition. The best efforts are made for eliminating those artifacts, such as breath holding technique to reduce artifacts by cardiac movement and navigator echo gating to monitor respiratory cycle of a patient.

In order to obtain a blood velocity field map of a cardiac region of interest, velocity encoded gradient echo imaging, or known as phase contrast magnetic resonance imaging (PC MRI) is used. With the introduction of positive magnetic field gradient, additional phase shifts for protons of the blood flow can be captured when an equal but opposite magnetic field is applied, whereas the stationary protons will be back in original phase. These phase shifting
information are stored in a phase velocity map, showing flow of proton movement in more black or white depending upon the direction and magnitude of the velocity field, whereas static proton remain grey. Thus, with selecting any region of interest, the time-varying velocity and flow rate curve can be generated. The validation of the result from PC MRI has been done using Doppler ultrasound by many researchers (Srichai et al., 2009, Yzet et al., 2010, Stadlbauer et al., 2010, Paelinck et al., 2005, Westenberg et al., 2006).

The accuracy of PC MRI is mainly dependent on the flow velocity and flow pulsatility. The sensitivity of velocity of the pulse sequence (velocity encoding, VENC) has to be well adjusted so that the velocity related phase shift can be close to $2\pi$ for the maximum velocity of protons; this avoids aliasing, which is the case of a velocity related phase shift for phase angle greater than $2\pi$ (Buonocore 1993, Yang et al., 1996). In order to overcome the flow pulsatility issue and improve the accuracy of measured velocity value, a combination of phase contrast velocity mapping and Fourier velocity imaging approach can be useful. When a beat-to-beat variation in flow velocity exists, the final phase contrast velocity map can be computed from the best fit of the Fourier velocity encoded result (Bittoun et al., 1993).

2.5 Non-invasive 4D Phase Contrast Magnetic Resonance Imaging (PC MRI)

Continuous monitoring of hemodynamics of patient heart with congenital heart disease is highly important for effective clinical treatment and intervention planning. Many clinical modalities, such as CMR, Doppler ultrasound, catheterization, 2D PC MRI, and magnetic resonance angiography (MRA), have been used to quantify hemodynamics of the heart for a comprehensive assessment of patient’s heart conditions. With recent development on 4D PC
MRI technologies and sequences, including parallel imaging and respiratory navigating, clinically reliable magnitude and three directional and dimensional phase images over the cardiac cycle covering the whole heart volume can be measured within a reasonable scan time of 15 ~ 30 mins, Fig. 2.8. (Hope et al., 2010, Eriksson et al., 2010, Markl et al., 2007)

4D PC MRI technique rapidly becomes a useful clinical measure since it gives us both qualitative information, such as the detail of heart structure and complex flow patterns with streamlines and pathlines of the blood flow, and quantitative information, such as average blood velocity, and flow rate for the intravascular region of the heart. In this research, 4D PC MRI was used to assess both the anatomic and hemodynamic information of the RV for CHD patients. Specifically, energy-based endpoint, energy loss in the branch PAs, was non-invasively computed using 4D PC MRI.

![Figure 2.8](image)

**Figure 2.8.** The stack of PC MRI images, magnitude images and three directional phase images containing the velocity information $(u_x, u_y, u_z)$, for the pulmonary arteries at different slice location.
Chapter 3  Methodologies for Computing Energy-based Endpoints

3.1  Right Ventricular Stroke Work Index (RV SW_i)

3.1.1  Cardiac MRI: RV Volume and Volume-Based Indices

Cardiac MRI (CMR) was performed under general anesthesia with breath holding or respiratory suspension technique. Standard CMR imaging parameters were used. They included steady state free precession (SSFP) in the 2-, 4- chamber and short axis planes (Knauth et al., 2008, Pohost et al., 2003). SSFP parameters were 20-30 phases per cardiac cycle and slice thickness of 5 - 8 mm. Stack of short axis aligned CMR images of each subject were analyzed using standard MRI planimetry techniques by semi-automated procedure using the computer software QMASS (Version 7.2, Medis Medical Imaging Systems, Leiden, the Netherlands) to compute RV volume, RV mass, ejection fraction (EF), peak ejection rate, and peak filling rate for each of our subjects (Gjesdal et al., 2008).

RV volume was computed by contouring RV inner wall on a spatially aligned CMR images as shown in Fig. 3.1. The RV volume at each time point was obtained by integrating the enclosed area of RV inner wall contour at each phase. RV volume data at all phases was used to construct the time varying RV volume curve over the cardiac cycle for each subject (Fig. 3.1D). RV EF was calculated as a ratio of RV stroke volume and RV end-diastolic volume (Eq. 3.1).

\[
\text{Ejection fraction} = \frac{\text{Stroke volume}}{\text{End diastolic volume}} \times 100 \,[\%] \quad (3.1a)
\]

RV volume rate of change with time was calculated from the first derivative of RV volume versus time curve (Bianco et al., 1985, Danielsen et al., 1988, Uebing et al., 2005). The negative
peak component of the rate of RV volume change during systole was considered as peak ejection rate. Similarly, the positive peak component of the rate of RV volume change during diastole was considered as peak filling rate. These were normalized by end-diastolic volume (EDV). Stroke volume was taken to be the difference between EDV and end-systolic volume (ESV).

\[
\text{Stroke volume} = \text{End diastolic volume} - \text{End systolic volume} \quad \text{(ml)} \quad (3.1b)
\]

The BSA indexed stroke volume was referred to as stroke volume index. Cardiac output was computed by multiplying stroke volume with heart rate.

\[
\text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate} \quad \text{(L/min)} \quad (3.1c)
\]

To facilitate intersubject comparisons, RV volumes were indexed to body surface area (BSA). Therefore, EDV, ESV, RV mass data with subscript ‘I’ was denoted.
Figure 3.1. A) Computation of RV volume variation over the cardiac cycle using QMASS. B) Stack of RV contours at an instant of time. C) Reconstructed 3D image of the RV. D) A typical time varying RV volume over the cardiac cycle by the integration of RV contours.
3.1.2 Cardiac Catheterization: RV and PA Pressure

All patients and subjects underwent diagnostic RV catheterization under general endotracheal anesthesia. The pressure in the RV and PA were measured using a fluid-filled catheter (Cook Medical Inc., Bloomington, Indiana, USA) under fluoroscopic guidance. The best effort was made to measure PA pressure at the similar location where PA flow was measured. RV and PA pressure curves were acquired in the standard fashion along with electrocardiogram (ECG) gating. For each subject, typically, 4 to 5 waveforms were recorded over the cardiac cycle. Some respiratory effects were present in the measured pressure waveforms, i.e. RV pressure slightly (a few mmHg) increased with expiration and decreased with inspiration. To compensate for the respiratory effects and for co-registration of RV pressure and volume, we used the pressure pulse, among several sequentially measured waveforms, that had systolic and diastolic pressures approximately matching its weighted means.

3.1.3 Co-registration of RV Volume and Pressure

RV SW calculation requires simultaneous measurements of RV volume and RV pressure. As mentioned above, simultaneous MRI and cardiac catheterization is difficult to perform under a clinical setting. Thus, independently measured RV volume versus time obtained from CMR and RV pressure versus time obtained from cardiac catheterization were co-registered (Das et al., 2010). This process was automated using an in-house MATLAB program (MATLAB, Inc., Waltham, MA). Figure 3.2 shows the RV pressure-volume (P-V) loop for a representative rTOF and control subject. It may be noted that the P-V loop of the normal subject had more pronounced isovolumic contraction and relaxation (i.e. vertical right and left lines on the P-V
loop), compared with that of the rTOF subject. In addition, the rTOF patient had an increased RV EDV and ESV as well as ESP compared to that of the control subject. For space limitation RV P-V curves of other subjects were not shown in Fig. 3.2, but the trend of RV P-V loop was similar for each group.

Figure 3.2. RV P-V loop for a representative rTOF and control subject.
RV Stroke Work Index (SW\textsubscript{I}) Formulation

RV stroke work (SW) represents the energy imparted to blood by the contracting RV over the cardiac cycle. RV SW was estimated by calculating the area enclosed by RV P-V loop derived from the co-registered RV volume and pressure versus time curve (Das et al., 2010).

\[
RV\ SW = \iint_A PdV
\]  

(3.2)

The area enclosed by the P-V loop was calculated by applying Gauss theorem. Applying the Gauss theorem to Eq. 3.2, we get,

\[
RV\ SW = \iint_A PdV = \frac{1}{2} \oint_C (PdV - VdP)
\]  

(3.3)

where, \(P\) and \(V\) are RV pressure and volume, respectively and \(C\) is the closed path of integration over the cardiac cycle. The right-hand side of Eq. 3.3 can be simplified to a summation over a sequence of sample points, \((P_1, V_1), (P_2, V_2), \ldots, (P_n, V_n), (P_1, V_1)\), along the P-V loop. The simplified equation is given by:

\[
RV\ SW = \sum_{i=1}^{n-1} \frac{1}{2} (P_i V_{i+1} - P_{i+1} V_i) + \frac{1}{2} (P_n V_1 - P_1 V_n)
\]  

(3.4)

BSA indexed SW (SW\textsubscript{I}) was computed by SW/BSA.
3.2 Energy Transfer Ratio \( (e_{MPA}) \) between RV and MPA

3.2.1 Phase Contrast (PC) MRI for MPA Flow Computation

Free breathing fast cine PC MR images of all subjects were obtained on a plane positioned approximately halfway between pulmonary valve and MPA bifurcation, perpendicular to the predominant flow direction to measure MPA flow. For subjects who did not have pulmonary valve, the PC MR velocity measuring plane was positioned approximately halfway between the end of RVOT and MPA bifurcation. Typical PC MRI parameters include 30 phases per cardiac cycle, slice thickness of 5 mm, and velocity encoding (VENC) of 150 - 450 cm/s.

PC MRI for flow at MPA were analyzed by using semi-automated computer software QFLOW (Version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands) to compute MPA flow volume over cardiac cycle. Regurgitation fraction,

\[
\text{Regurgitation fraction} = \frac{\text{Backwardflowvolume}}{\text{Forwardflowvolume}} \times 100 \text{ [%]} \quad (3.5)
\]

was computed from the flow volume at either pulmonary valve or MPA of the subjects (Eq. 3.5). The forward and backward flow volumes were calculated by numerically integrating positive and negative flow rate portions of the flow versus time curve.

3.2.2 Energy Transfer Ratio \( (e_{MPA}) \) Computation

We define \( e_{MPA} \) as the ratio of the total energy of blood flow at the MPA to the RV SW which is described earlier (Eq. 3.3). The energy transferred to the blood by the RV varies over the cardiac cycle, increasing rapidly during systole and decreasing during diastole. The rate of
energy transferred at the MPA can be expressed in integral form using fundamental fluid mechanics principles (Das et al., 2010)

\[ E_m = \iint_A \left( p_m + \frac{1}{2} \rho \bar{u}_m \cdot \bar{u}_m \right) \bar{u}_m \cdot ndA_m \]  

(3.6)

where, \( p_m \) the time varying MPA pressure measured during catheterization, \( A \) cross-sectional area of the MPA plane, \( \bar{u}_m(x, t) \) the blood velocity at any point \( x \) on the MPA plane and at any instant of time \( t \), \( n \) the unit normal vector to the MPA plane, and \( \rho \) the blood density (= 1,050 kg/m\(^3\)). Equation 3.6 can be simplified to Eq. 3.7 by the MPA volumetric flow rate defined as

\[ Q_m = \iint_A \bar{u}_m \cdot ndA_m \]  

(3.7)

Therefore, spatial average of \( \bar{u}_m(x, t) \) at the MPA plane leads to \( u_m = Q_m/A_{MPA} \).

\[ E_m = p_m \cdot Q_m + \frac{1}{2} \rho u_m^2 \cdot Q_m \]  

(3.8)

where \( Q_m \) the time varying blood flow rate at the MPA. The blood velocity and flow rate were measured by PC MR imaging. The first term on the right-hand side of Eq. 3.8 is the rate of the pressure-flow energy. The second term on the right-hand side is the rate of the kinetic energy associated with the velocity of blood at the MPA.

The quantity \( E_m \) is the rate of total energy being transferred by the RV to the blood flowing into the MPA. The representative \( E_m \) curves for the patient and control groups were given in Fig. 3.3. The net energy transferred by RV (\( E_{net} \)) over one cardiac cycle (\( T \)) was computed by integrating the rate of total energy transferred to the MPA (\( E_m \)) over \( T \).

\[ E_{net} = \int_0^T E_m(t) dt \]  

(3.9)
Based on RV SW we computed earlier and net energy transferred to the blood at the MPA ($E_{\text{net}}$), we define an index, energy transfer ratio ($e_{\text{MPA}}$) as

$$e_{\text{MPA}} = \frac{E_{\text{net}}}{\text{SW}}$$  \hspace{1cm} (3.10)

It may be noted that $e_{\text{MPA}}$ is a non-dimensional number since both the numerator and denominator are in energy units. Further, $e_{\text{MPA}}$ accounts for energy values at the RV and at the MPA. The RV energy condition is determined by RV SW that combines changes in pressure and volume in the RV, whereas MPA energy status is obtained from MPA pressure and velocity data.

![Graph of energy at MPA](image)

**Figure 3.3.** The patient had a large negative energy during diastole leading to a decrease in the value of total energy ($E_{\text{net}}$) at the MPA, whereas the control subject showed no negative energy contribution.
3.3 Non-invasive Energy Loss in the Branch PAs using 4D PC MRI

The 4D PC MRI was performed with a 3.0 Tesla MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands). The three directional velocity encoded phase contrast images and magnitude images were acquired over the cardiac cycle for all subjects in the study (Fig. 3.4).

Figure 3.4. The stack of PC MRI images, magnitude images and three directional phase images containing the velocity information \((u_x, u_y, u_z)\), for the pulmonary arteries at different slice location. 24 and 40 phases during the cardiac cycle were recorded per each slice for the control and patient subjects, respectively.
The 4D velocity encoded PC MRI data was analyzed using an in-house MATLAB program (MATLAB, Inc., Waltham, MA) and semi-automated flow analysis software Ensight (Version 9.2, CEI, Apex, NC), to calculate spatially averaged blood velocity and flow rate at the PAs.

### 3.3.1 Comparison of Computed Flow Rate: Ensight and QFLOW

The flow rate at the MPA calculated by Ensight was confirmed with that computed by QFLOW (Version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands), which is the current flow analysis software in Cincinnati Children’s Hospital Medical Center (CCHMC) (Fig. 3.5). 2D PC MRI data at the MPA from 2 subjects (one patient with abnormal PA physiology and one control subject with normal PA physiology), were analyzed using both Ensight and QFLOW for comparison. As shown in Fig 3.6 and Table 3.1, the average flow rates at the MPA for a patient and a control subject were similar with errors less than 3% in both cases.
Figure 3.5. Computation of flow rate over the cardiac cycle using (A) QFLOW and (B) Ensight.
Comparison of MPA flow rate calculated from two different modalities, Ensight and QFLOW, for (A) a patient and (B) a control subject. The difference in flow rate between two modalities was less than 3% for both the patient and control subjects.

**Figure 3.6.** Comparison of MPA flow rate calculated from two different modalities, Ensight and QFLOW, for (A) a patient and (B) a control subject. The difference in flow rate between two modalities was less than 3% for both the patient and control subjects.
TABLE 3.1. Comparison of average flow rate at the MPA between Ensight and QFLOW for a patient and a control subject.

<table>
<thead>
<tr>
<th></th>
<th>Average MPA flow rate [ml/s]</th>
<th>Error [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ensight</td>
<td>QFLOW</td>
</tr>
<tr>
<td>Patient (with abnormal PA physiology)</td>
<td>54.9</td>
<td>56.6</td>
</tr>
<tr>
<td>Control (with normal PA physiology)</td>
<td>95.7</td>
<td>93.4</td>
</tr>
</tbody>
</table>

3.3.2 Data Preprocessing

The measured 4D velocity encoded PC MRI data was analyzed with an in-house MATLAB program (MATLAB, Inc., Waltham, MA) and semi-automated flow analysis software Ensight (CEI, Apex, NC), following the procedures presented in Fig. 3.7. After reading 4D PC MR images, the transient blood velocity information, $u_x(t), u_y(t),$ and $u_z(t),$ at each node was obtained from each directional phase images, AP (anterior to posterior), FH (foot to head), and RL (right to left), respectively. The pressure gradient field ($\nabla P = \frac{\partial P}{\partial x_i},$ where $x$ is the axial direction), which will be explained later, was calculated using the previously computed velocity information. Then, the computed data for each subject was converted into Ensight file formats such as geometry, velocity, and pressure gradient data ($\nabla P$) for further analysis in Ensight.

In Ensight, the PA anatomy for each subject was confirmed by magnitude images of the PA (Fig. 3.8A for a representative control subject). Then, a 3D PA image for each subject was constructed using 3D velocity data at the systolic phase and was visualized as a semi-transparent iso-surface. A representative 3D PA image of the control subject is shown in Fig. 3.8B.
The MPA plane was placed approximately halfway between the pulmonary valve and the MPA bifurcation for the control subject. For the patient, the MPA plane was located at the distal end of the conduit, which assumed to be the origin of the MPA. Further, the planes for the branch PAs, RPA and LPA, were positioned at the location approximately 1 cm away from the first daughter branch of the RPA and LPA, to ensure that measured blood flow data were not affected by flow separation due to the bifurcation of PA’s daughter branches. The planes positioned perpendicular to the MPA, RPA, and LPA for creating subplanes, to measure the flow information in the PAs, are also shown in Fig. 3.8B. The subplanes were created on the respective planes covering the PA regions for computing the blood velocity and flow rate over the cardiac cycle at the PAs for the control.
Figure 3.7. The flow chart to calculate the pressure drop and energy loss between the MPA and branch PAs using the velocity information obtained from 4D PC MR images.
Figure 3.8. The detail of PA anatomy confirmed by A) the magnitude image of 4D PC MRI and B) 3D image of the PA for the representative control subject.
The streamlines of each pulmonary flow, MPA-RPA and MPA-LPA flows, and the velocity vectors in the respective subplanes during a systole phase are also shown in Fig. 3.9. The streamlines that passed through the predominant portion of each pulmonary flow were chosen. The streamlines were initiated from uniformly distributed $3 \times 3$ seed points with a distance of approximately 2 mm on the plane (Fig. 3.10). The time varying pressure drop calculation between the branch PAs and the MPA over the cardiac cycle was performed along those streamlines (described in the following section). Multiple streamlines were used for the pressure drop calculation since the calculated pressure drop may be dependent upon the selected streamline. Thus, the average pressure drop values for each pulmonary flow were reported.
Figure 3.9. The streamlines originating from the MPA for the representative subjects, A) control and B) patient.
Figure 3.10. The subplanes of the PAs for the flow computation and respective velocity vector fields for the representative subjects, A) control and B) patient.
3.3.3 Pressure Drop Calculation

The time varying pressure drop between the branch PAs and the MPA ($= P_{\text{Branch PA}} - P_{\text{MPA}}$) can be calculated by integrating the pressure gradient along the streamline from the MPA to the branch PAs over the cardiac cycle (Ebbers et al., 2001). As mentioned earlier, the pressure gradient field, $\nabla P$ ($= \frac{\partial P}{\partial x_i}$), was computed from the velocity information using the Navier-Stokes equation (Eq. 3.11a). For pressure drop calculation the blood is assumed Newtonian having higher shear rate viscosity of 0.00345 Pa/s. The flow is considered incompressible, unsteady, and laminar. The pressure gradient field ($\nabla P$) was calculated using a second-order central difference discretization method.

$$\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial P}{\partial x_i} + \frac{\mu}{\rho} \nabla^2 u_i + F_i \quad (3.11a)$$

$$\frac{\partial P}{\partial x_i} = \rho \left( \frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} \right) + \mu (\nabla^2 u_i) + \rho F_i \quad (3.11b)$$

where, $u$ is blood velocity data, $\rho$ the blood density ($= 1,050$ kg/m$^3$), $\mu$ the blood viscosity ($= 0.00345$ Pa/s). The first two terms of the right-hand side of Eq. 3.11b result from the temporal and spatial convective acceleration terms of the momentum equation. The third term represents the viscous dissipation term. The last term is the body force term such as the gravity which has an insignificant effect on the blood flow.

Since the streamline created was a 3D spline, each streamline was divided into 20 discrete points along the direction of streamline, generating 19 line segments connecting two adjacent points. The pressure gradient along the line segments on the streamline, $\nabla P_s$ ($= \frac{\partial P}{\partial s_n}$),
was obtained by the dot product between the pressure gradient field \( \nabla P = \frac{\partial P}{\partial x_i} \), calculated using Eq. 3.11b, and the normalized line vector of the line segment \( (\vec{s}_n) \), as shown in Eq. 3.12.

\[
\nabla P_s (\equiv \frac{\partial P}{\partial s_n}) = \nabla P \cdot \vec{s}_n \quad \text{where, } n = 1, 2 \ldots N
\]  

(3.12)

The pressure drop along the PAs \( (dP_{\text{Branch PA}}) \), i.e., the pressure difference between two endpoints of the streamline, was calculated by integrating the pressure gradient along the streamline (Eq. 3.13), as mentioned earlier.

\[
dP_{\text{Branch PA}} = P_{\text{Branch PA}} - P_{\text{MPA}} = \int_0^L \frac{\partial P}{\partial s_n} ds \quad \text{where, } L = \text{length of a streamline}
\]  

(3.13)

Thus, there are two \( dP_{\text{Branch PAs}} \); one is \( dP_{\text{RPA}} \) and the other is \( dP_{\text{LPA}} \).

The calculation procedures (Fig. 3.7) to compute pressure drop were verified with the pressure drop computed for a simplified 2D stenosis model using a finite difference CFD solver (Fluent, ANSYS, Inc., Canonsburg, PA, USA). The detail of the verification procedures and results are provided in the following section.

### 3.3.4 The Verification of the Pressure Drop Computation

Physiologic pressure drop in the PAs was not available because catheterization was not performed for the subjects in the study using 4D PC DRI (Section 3.3). Thus, the pressure drop calculation in this study was verified with CFD result using a simplified geometry as following.
Computation model. A 2D geometry (length of 10 cm and depth of 3 cm; Fig. 3.11) with a stenosis in the middle section was created in GAMBIT. After mesh generation with the resolution of 2.5 mm × 2.5 mm, which is the same as the one that 4D PC MR images have in the study, the mesh was exported from GAMBIT for CFD analysis. The CFD analysis was performed in finite volume solver (FLUENT, ANSYS, Inc., Canonsburg, PA, USA) assuming the blood to be Newtonian fluid with the viscosity of 3.45 cp (= 0.00345 Pa·s) and the density of 1,050 kg/m³. The average MPA blood velocity over the cardiac cycle, 0.137 m/s, for the control subject in the study was applied at the inlet. At the outlet boundary, a stress-free boundary condition was used.

Verification of Pressure Drop Computation. After CFD analysis, the 2D velocity information was extracted from the converged solution. The pressure gradient field \((\nabla P = \frac{\partial p}{\partial x_i})\) was computed using the extracted velocity field (Eq. 3.11b). Then, in Ensight six streamlines originating from the inlet were generated with a distance of approximately 2.5 mm and the pressure gradient along each streamlines \((\nabla P = \frac{\partial p}{\partial s_n})\) was obtained (Eq. 3.12). The pressure drop at the outlet was computed by integrating the pressure gradient along each streamline (Eq. 3.13). The time average pressure drop value was obtained from six streamlines (0.22 mmHg) using the proposed method (Fig. 3.7) and was compared with the pressure drop computed from CFD solution (0.24 mmHg). The difference in the pressure drop between two methodologies was 7.3 % \([= (0.24-0.22)/0.24\times100]\).
Figure 3.11. A computation model used in CFD analysis for the verification of pressure drop computation. The difference in the pressure drop between two methodologies was 7.3%.

3.3.5 Energy Loss Calculation

The rate of total energy loss in each branch PA ($\dot{E}_{\text{Loss,Branch PA}}$) was defined as the difference in the rate of total energy transferred between the branch PAs and the MPA, resulting in two terms, major and minor energy losses, as shown in Eq. 3.14.

$$\dot{E}_{\text{Loss,Branch PA}} = \dot{E}_{\text{Loss,major}} + \dot{E}_{\text{Loss,minor}} \quad (3.14)$$

The $\dot{E}_{\text{Loss,major}}$ is the difference in the rate of the pressure-flow and kinetic energies transferred between the branch PAs and the MPA as shown in Eq. 3.15a:

$$\dot{E}_{\text{Loss,major}} = (\dot{E}_{\text{RPA}} + \dot{E}_{\text{LPA}}) - \dot{E}_{\text{MPA}} \quad (3.15a)$$

$$\dot{E}_{\text{RPA}} = P_{\text{RPA}} \cdot Q_{\text{RPA}} + \frac{1}{2} \rho \bar{u}_{\text{RPA}}^2 \cdot Q_{\text{RPA}} \quad (3.15b)$$

$$\dot{E}_{\text{LPA}} = P_{\text{LPA}} \cdot Q_{\text{LPA}} + \frac{1}{2} \rho \bar{u}_{\text{LPA}}^2 \cdot Q_{\text{LPA}} \quad (3.15c)$$
\[ E_{MPA} = P_{MPA} \cdot Q_{MPA} + \frac{1}{2} \rho \bar{u}_{MPA}^2 \cdot Q_{MPA} \]  

(3.15d)

The \( \dot{E}_{Loss, major} \) (Eq. 3.15a) can be rewritten in terms of pressure drop, flow rate, and velocity at the PAs. The right-hand side of Eq. 3.15b, 15c, and 15d, i.e., the rate of the pressure-flow and kinetic energy terms at the PAs (Lee et al., 2011), respectively, can be substituted into Eq. 3.15a while maintaining flow balance at the PAs (\( Q_{MPA} = Q_{RPA} + Q_{LPA} \)). As a result, the revised equation for \( \dot{E}_{Loss, major} \) becomes Eq. 3.15e:

\[ \dot{E}_{Loss, major} = dP_{RPA} \cdot Q_{RPA} + \frac{1}{2} \rho (\bar{u}_{RPA}^2 - \bar{u}_{MPA}^2) \cdot Q_{RPA} + dP_{LPA} \cdot Q_{LPA} + \frac{1}{2} \rho (\bar{u}_{LPA}^2 - \bar{u}_{MPA}^2) \cdot Q_{LPA} \]

(3.15e)

where, \( dP_{\text{branch } PA} \) is the time varying pressure drop in the branch PAs computed previously. The first two terms of the right-hand side of Eq. 3.15e account for the rate of pressure-flow and kinetic energy losses in the RPA, respectively, and the next two terms represent those energy losses in the LPA.

The \( \dot{E}_{Loss, minor} \) in Eq. 3.14 is the energy loss in the branch PA due to flow separation at the MPA bifurcation. The minor energy loss at each branch PA (\( \dot{E}_{Loss, minor} \)) can be computed using a flow resistance coefficient (\( \zeta \)) derived based on the ratio of the flow rate at the PA (= \( Q_{\text{branch } PA}/Q_{MPA} \)) (Idelchik, 2001) as shown in Eq. 3.16.

\[ \dot{E}_{Loss, minor} = \zeta_{\text{branch } PA} \cdot \frac{1}{2} \rho \bar{u}_{\text{branch } PA}^2 \cdot Q_{\text{branch } PA} \]

(3.16)

Therefore, the final form of the equation we used to calculate the rate of total energy loss in each branch PA (\( \dot{E}_{Loss, \text{branch } PA} \)) becomes Eq. 3.17:

\[ \dot{E}_{Loss, \text{branch } PA} = dP_{\text{branch } PA} \cdot Q_{\text{branch } PA} + \frac{1}{2} \rho (\bar{u}_{\text{branch } PA}^2 - \bar{u}_{MPA}^2) \cdot Q_{\text{branch } PA} + \zeta_{\text{branch } PA} \cdot \frac{1}{2} \rho \bar{u}_{\text{branch } PA}^2 \cdot Q_{\text{branch } PA} \]

(3.17)
The rate of total energy loss in the branch PAs can be obtained by combining the total energy loss in the RPA and the LPA (Eq. 3.18).

\[ \dot{E}_{\text{loss,Branch PAs}} = \dot{E}_{\text{loss,RPA}} + \dot{E}_{\text{loss,L PA}} \]  

(3.18)

The average total energy loss in the branch PA \( (E_{\text{loss,Branch PA}}) \) over the cardiac cycle \( (T) \) was computed by integrating the rate of total energy loss in the PA \( (\dot{E}_{\text{loss,branch PA}}); \) Eq. 3.17 over \( T \) as shown in Eq. 3.19.

\[ E_{\text{loss,Branch PA}} = \frac{1}{T} \int_0^T \dot{E}_{\text{loss,Branch PA}}(t)dt \]  

(3.19)

### 3.4 Statistical Analysis

The two sample student \( t \) test was performed to compare the statistical difference in RV pressure and volume, RV volume-based parameters such as regurgitation fraction and ejection fraction, and energy-based endpoints, i.e. RV SW\(_1\), \( e_{MPA}\), and energy loss in the branch PAs, between the patient and control groups. Prior to performing the two sample \( t \) test, the normality test for all data was performed using both the Shapiro-Wilk test and Kolmogorov-Smirnov test. Instead of the two sample student \( t \) test, the two-tailed Wilcoxon test was used when an index failed the normality test. Pearson’s correlation coefficient \( (r) \) of RV SW\(_1\) and \( e_{MPA}\) with RV cardiac indices was obtained to measure the linear relationship between the endpoints. A probability value of less than 0.05 \( (p<0.05) \) was considered to be statistically significant. All statistical analysis was done with SAS 9.3 (SAS Institute, Cary, NC).
3.5 CFD Analysis for Evaluation of Hemodynamics and Energy loss in the Pulmonary Arteries using 4D Phase Contrast MRI

3.5.1 Data Preprocessing

The original 4D PC MR image of the control subject set, which has the axial volume of 32.0 cm × 32.0 cm × 3.5 cm, 15 slices, and gap of 2.5 mm, is shown in Fig. 3.12A. The gap between the slices, 2.5 mm, was quite large that can cause the loss of PA boundary information during 3D geometry reconstruction process. Thus, in Ensight14 additional slices were created in the middle of two adjacent slices and two slices were added on the top and bottom of the original 4D PC MR image set using linear interpolation. As a result, the new 4D PC MR image data set has 31 slices with the gap of 1.25 mm (Fig. 3.12B). The increased number of images enabled better 3D geometry reconstruction of the PAs.

![Figure 3.12](image)

**Figure 3.12.** A) Original 4D PC MR image set with the axial volume of 32.0 cm × 32.0 cm × 3.75 cm, 15 slices, and gap of 2.5 mm. B) 4D PC MR image set with the axial volume of 32.0 cm × 32.0 cm × 3.75 cm, 31 slices, and gap of 1.25 mm.
3.5.2 Image Enhancement for 4D PC MR Images

A sample of the raw 4D PC MR image with the resolution of $128 \times 128$, pixel size of $2.5 \text{ mm} \times 2.5 \text{ mm}$ is shown in Fig. 3.13A. Due to low quality of the raw image, enhancement techniques, including resolution enhancement, edge sharpening, and median filtering, were applied to the original image. As a result, the enhanced image had the finer resolution, $512 \times 512$, and smaller pixel size of $0.63 \text{ mm} \times 0.63 \text{ mm}$ than the original, as shown in Fig. 3.13B. The final enhanced images were used for PA 3D geometric reconstruction.

![Image](image_url)

**Figure 3.13.** A) A sample of the original 4D PC MR image with the resolution of $128 \times 128$, pixel size of $2.5 \text{ mm} \times 2.5 \text{ mm}$. B) An enhanced 4D PC MR image with the resolution of $512 \times 512$, pixel size of $0.63 \text{ mm} \times 0.63 \text{ mm}$. 
3.5.3 3D PA Geometry Reconstruction and Registration

A set of enhanced 4D PC MR images of the control subject at the systolic phase was used for 3D PA geometric reconstruction with MIMICS (Materialise, Inc., Leuven, Belgium). For blood oxygenation, the RPA and LPA have numbers of daughter branches towards the lungs. Smaller branches of the RPA and LPA were removed in order to avoid flow complication due to secondary flow, such as possible flow separation due to the smaller bifurcated arteries from the daughter branches (Fig. 3.14). The surface of the reconstructed PA geometry was extracted as a stereo-lithographic (STL) file from MIMICS (Fig. 3.14A). Then, the STL file of reconstructed PA geometry was imported into Ensight. In order to remove the secondary branches in the PAs and obtain flow information from the same planes, the 3D image, which was created in Ensight using 3D velocity data at the systolic phase, was superimposed on the reconstructed PA (Fig. 3.14C).
Figure 3.14. A) The reconstructed 3D PA geometry of the control subject using MIMICS. B) 3D image of the control subject from Ensight. C) The superimposed image with both 3D PA geometry reconstruction and 3D image.
As shown in Fig. 3.15A, the cutting planes for the branch PAs, RPA and LPA, were positioned at the location approximately 1 cm away from the first daughter branch of the RPA and LPA. The MPA plane was placed approximately halfway between the pulmonary valve and the MPA bifurcation. The planes were positioned perpendicular to the MPA, RPA, and LPA. Using those planes, the redundant domains of PAs were removed for CFD analysis (Fig. 3.15B). The final PA reconstructed geometry was extracted as a STL file from Ensight for the numerical computation (Fig. 3.15C). Further, the cylindrical subplanes were created on respective planes covering the PA regions in Ensight for computing the blood velocity and flow rate over the cardiac cycle in the PAs, which is explained in detail in the following section. The advantage from this registration process in Ensight is that the accurate cut (cross-sectional) planes can be generated in order to remove the redundant arteries of the branch PAs for PA geometry reconstruction. At the same time, PA flow data for numerical computation can be measured from the same PA cut planes that we used for PA reconstruction.
Figure 3.15. A) The respective cross-sectional plane was positioned on each PA location. B) The redundant sections of the PAs were removed using those planes. C) The final 3D geometry reconstruction with PA planes for CFD analysis.
3.5.4 Numerical Blood Flow Computation

The final 3D PA geometry reconstruction was imported in GAMBIT (ANSYS, Inc., Canonsburg, PA). The PA geometry reconstruction was meshed by tetrahedral voxel elements of the size smaller than 1 mm$^3$. The transient and non-Newtonian blood flow, and rigid arterial wall assumptions were used for an initial CFD analysis. A cylindrical extension with the length of 20D (diameter) was attached to each branch PA for blood flow to be of developed at the downstream of the branch PAs (Fig. 3.16), ensuring a boundary condition applied to the outlet does not affect the flow in each branch PA. Since the distance between the MPA and pulmonary valve (PV), where the blood began to flow into the MPA, was approximately 1.5 cm, a short extension with length of 1.5 cm was attached to the MPA. This will generate a developing flow in the MPA. The time varying uniform blood velocity profile was applied to the MPA inlet and LPA outlet as a boundary condition for this study although it is a limiting approximation. At each time point the average velocity was maintained to be the same as the measured velocity. The RPA outlet was set as an outflow boundary condition.
Figure 3.16. The reconstructed 3D PA geometry with a cylindrical extension for each PA. The time varying uniform velocity profile was applied as a boundary condition for the MPA and LPA. The RPA, which is the validation point, was set to be outflow condition.

The time varying blood velocity profiles at the MPA inlet and LPA outlet are shown in Fig. 3.17. As mentioned earlier, the MPA inlet and LPA outlet velocity profiles were applied as boundary conditions for the numerical computation. For the flow validation, the flow rate at the RPA was numerically computed and was compared with the RPA flow rate obtained from the 4D MRI measurements.
Figure 3.17. The time varying blood velocity at the MPA and LPA measured from 4D MRI data were applied as inputs for the numerical computation.
Chapter 4  Right Ventricular Stroke Work Index

4.1  Introduction

Pulmonary valve replacement (PVR) surgery is performed to renormalize the RV overloading. The right timing for PVR is crucial for a rTOF patient. Many RV volume based indices, such as RV ejection fraction and end-diastolic and end-systolic volumes, as well as RV pressure based indices have been used to diagnose the severity of lesions for a patient. (Pohost 2003) have also reported the use of RV pressure based indices to diagnose RV dysfunction in rTOF patients. However, due to the complexity of the symptoms, it is sometimes difficult to determine the timing for a surgical intervention for a rTOF patient based on current RV volume and pressure indices alone.

In present study, an energy based endpoint, RV stroke work (SW), that combines both RV volume and pressure data, was calculated using fundamental thermodynamic and fluid mechanics principles, to quantify RV hemodynamics in rTOF patients (Das et al., 2010). The computed RV stroke work was indexed by body surface area (BSA), RV SW1, and compared between the rTOF patients and controls to test the hypothesis of the task 1-1 (specific aim 1) of the dissertation that the required RV SW1 for dysfunctional RV in a rTOF patient would be significantly higher than that of the RV in a normal subject.
4.2 Study Population

A total of nineteen patients with and without rTOF pathophysiology who underwent both CMR imaging and catheterization at Cincinnati Children’s Hospital Medical Center (CCHMC) between 2006 and 2010 were registered for this study. The 19 patients consisted of 11 male and eight female patients. A total of 11 patients out of 19 had rTOF pathophysiology. Out of the 11 rTOF subjects nine had a pulmonary conduit repair to relieve RVOT obstruction. Two patients were excluded from the study since they either obstructed RVOT or moderate-to-severe tricuspid valve regurgitation. As a result, seven subjects were classified as rTOF group.

Out of 19 patients the remaining eight subjects were not rTOF patients, but they had cardiovascular diseases. For example, two of the subjects had constrictive pericarditis and one had Kawasaki syndrome. However, all eight had native RV with normal global systolic function, as well as normal pulmonary physiology with a functioning PV. These patients were classified as control group, which were designated as normal subjects for this study. Proper procedures and protocols in accordance of CCHMC regulation were performed in handling patient data. The Institutional Review Board of CCHMC approved the study.

4.3 Data Acquisition

4.3.1 CMR Imaging Data

Three different scanners: 1) 1.5 Tesla GE Excite Magnet1.5-Tesla imager (General Electric USA); 2) 3.0 Tesla Siemens Trio Magnet (Siemens Healthcare, Erlangen, Germany);
and 3) 1.5 Tesla Achieva MRI scanner (Philips Medical Systems, Netherlands) were used to acquire CMR image of the subjects. Typical CMR imaging protocols that were followed included breath holding technique (whenever applicable), steady state free precession (SSFP) 2 and 4 chamber single slice cines, as well as cine SSFP short axis stack (Knauth et al., 2008, Pohost et al., 2003). Typically, 20-30 phases per cardiac cycle were recorded with 13-18 slices per each phase. Slice thickness typically was 5.5-8 mm and gap between slices was a maximum of 1.2 mm. Field of view (FOV) was in the range of [222 - 444] mm× [230 - 360] mm, image resolution was in the range of [144 - 288] × [192 - 288] pixels, and flip angle was from 43° to 53°.

4.3.2 Phase Contrast Magnetic Resonance Imaging (PC MRI)

Fast cine PC MRI data were obtained in a plane perpendicular to the main pulmonary artery (MPA), and the pulmonary valve in some patients. PC MRI data were taken at 30 phases per cardiac cycle with 5 - 6 mm of slice thickness and 150 - 450 cm/s of velocity encoding (VENC). Typical scan parameter was: FOV was in the range of [200 - 280] mm× [210 - 360] mm, image resolution was in the range of [192 - 256] × [192 - 256], and flip angle was in the range of 10° to 20°.

4.4 Results

The measured or calculated RV endpoints for the rTOF and control groups are presented in Table 4.1 and 4.2 with their mean ± SD (standard deviation). The quantities designated with
an asterisk (*) in the left-hand side column in Table 4.2 showed a statistically significant difference ($p<$0.05) between TOF patients and controls.

### 4.4.1 Patient Demographic and Clinical Data

Table 4.1 summarizes the patient demographic and clinical data of our patient sample. The rTOF group in our study consisted of 2 males and 5 females with a mean age and BSA of $14.9 \pm 13.1$ years and $1.3 \pm 0.6 \text{ m}^2$, respectively. The control group consisted of eight subjects with 5 males and 3 females with a mean age and BSA of $12.4 \pm 5.8$ years and $1.5 \pm 0.5 \text{ m}^2$, respectively.

The rTOF group had mean heart rate of $81.1 \pm 24.4$ bpm and $79.0 \pm 25.7$ bpm during CMR and catheterization, respectively. The mean heart rate of the control group was $75.0 \pm 14.7$ bpm and $74.4 \pm 14.4$ bpm during CMR and catheterization, respectively. The mean heart rate change between CMR and catheterization was $9.4\%$ for the rTOF group and $8.9\%$ for the control group.
Table 4.1. Demographic and clinical data of rTOF patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>rTOF (n=7)</th>
<th>control (n=8)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.9 ± 13.1</td>
<td>12.4 ± 5.8</td>
<td>&lt; 0.7</td>
</tr>
<tr>
<td>Male/Female</td>
<td>2/5</td>
<td>5/3</td>
<td></td>
</tr>
<tr>
<td>BSA (m(^2))</td>
<td>1.3 ± 0.6</td>
<td>1.5 ± 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Heart rate, MRI (bpm)</td>
<td>81.1 ± 24.4</td>
<td>75.0 ± 14.7</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>Heart rate, Catheterization (bpm)</td>
<td>79.0 ± 25.7</td>
<td>74.4 ± 14.4</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>Heart rate change (%)</td>
<td>9.4</td>
<td>8.9</td>
<td></td>
</tr>
</tbody>
</table>

Values are means and standard deviations. Heart rate change (%) = \((HR_{\text{MRI}} - HR_{\text{cath}}) / HR_{\text{MRI}} \times 100\).

4.4.2 RV Volume and Ventricular Pressure Characteristics

RV Volume. The results for mean RV end-diastolic and systolic volumes indexed to BSA (EDV\(_1\) and ESV\(_1\), respectively) of the rTOF group and control group are presented in Table 4.2. The mean EDV\(_1\) of the rTOF group (101.1 ± 25.7 ml/m\(^2\)) was higher by 31.7 % than that of the control group (76.8 ± 19.1 ml/m\(^2\)), however, the statistical difference was marginal, \( p = 0.0556 \), due to large variation in value. The mean ESV\(_1\) of the rTOF group was 51.7 ± 19.5 ml/m\(^2\) and was found to be significantly higher by 77.7 % with \( p = 0.0214 \) than that of the control group (29.1 ± 6.9 ml/m\(^2\)). Therefore, the higher RV EDV\(_1\) and ESV\(_1\) of the rTOF group resulted from RV volume overloading.

Ventricular Pressure. The mean RV end-systolic pressure (ESP) and end-diastolic pressure (EDP) were obtained for the rTOF and control groups (Table 4.2). The mean RV ESP of the rTOF group was 51.2 ± 6.0 mmHg and was significantly higher by 76.1 % with \( p<0.001 \)
than that of the control group (29.1 ± 4.6 mmHg). There was no statistically significant difference observed ($p = 0.3257$) between the mean RV EDP of the rTOF group (5.4 ± 2.7 mmHg) and that of the control group (3.7 ± 3.6 mmHg). The mean LV ESP was similar in magnitude between the two groups: 81.1 ± 7.0 mmHg for the rTOF group and 82.4 ± 7.5 mmHg for the control group. The ratio of RV ESP to LV ESP (= RV ESP/LV ESP) for the rTOF group (0.63 ± 0.06) was significantly higher ($p<0.001$) than that for the control group (0.32 ± 0.05).

RV Volume-based Indices. The mean EF of the rTOF group (50.0 ± 8.0 %) was significantly lower by 18.0 % with $p = 0.0086$ compared with that of the control group (61.0 ± 5.8 %). The mean regurgitation fraction of the control group (0.7 ± 2.1 %) was significantly lower than that of the rTOF group (31.8 ± 9.6 %) with $p<0.001$. Peak ejection rate of the rTOF group (2.0 ± 0.5 EDV/s) was lower by 35.2% with $p = 0.01$ than that of the control group (3.1 ± 0.7 EDV/s). No statistically significant difference ($p = 0.7142$) in peak filling rate was observed between the two groups (2.7 ± 0.8 EDV/s for the rTOF group and 2.9 ± 0.7 EDV/s for the control group, respectively). Although, the mean RV mass index of the rTOF group (33.3 ± 13.1 g/m²) was higher by 46.3 % than that of the control group (22.8 ± 9.5 g/m²), there was no statistical significant difference ($p = 0.0946$) in RV mass index between the two groups due to large variation. The mean stroke volume index and cardiac output of the rTOF group (49.4 ± 9.9 ml/beat/m² and 4.6 ± 1.4 L/min, respectively) was not significantly different from those of the control group (47.7 ± 14.1 ml/beat/m² and 5.0 ± 1.3 L/min) with $p = 0.7925$ and $p = 0.5749$, respective
Table 4.2. RV volume and ventricular pressure characteristics and BSA indexed SW (SW$_1$).

<table>
<thead>
<tr>
<th>Ventricular volume and pressure characteristics</th>
<th>rTOF</th>
<th>control</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV Cardiac MRI data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic volume index, EDVI (ml/m$^2$)</td>
<td>101.1 ± 25.7</td>
<td>76.8 ± 19.1</td>
<td>0.0556</td>
</tr>
<tr>
<td>End-systolic volume index, ESVI (ml/m$^2$)*</td>
<td>51.7 ± 19.5</td>
<td>29.1 ± 6.9</td>
<td>0.0214</td>
</tr>
<tr>
<td>Ejection fraction, EF (%)*</td>
<td>50.0 ± 8.0</td>
<td>61.0 ± 5.8</td>
<td>0.0086</td>
</tr>
<tr>
<td>Regurgitation fraction, RF (%)*</td>
<td>31.8 ± 9.6</td>
<td>0.7 ± 2.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak ejection rate (EDV/s)*</td>
<td>2.0 ± 0.5</td>
<td>3.1 ± 0.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak filling rate (EDV/s)</td>
<td>2.7 ± 0.8</td>
<td>2.9 ± 0.7</td>
<td>0.7142</td>
</tr>
<tr>
<td>RV mass index (g/m$^2$)</td>
<td>33.3 ± 13.1</td>
<td>22.8 ± 9.5</td>
<td>0.0946</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m$^2$)</td>
<td>49.4 ± 9.9</td>
<td>47.7 ± 14.1</td>
<td>0.7925</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.6 ± 1.4</td>
<td>5.0 ± 1.3</td>
<td>0.5749</td>
</tr>
<tr>
<td>RV Cardiac catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic pressure, RV ESP (mmHg)*</td>
<td>51.2 ± 6.0</td>
<td>29.1 ± 4.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>End-diastolic pressure, RV EDP (mmHg)</td>
<td>5.4 ± 2.7</td>
<td>3.7 ± 3.6</td>
<td>0.3257</td>
</tr>
<tr>
<td>LV Cardiac catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV End-systolic pressure, LV ESP (mmHg)</td>
<td>81.1 ± 7.0</td>
<td>82.4 ± 7.5</td>
<td>0.7461</td>
</tr>
<tr>
<td>RV/LV ESP ratio*</td>
<td>0.63 ± 0.06</td>
<td>0.32 ± 0.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BSA indexed SW, SW$_1$ (J/m$^2$)*</td>
<td>0.176 ± 0.055</td>
<td>0.091 ± 0.030</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

Values are means and standard deviations. The parameters with an asterisk (*) have a statistically significant difference ($p<0.05$) between rTOF patients and controls.
4.4.3 RV Stroke Work Index (SW₁)

The RV SW₁ for the rTOF and control group is presented in the Table 4.2, as well as Fig. 4.1. RV SW₁ of the rTOF group (0.176 ± 0.055 J/m²) was significantly higher by 93.4% with $p = 0.0026$ than that of the control group (0.091 ± 0.030 J/m²).

![Box plot](image)

**Figure 4.1.** The comparison of RV SW₁ between the rTOF and control groups. The rTOF group had a significantly higher RV SW₁ (0.176 ± 0.055 J/m²) than the control group (0.091 ± 0.030 J/m²) by 92.3 %, $p<0.01$. 

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4.4.4 Relationships between RV SW$_1$ and RV Volume and Pressure Measurements

Figure 4.2 shows the variations of RV SW$_1$ with EDV$_1$ and ESV$_1$ respectively for all subjects. RV SW$_1$ was found to correlate significantly with EDV$_1$ for the control group with $r = 0.91$, $p<0.01$, and moderately for the rTOF group with $r = 0.75$, $p<0.06$ (Fig. 4.2A). Moderate positive correlations were observed between RV SW$_1$ and ESV$_1$ for the two groups with $r = 0.68$, $p = 0.09$ for the rTOF group and $r = 0.73$, $p<0.04$ for the control group (Fig. 4.2B).

Figure 4.3 shows the variations of RV SW$_1$ with RV ESP and EDP. Interestingly, a moderate positive correlation existed between RV SW$_1$ and ESP in the rTOF group with $r = 0.48$ and $p<0.3$, whereas a moderate negative correlation was found for the control group with $r = -0.70$ and $p<0.07$ (Fig. 4.3A). A moderate negative correlation was found between RV SW$_1$ and EDP for the control group with $r = -0.75$ and $p<0.01$, whereas no correlation was observed for the rTOF group (Fig. 4.3B). As seen in Table 2, overall magnitude of SW$_1$ and RV ESP of the rTOF group was significantly higher than that of the control group, whereas that of EDP was insignificantly different between the two groups.

Figure 4.4 shows the variation of RV SW$_1$ with stroke volume index. A significant positive correlation was observed between RV SW$_1$ and stroke volume index in the control group with $r = 0.89$ and $p<0.01$, whereas a moderate positive correlation was found for the rTOF group with $r = 0.59$ and $p<0.2$. 

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**Figure 4.2.** A) Correlations of RV SW\(_1\) with end-diastolic volume index (EDV\(_1\)). RV SW\(_1\) significantly correlated with EDV\(_1\) for the two groups with \( r = 0.75 \) and \( p < 0.06 \) for the rTOF group, \( r = 0.91 \) and \( p < 0.01 \) for the control group. B) Correlations of RV SW\(_1\) with end-systolic volume index (ESV\(_1\)). RV SW\(_1\) moderately correlates with ESV\(_1\) for the two groups with \( r = 0.68 \) and \( p = 0.09 \) for the rTOF group, \( r = 0.73 \) and \( p < 0.04 \) for the control group.
**Figure 4.3.** A) Correlations of RV SW$_1$ with end-systolic pressure (ESP). RV SW$_1$ had a moderate positive correlation with ESP in the rTOF group with $r = 0.48$ and $p<0.3$, whereas a moderate negative correlation was found for the control group with $r = -0.70$ and $p<0.07$. B) Correlations of RV SW$_1$ with end-diastolic pressure (EDP). RV SW$_1$ showed a moderately negative correlation with EDP for the control group with $r = -0.75$ and $p<0.01$, whereas an insignificant correlation was observed for the rTOF group.
**Figure 4.4.** Correlation of RV SW1 with stroke volume index. RV SW1 significantly correlated with stroke volume index in the control group with $r = 0.89$ and $p < 0.01$, whereas a moderate correlation was observed for the rTOF group with $r = 0.59$ and $p < 0.2$. 
4.4.4 Relationship between RV EDV$_1$ and other Indices

Figure 4.5 shows the variations of RV EDV$_1$ with RV ESP and EDP. A moderate negative correlation was found between RV EDV$_1$ and ESP in the control group with $r = -0.78$ and $p = 0.02$, however, there was insignificant correlation observed in the rTOF group (Fig. 4.5A). RV EDP showed a moderate negative correlation with RV EDV$_1$ in the control group with $r = -0.89$ and $p<0.01$, whereas no correlation was observed for the rTOF group (Fig. 4.5B).

The correlations of RV EDV$_1$ with RV SW$_1$ and other RV volume based indices such as ejection fraction (EF), regurgitation fraction (RF), and peak ejection rate for the rTOF group are shown in Table 4.3. The RV SW$_1$ correlated well with RV EDV$_1$ having $r = 0.75$ with moderate significance ($p<0.06$), whereas the correlation of RV EDV$_1$ with all other RV volume based indices were insignificant ($p>0.05$).
Figure 4.5 A) Correlation of RV EDV$_1$ with ESP. EDV$_1$ negatively correlated with ESP for the control group with $r = -0.78$, $p = 0.02$. However, there was an insignificant correlation found for the rTOF group between RV EDV$_1$ and ESP. B) Correlation of RV EDV$_1$ with EDP. EDV$_1$ had a negative correlation with ESP for the control group with $r = -0.89$, $p<0.01$, whereas, RV EDP showed an insignificant correlation with RV EDV$_1$ for the rTOF group.
Table 4.3 The correlations of ejection and regurgitation fractions and peak ejection rate with RV EDV₁, ESP, and SW₁ for the rTOF group.

<table>
<thead>
<tr>
<th></th>
<th>Correlation with</th>
<th>r value</th>
<th>p value</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ejection fraction</strong></td>
<td>RV EDV₁</td>
<td>-0.56</td>
<td>&lt; 0.2</td>
<td>Negative moderate</td>
</tr>
<tr>
<td></td>
<td>RV ESP</td>
<td>0.12</td>
<td>&lt; 0.8</td>
<td>Insignificant</td>
</tr>
<tr>
<td></td>
<td>RV SW₁</td>
<td>-0.27</td>
<td>&lt; 0.6</td>
<td>Negative weak</td>
</tr>
<tr>
<td><strong>Regurgitation fraction</strong></td>
<td>RV EDV₁</td>
<td>0.10</td>
<td>&lt; 0.9</td>
<td>Insignificant</td>
</tr>
<tr>
<td></td>
<td>RV ESP</td>
<td>0.25</td>
<td>&lt; 0.6</td>
<td>Positive weak</td>
</tr>
<tr>
<td></td>
<td>RV SW₁</td>
<td>0.56</td>
<td>&lt; 0.2</td>
<td>Positive moderate</td>
</tr>
<tr>
<td><strong>Peak ejection rate</strong></td>
<td>RV EDV₁</td>
<td>0.42</td>
<td>&lt; 0.5</td>
<td>Positive weak</td>
</tr>
<tr>
<td></td>
<td>RV ESP</td>
<td>-0.37</td>
<td>&lt; 0.5</td>
<td>Negative weak</td>
</tr>
<tr>
<td></td>
<td>RV SW₁</td>
<td>0.18</td>
<td>&lt; 0.8</td>
<td>Insignificant</td>
</tr>
</tbody>
</table>
4.5 Discussion

The stroke work calculation requires simultaneous pressure and volume measurement which is clinically difficult. This is because, simultaneous cardiac catheterization and MRI is not trivial under the clinical settings. We have employed the methodology (Das et al., 2010) that used ECG gating to synchronize non-simultaneously measured clinical RV pressure and volume data to compute $RV\ SW_I$ (BSA indexed SW) for all subjects in our study. Our findings show that $RV\ SW_I$ of rTOF patients ($0.176\pm\ 0.055\ J/m^2$) was significantly higher (93.4 %, $p = 0.0026$) than controls ($0.091\pm\ 0.030\ J/m^2$). It may be noted that the rTOF subject in a pilot study by Das et al., 2010 had a lower stroke work than normal subject. They had two subjects, a rTOF patient and a control, in their study. Their rTOF patient had native RV outflow track and did not have any pulmonary artery (PA) conduit. Whereas, all our rTOF subjects had a PA conduit along with elevated levels of RV pressure and volume (Table 4.2). It is possible that stiffer PA conduit compared to native RV outflow tract without PA conduit alters the hemodynamic condition in PA and induces higher RV pressure for rTOF patients.

The rTOF group had significantly lower EF (50.0 ± 8.0 %, $p = 0.0086$; Table 4.2) than the control group (61.0 ± 5.8 %). Our result for EF was similar to those obtained by (Schamberger et al., 2000). Schamberger et al. found significantly lower EF (45.0 ± 9.0 %, $p<0.01$) in their rTOF patients. Further, our rTOF patients had significantly higher main pulmonary regurgitation fraction as well (31.8 ± 9.6 %, $p<0.001$; Table 2) than controls (0.7 ± 2.1 %). The lower EF and large main pulmonary regurgitation fraction in rTOF patients are indicative of severe PI. Thus, as expected, large regurgitation fraction and lower EF, over time leads to RV volume overloading in rTOF patients.
The decision for the right timing for PVR surgery is a clinically challenging question for rTOF RV renormalization. PVR is required to alleviate the deteriorating effect of RV myocardial dysfunction due to RV overloading. Currently, PVR has mostly been performed based on subjective assessment of MRI scans of patient’s RV. One quantitative criteria to decide on the right timing for PVR that has been clinically used is RV EDV\(_1\) (BSA indexed EDV) which has been proposed by (Therrien et al., 2005). They have suggested a cutoff value of 170 ml/m\(^2\) for RV EDV\(_1\) based on a 17 patient study. Their study found that RV renormalization was not possible once RV EDV\(_1\) exceeded the cutoff value of 170 ml/m\(^2\). None of our subjects in the rTOF group had RV EDV\(_1\) exceeding 170 ml/m\(^2\). On a similar note, our study found significant correlations between RV SW\(_1\) and EDV\(_1\) for both the rTOF and control group (\(r = 0.75\) for the rTOF group and \(r = 0.91\) for the control group). However, it was not possible to establish a cutoff value for SW\(_1\) from our sample of rTOF subjects because none had EDV\(_1\) greater than 170 ml/m\(^2\).

It is well known that volume overloading leads to severe RV myocardial stresses resulting from increased RV pressure in rTOF patients (Rosenthal et al., 1993, Walsh et al., 1988). Our rTOF group had higher mean RV ESP (51.2 ± 6.0 mmHg; Table 4.2) than those reported by (Walsh et al., 1988), which is the mean ESP of 43.0 ± 25.0 mmHg. This could be because all our rTOF subjects had a PA conduit and in addition, majority of them had various levels of conduit stenosis from mild (< pressure gradient of 25 mmHg) to severe (>65 mmHg). Transconduit pressure gradient in the PA of the rTOF patients was calculated from the peak blood velocity at MPA using approach described by (Hatle et al., 1978). Thus, we speculate that RV pressure overloading in our rTOF subjects was due to combined effects of RV volume.
overloading resulting from MPA regurgitation fraction and altered hemodynamics because of the stenoses in the PA conduit.

The other diagnostic criteria (other than EDV$_1$) that has been used to decide on the surgical treatment to alleviate RV pressure overloading in rTOF patients such as PVR, balloon angioplasty, and percutaneous pulmonary valve implantation (Khambadkone et al., 2005, Momenah et al., 2009) is RV/LV ESP ratio (Warnes et al., 2008). Warnes et al. have recommended a cutoff value of 0.7 for RV/LV ESP ratio. They noted the possibility of irreversible RV myocardial dysfunction if RV/LV ESP ratio exceeded 0.7. In our study only one subject in our rTOF group had ESP ratio equal to 0.704 and had undergone PA stent insertion surgery to relieve high RV pressure. The elevated level of RV/LV ESP ratio in the rTOF group in Table 4.2 was due to elevated RV ESP for rTOF patients in our study. For both the groups LV ESP was similar in magnitude with 81.1 ± 7.0 mmHg for the rTOF group and 82.4 ± 7.5 mmHg for the control group. The primary cause of higher RV ESP in rTOF patients was due to the progressive RV dysfunction over time caused by RV overloading.

As noted from the discussion in the preceding paragraphs, RV volume based indices such as RV EDV$_1$, EF, RF, and peak ejection rate have been widely used as diagnostic endpoints for various surgical procedures such as PVR. However, based on our data, $p$ values for comparing the group mean between the rTOF and control groups for RV SW$_1$ (0.0026) was appreciably lower than the corresponding $p$ values for RV EDV$_1$ (0.0556), EF (0.0086), and peak ejection rate (0.01) (Table 4.2). In addition, RV SW$_1$ had a better correlation with RV EDV$_1$ which is an important indicator of RV volume overloading in rTOF patients, compared to EF, RF, and peak
ejection rate (Table 4.3). Further, RV SW₁ has an advantage of incorporating both RV volume and pressure into one single index.

Stroke work calculation requires invasive catheterization for pressure measurement. Cardiac catheterization is generally not part of standard of care for typical rTOF patients unless a patient has an obstruction in RVOT and PA, or has severely hypertrophied RV resulting in elevated levels of RV pressure. This limits the applicability of our approach in a clinical setting. However, with future development of non-invasive pressure estimation using 4D MRI (Ebbers et al., 2001, Tyszka et al., 2000) our method may be adopted in a clinical setting. Secondly, our method requires co-registration of non-simultaneously measured RV pressure and volume. Therefore, we do not preclude the possibility of inducing small variation in the estimation of RV SW due to the small difference (less than 10 %) in heart rate between CMR and catheterization. Again this limitation can be eliminated in future with MRI based pressure estimation.

4.6 Conclusions

In this study, we have used a simple methodology to compute RV SW₁ (BSA indexed SW) by using non-simultaneously measured RV volume and pressure data from clinical cardiac MRI and catheterization, respectively. Our data showed that the RV of the rTOF patients was under severe RV overloading conditions compare to that of the control subjects. The result of the statistical analysis confirmed our hypothesis that the required RV SW₁ of rTOF patients with dysfunctional RV is significantly higher than that of controls with normal RV. Further, RV SW₁ correlated well with RV volume and pressure data. Therefore, we conclude that RV SW₁ may be
useful to quantify RV inefficiency and to delineate the abnormal RV hemodynamic status in rTOF patients.
Chapter 5  Energy Transfer Ratio between Right Ventricle and Main Pulmonary Artery

5.1  Introduction

With excellent survival rate after the repair for these defects, the primary concern is the long term effects of the repair itself. The major hemodynamic sequela of the repair is pulmonary regurgitation resulting in right ventricular dilatation and varying degrees of RV myocardial dysfunction (Murphy et al., 1993, Pigula et al., 1999). Also, a considerable number of repaired TOF patients develop RVOT obstruction from either PA conduit stenosis or native pulmonic stenosis (Khambadkone et al., 2005, Oosterhof et al., 2006). Irrespective of the etiology of obstruction, both adversely affect RV-PA hemodynamics by increasing flow resistance. Clinically, a dilated dysfunctional RV and RVOT obstruction can be manifested as exercise intolerance, arrhythmias, and even sudden death (Hazekamp et al., 2001, Davlouros et al., 2006, Harrild et al., 2009, d'Udekem et al., 2000).

Surgical or catheter based intervention is often required to alleviate the regurgitation or obstruction. Interventions such as pulmonary valve replacement, RV-PA conduit replacement, or PA stent insertion are often performed to stop pulmonary regurgitation, alleviate obstruction, and subsequently prevent development of RV dilation and dysfunction. However, the appropriate timing of intervention is difficult to determine due to lack of suitable quantifiable diagnostic parameters. In practice, clinicians use a variety of clinical and imaging measures, including RV cardiac indices, such as RV end-diastolic volume (EDV), end-systolic volume (ESV), end-systolic pressure (ESP), ejection fraction, and QRS duration to estimate the right
timing of interventions (Geva 2011, Therrien et al., 2005, Warnes et al., 2008, Uebing et al., 2007, Shenkman et al., 2002). However, timing of interventions based on individual indices is inherently inaccurate because the RV-pulmonary interaction is complex, and there is interdependence of the parameters.

In this research energy transfer ratio \( e_{MPA} \), between the RV and the MPA was evaluated, expanding present energy-based approach to assess RV pathophysiologic status for rTOF patients. The mean \( e_{MPA} \) was compared between the two groups, rTOF patient and control, to test the hypothesis of the task 1-2 (specific aim 1) of the dissertation that the \( e_{MPA} \) for patients with RV pathophysiology would be significantly lower than that of controls with normal RV-PA physiology. It is expect that \( e_{MPA} \) may be useful measure to assess the progression of RV dysfunction in patients with repaired CHD and possibly assist with timing of intervention.

5.2 Study Population

The details of demographic and clinical data of the subjects in our study are presented in Table 5.1. Patients who had undergone both cardiac MRI (CMR) and right heart catheterization at CCHMC from 2006 to 2010 were registered for the study. There were sixteen subjects, eight males and eight females, who met the inclusion criteria for the study.

Out of 16 subjects, 10 had abnormal RV and PA physiology. Two subjects out of the 10 who had either moderate-to-severe tricuspid valve regurgitation or an extremely severe PA conduit stenosis were excluded from the study. As a result, eight subjects with RV
pathophysiology were identified to be in the patient group. They included three male and five
females with age: 13.3 ± 11.3 years and BSA: 1.2 ± 0.5 m$^2$. The patient group had a mean heart
rate of 82.6 ± 20.6 bpm and 78.3 ± 23.6 bpm during CMR and catheterization, respectively. The
difference in mean heart rate between CMR and catheterization was only 5.2 % for the patient
group. Seven patients had a PA conduit as a result of a surgical intervention during infancy or
childhood. The remaining patient had a RVOT patch. Among the patients, the levels of PA or
conduit stenosis varied.

The patient group was again subdivided into two subgroups designated by group 1 and 2.
The Group 1 consisted of four patients who had TOF and had undergone TOF repair. The
Group 2 consisted of four patients who had other lesions requiring RV-PA conduits (Ross
procedure, aortic autograft with RV-PA homograft for aortic valve disease, or transposition of
the great arteries with pulmonary stenosis, the aorta and pulmonary artery connected to the
wrong ventricles).

Out of the total 16 subjects and excluding 10 patients mentioned above, the remaining six
subjects underwent diagnostic CMR and catheterization for conditions not related to the RV and
PA. All six subjects were found to have normal RV structure and function and normal PA
anatomy and physiology. Therefore, the RV performance and PA physiology was assumed to be
normal. These subjects were considered as the control group for the study (three male and three
females, age: 13.8 ± 8.5 years and BSA: 1.5 ± 0.6 m$^2$). The subjects in the control group had
mean heart rate of 75.3 ± 12.8 bpm and 73.5 ± 13.1 bpm during CMR and catheterization,
respectively. The mean heart rate change between CMR and catheterization was only 2.4 % for
the control group. The difference in physical characteristics between the patient and control groups was insignificant (Table 5.1).

**Table 5.1.** Demographic and clinical data of patients with RV-PA pathophysiology and controls with normal RV-PA physiology. Values are means and standard deviations.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6)</th>
<th>Patient (n=8)</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>13.8 ± 8.5</td>
<td>13.3 ± 11.3</td>
<td>&gt; 0.9</td>
</tr>
<tr>
<td>Male/Female</td>
<td>3/3</td>
<td>3/5</td>
<td></td>
</tr>
<tr>
<td>BSA(m²)</td>
<td>1.5 ± 0.6</td>
<td>1.2 ± 0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Heart rate,CMR (bpm)</td>
<td>75.3 ± 12.8</td>
<td>82.6 ± 20.6</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Heart rate,Catheterization (bpm)</td>
<td>73.5 ± 13.1</td>
<td>78.3 ± 23.6</td>
<td>&lt; 0.7</td>
</tr>
<tr>
<td>Heart rate change (%), see note</td>
<td>2.4</td>
<td>5.2</td>
<td></td>
</tr>
</tbody>
</table>

Note: Heart rate change (%) = (HR\textsubscript{CMR}-HR\textsubscript{Cath})/HR\textsubscript{CMR}×100
5.3 Data Acquisition

All patients and control subjects underwent CMR studies including functional analysis, phase contrast magnetic resonance (PC MR) imaging, and magnetic resonance angiography (MRA). Three different MRI scanners were used for CMR studies: 1) 1.5 Tesla GE Excite Magnet (General Electric, USA), 2) 3.0 Tesla Siemens Trio Magnet (Siemens Healthcare, Erlangen, Germany), and 3) 1.5 Tesla Achieva MRI scanner (Philips Medical Systems, Netherlands). The standard CMR parameters were used as described in the section 4.3 of Chapter 4.

5.4 Results

Table 5.2 shows the measured RV pressures, volumes, and volume-based parameters (EF, RF, peak ejection and filling rates, RV mass index, stroke volume index, and cardiac output) of all patients and controls. The computed energy-based endpoints, $e_{MPA}$ and RV SW, for both the patient and control group are presented in Table 5.3 and Fig. 5.1. The results for the patient subgroup 1 and 2 are provided in the Table 5.4. The mean and standard deviation of individual quantities are reported in Tables. The quantities showing significant statistical difference ($p<0.05$) between patients and controls are designated by asterisk (*).
5.4.1 RV Volumes and RV Volume-based RV Parameters

The mean RV end-diastolic volume index (EDV<sub>1</sub>) and end-systolic volume index (ESV<sub>1</sub>) of the patient and control group are presented in Table 5.2. The EDV<sub>1</sub> of the patient group was 102.2 ± 25.3 ml/m<sup>2</sup> and that of the control group was 77.9 ± 18.3 ml/m<sup>2</sup>. The difference in EDV<sub>1</sub> between the two groups was marginally significant (\(p = 0.07\)). There was no difference in the ESV<sub>1</sub> between the two groups (\(p<0.2\)). The ESV<sub>1</sub> for the patient group was found to be 47.3 ± 21.0 ml/m<sup>2</sup>, whereas it was 31.6 ± 8.4 ml/m<sup>2</sup> for that of the control group. Despite the fact that both EDV<sub>1</sub> and ESV<sub>1</sub> of the patient group were larger than those of the control group by 31.2 % and 49.9 %, respectively, the differences were only marginally significant in EDV<sub>1</sub> due to large variation among individual subjects in the group.

The patient group had a significantly higher RF (32.1 ± 8.5 %) than the control group (0.0 ± 0.0 %; \(p<0.01\)). The systolic function as measured by mean EF of the patient group (53.5 ± 7.5 %) was not different than the control group (58.3 ± 7.8 %; \(p<0.3\)). The patient group had a significantly lower peak systolic ejection rate (2.2 ± 0.5 EDV/s) compared to the control group (3.0 ± 0.8 EDV/s; \(p<0.05\)). However, the peak diastolic filling rate was not significantly different between the two groups (2.6 ± 0.8 EDV/s for the patient group and 2.8 ± 0.7 EDV/s for the control group, respectively; \(p<0.8\)). Further, the patient group had a significantly higher RV mass index (33.9 ± 11.4 g/m<sup>2</sup>) than the control group (19.8 ± 4.6 g/m<sup>2</sup>; \(p<0.02\)). In summary, the patient group had somewhat larger RV with equivalent function, increased RV mass, and lower peak ejection rate compared to the control group.
Interestingly, the stroke volume index of the patient group, 54.9 ± 9.5 ml/beat/m$^2$, was not different from that of the control group (46.3 ± 13.9 ml/beat/m$^2$; $p<0.2$). Similarly, no significant difference in cardiac output between the two groups was found (5.1 ± 1.3 L/min for the patient group and 4.8 ± 1.5 L/min for the control group, respectively; $p<0.8$).

5.4.2 RV Pressure

The mean RV end-systolic pressure (ESP) and end-diastolic pressure (EDP) for the patient and control groups are presented in Table 5.2. The ESP of the patient group (53.6 ± 7.1 mmHg) was significantly higher (2.2 times; $p<0.01$) than that of the control group (24.6 ± 5.5 mmHg). However, the EDP of the patient group (5.0 ± 2.4 mmHg) and that of the control group (3.2 ± 4.0 mmHg) were not different ($p<0.4$).
Table 5.2. RV pressure, volume data, and volume-based parameters for the patient and control groups.

<table>
<thead>
<tr>
<th>RV pressure and volume characteristics</th>
<th>Patient</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac MRI data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic volume index, EDV₁ (ml/m²)</td>
<td>102.2 ± 25.3</td>
<td>77.9 ± 18.3</td>
<td>0.07</td>
</tr>
<tr>
<td>End-systolic volume index, ESV₁ (ml/m²)</td>
<td>47.3 ± 21.0</td>
<td>31.6 ± 8.4</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>Ejection fraction, EF (%)</td>
<td>53.5 ± 7.5</td>
<td>58.3 ± 7.8</td>
<td>&lt; 0.3</td>
</tr>
<tr>
<td>Regurgitation fraction, RF (%)</td>
<td>32.1 ± 8.5</td>
<td>0.0 ± 0.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Peak ejection rate (EDV/s)</td>
<td>2.2 ± 0.5</td>
<td>3.0 ± 0.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Peak filling rate (EDV/s)</td>
<td>2.6 ± 0.8</td>
<td>2.8 ± 0.7</td>
<td>&lt; 0.8</td>
</tr>
<tr>
<td>RV mass index (g/m²)*</td>
<td>33.9 ± 11.4</td>
<td>19.8 ± 4.6</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m²)</td>
<td>54.9 ± 9.5</td>
<td>46.3 ± 13.9</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.1 ± 1.3</td>
<td>4.8 ± 1.5</td>
<td>&lt; 0.8</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic pressure, ESP (mmHg)*</td>
<td>53.6 ± 7.1</td>
<td>24.6 ± 5.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>End-diastolic pressure, EDP (mmHg)</td>
<td>5.0 ± 2.4</td>
<td>3.2 ± 4.0</td>
<td>&lt; 0.4</td>
</tr>
</tbody>
</table>

Values are means and standard deviations. The parameters with an asterisk (*) have a statistically significant difference (p<0.05) between the two groups.
5.4.3 The Computed RV Energy-based Endpoints: Total energy at the MPA ($E_{net}$), RV SW, BSA-indexed RV SW ($SW_I$), and Energy Transfer Ratio ($e_{MPA} = E_{net}/RV SW$)

The computed RV energy-based endpoints are shown in Table 5.3. The control group had a higher $E_{net}$ (0.19 ± 0.11 J) compared to the patient group (0.13 ± 0.07 J; $p = 0.2$). As expected, the patient group had a significantly higher ($p<0.05$) RV SW and RV $SW_I$ (0.24 ± 0.12 J and 0.21 ± 0.10 J/m$^2$, respectively) than the control group (0.12 ± 0.04 J and 0.09 ± 0.04 J/m$^2$, respectively). As a result, the $e_{MPA}$ was significantly lower in the patient group (0.56 ± 0.33) compared to that of the control group (1.56 ± 0.85; $p<0.01$).

![Table 5.3. Total energy at the MPA ($E_{net}$), RV SW, BSA indexed RV SW ($RV SW_I$), and Energy transfer ratio ($e_{MPA}$)](image)

<table>
<thead>
<tr>
<th>Computed RV endpoints</th>
<th>Patient</th>
<th>Control</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy, $E_{net}$ (J)</td>
<td>0.13 ± 0.07</td>
<td>0.19 ± 0.11</td>
<td>0.2</td>
</tr>
<tr>
<td>RV SW (J)*</td>
<td>0.24 ± 0.12</td>
<td>0.12 ± 0.04</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>RV $SW_I$ (J/m$^2$)*</td>
<td>0.21 ± 0.10</td>
<td>0.09 ± 0.04</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Energy transfer ratio, $e_{MPA}$* ($= E_{net}/RV SW$)</td>
<td>0.56 ± 0.33</td>
<td>1.56 ± 0.85</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values are means and standard deviations. The parameters with an asterisk (*) have a statistically significant difference ($p<0.05$) between the two groups.
Figure 5.1. The mean energy transfer ratio ($e_{MPA}$) was significantly lower in the patient group (0.56 ± 0.33) than control group ((1.56 ±0.85; $p<0.01$), whereas, the mean RV BSA indexed SW (SW$_I$) was significantly higher in the patient group (0.21 ± 0.10 J/m$^2$) than control group (0.09 ± 0.04 J/m$^2$; $p<0.02$).
5.4.4 The RV Volume, Volume-based Parameters, Pressure, and RV Energy-based Endpoints: Total energy at the MPA ($E_{net}$), RV SW, BSA-indexed RV SW (SW$_I$), and Energy Transfer Ratio ($e_{MPA} = E_{net} / \text{RV SW}$) for Subgroup 1 and 2

The demographic of each subgroup was comparable to the controls ($p>0.05$) as shown in Table 5.4. Both the subgroups had a significantly higher RF (30.0 ± 4.8 % with $p<0.01$ and 34.2 ± 11.5 % with $p<0.01$, for the subgroup 1 and 2, respectively) than that for the control group with no regurgitant flow to the RV. The increase of RF was more pronounced in the subgroup 2 than 1. RV ESP in both the subgroups was significantly higher (50.6 ± 7.0 mmHg with $p<0.01$ and 56.7 ± 6.6 mmHg with $p<0.01$, for the subgroup 1 and 2, respectively) than the control group (24.6 ± 5.5 mmHg). Other parameters, RV EDP, EDV$_I$, ESV$_I$, EF, peak ejection/filling rate, stroke volume index, and cardiac output for both the subgroups were not different from those of the control group.

As shown in Table 5.5, the control group had a higher $E_{net}$ (0.19 ± 0.11 J) compared to both the patient subgroups (0.15 ± 0.06 J and 0.10 ± 0.08 J for group 1 and 2, respectively) as shown in Table 5.6. Whereas, the control group had a lower RV SW (0.12 ± 0.04 J) than both the patient subgroups (0.21 ± 0.12 J and 0.28 ± 0.13 J for the subgroup 1 and 2, respectively). The difference in $E_{net}$ and RV SW between the patient subgroups and control group were not statistically significant except RV SW between the patient subgroup 2 and the control group ($p<0.02$). RV SW$_I$ for both the patient subgroups was significantly higher (0.147± 0.035 J/m2 with $p = 0.05$ and 0.262 ± 0.104 J/m2 with $p<0.01$, for the subgroup 1 and 2, respectively) than that of the control (0.090 ± 0.038 J/m2). However, only the subgroup 2 had a significantly lower $e_{MPA}$ (0.35± 0.24; $p<0.03$) compared to that of the control group (1.56 ± 0.85).
Table 5.4. The detail of demographic and clinical data of subjects in the patient subgroup 1 and 2.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patient</th>
<th>p value</th>
</tr>
</thead>
</table>
|                          | Group 1       | Group 2                   | 1 vs.  
|                          |               |                           | Control | 2 vs.  
|                          |               |                           | Control |
| Age (years)              | 13.8 ± 8.5    | 17.8 ± 15.0               | 8.8 ± 4.6 | 0.6   | < 0.4 |
| Male/Female              | 3/3           | 1/3                       | 2/2     |
| BSA(m²)                  | 1.5 ± 0.6     | 1.4 ± 0.7                 | 1.1 ± 0.3 | < 0.9 | < 0.3 |
| Heart rate, CMR (bpm)    | 75.3 ± 12.8   | 78.8 ± 21.7               | 86.5 ± 21.9 | < 0.9 | < 0.4 |

Values are means and standard deviations.

Table 5.5. Total energy at the MPA (E_{net}), RV SW, RV SW_I, and energy transfer ratio (e_{MPA}) for subjects in patient subgroup 1 and 2.

<table>
<thead>
<tr>
<th>Computed RV endpoints</th>
<th>Control</th>
<th>Patient</th>
<th>p value</th>
</tr>
</thead>
</table>
|                          | Group 1       | Group 2                   | 1 vs.  
|                          |               |                           | Control | 2 vs.  
|                          |               |                           | Control |
| Total energy, E_{net} (J)| 0.19 ± 0.11   | 0.15 ± 0.06               | 0.10 ± 0.08 | < 0.5 | < 0.3 |
| RV SW (J)                | 0.12 ± 0.04   | 0.21 ± 0.12               | 0.28 ± 0.13 | < 0.2 | < 0.02 |
| RV SW_I (J/m²)           | 0.09 ± 0.04   | 0.15 ± 0.04               | 0.26 ± 0.10 | 0.05  | < 0.01 |
| Energy transfer ratio, e_{MPA}| 1.56 ± 0.85 | 0.78 ± 0.27               | 0.35 ± 0.24 | < 0.12 | < 0.03 |

The parameters underlined have a statistically significant difference (p<0.05) between either the group 1 and control or the group 2 and control.
5.4.5 The Variations of $e_{MPA}$ and RV SW$_1$ with RV Volume and Pressure Measurements

The variation of $e_{MPA}$ with EDV$_1$ for the subjects in our study is shown in Fig. 5.2A. A negative correlation for the $e_{MPA}$ was found with EDV$_1$ for both the patient and control groups ($r = -0.63$ with $p = 0.1$ for the patient group and $r = -0.80$ with $p<0.06$ for the control group). The negative trend of $e_{MPA}$ with EDV$_1$ was more pronounced in the control group. A positive correlation between RV SW$_1$ and EDV$_1$ was shown in both the groups in Fig. 5.2B ($r = 0.87$ with $p<0.03$ and $r = 0.59$ with $p<0.2$, for the control and the patient groups, respectively).

The variation of $e_{MPA}$ with ESV$_1$ showed a trend similar to the correlation between $e_{MPA}$ and EDV$_1$(Fig. 5.3A). A negative correlation was found between $e_{MPA}$ and ESV$_1$ of both the groups ($r = -0.69$ with $p<0.07$ in the patient group and $r = -0.33$ with $p<0.6$ in the control group). RV SW$_1$ showed a positive correlation with ESV$_1$ in both the groups ($r = 0.41$ with $p = 0.3$ for the patient group and $r = 0.25$ with $p<0.7$ for the control group, respectively; Fig. 5.3B).

The variation of $e_{MPA}$ with ESP is shown in Fig. 5.4A. The control group showed a positive correlation between $e_{MPA}$ and ESP ($r = 0.74; p<0.1$). However, the patient group had a negative correlation between $e_{MPA}$ and ESP ($r = -0.45; p<0.3$). RV SW$_1$ had a significant positive correlation with ESP of the patient group ($r = 0.74; p<0.04$), whereas, the correlation between RV SW$_1$ and ESP was insignificant for the control group (Fig. 5.4B).

Figure 5.5A shows the variation of $e_{MPA}$ with EDP. A significant positive correlation ($r = 0.94; p<0.01$) was found between $e_{MPA}$ and EDP for the control group, whereas, no significant correlation was found between $e_{MPA}$ and EDP in the patient group. The variation of RV SW$_1$
with EDP is shown in Fig. 5.5B. The control group had a negative correlation between RV SW\(_1\) and EDP (\(r = -0.57; p<0.3\)), whereas no significant correlation between RV SW\(_1\) and EDP for the patient group.

The variation between RV EDV\(_1\) and ESP is shown in Fig. 5.6A. The control group had a negative correlation between EDV\(_1\) and ESP (\(r = -0.46; p<0.4\)), whereas, the patient group showed insignificant correlation between EDV\(_1\) and ESP. Similarly, the control group had a significant negative correlation between EDV\(_1\) and EDP (\(r = -0.81; p<0.05\)), whereas, the patient group showed insignificant correlation between EDV\(_1\) and EDP (Fig. 5.6B).
Figure 5.2. A) Both the patient and control groups showed a negative correlation between $e_{MPA}$ and EDV$_1$ ($r = -0.63$; $p = 0.1$ and $r = -0.80$; $p<0.06$, for the patient and control group, respectively). B) A positive correlation was shown between RV SW$_1$ and EDV$_1$ in both the patient and control groups. ($r = 0.59$; $p<0.2$ and $r = 0.87$; $p<0.03$, for the patient and control group, respectively).
Figure 5.3. A) A negative correlation between $e_{MPA}$ and $ESV_1$ was found in both the patient and control groups ($r = -0.69; p<0.07$ and $r = -0.33; p<0.6$, for the patient and control groups, respectively). B) Both the patient and control groups had a positive correlation between $e_{MPA}$ and $ESV_1$ ($r = 0.41; p = 0.3$ and $r = 0.25; p<0.7$, for the patient and control groups, respectively).
Figure 5.4. A) A negative correlation between $e_{MMP}$ and ESP was observed in the patient group ($r = -0.45; p<0.3$), whereas a positive correlation was found in the control group ($r = 0.74; p<0.1$). B) The patient group had a significant positive correlation between RV SW and ESP ($r = 0.74; p<0.04$), whereas no correlation was found in the control group.
Figure 5.5. A) The control group had a positive correlation between $e_{MPA}$ and EDP ($r = 0.94; p<0.01$), whereas no correlation was observed in the patient group. B) A negative correlation between RV SW$_I$ and EDP was found in the control group ($r = -0.57; p<0.3$), whereas no correlation was observed in the patient group.
Figure 5.6. A) No correlation was observed between ESP and EDV₁ in the patient group, whereas the control group had a weak negative correlation between ESP and EDV₁ ($r = -0.46; p<0.4$). B) A significant negative correlation was observed between EDP and EDV₁ of the control group ($r = -0.81; p<0.05$), whereas an insignificant correlation was shown between EDP and EDV₁ of the patient group.
5.5 Discussion

Pulmonary regurgitation with or without obstruction is the primary long-term hemodynamic consequence of many CHDs, especially repaired TOF (Geva 2011, Kuehne et al., 2003, Kuehne et al., 2001). The chronic pulmonary regurgitation may result in progressive RV dilatation leading to RV dysfunction, arrhythmias, exercise intolerance, and rarely sudden cardiac death (Gatzoulis et al., 2000). As expected, our patient group had higher mean RV volumes than the control group (by 31.2 % in EDV₁ and 49.9 % in ESV₁).

The majority of our patients had a PA conduit as a result of the surgical intervention performed in their childhood. They had various levels of the PA or the PA conduit obstruction, which also adversely affect the RV hemodynamics eventually leading to increased RV pressure. As shown in Table 4.2, the mean RV ESP of the patient group (53.6 ± 7.1 mmHg) was significantly higher than that of the control group (24.6 ± 5.5 mmHg). Interestingly, the RV SW₁ had a positive correlation with ESP in the patient group (Fig. 5.4B). Apparently, the increased RV ESP of the patient group provides the RV with additional momentum to the blood flow towards the PA. Although RV ESP increases, the energy transfer ratio ($e_{MPA}$) decreases in the patient group (Fig. 5.4A).

The PA regurgitant flow and PA obstruction directly affect the RV performance and efficiency as confirmed in our previous work (Lee et al., 2011). It showed that patients with rTOF physiology had a significantly higher RV SW₁, including PA regurgitation and PA obstruction, compared to subjects with normal RV physiology. Thus, both RV pressure and volume overloading, resulting from PA obstruction and PA regurgitation, need to be taken into account in the management of these patients.
account for long-term follow up for patients after repair. As a longitudinal measure of hemodynamics $e_{MPA}$ is advantageous because it incorporates both RV volume and pressure data.

No correlation was observed between RV EDV$_1$ and ESP and EDP for the patient group (Fig. 5.6A and 5.6B, respectively), suggesting that simply using volumes or pressures does not adequately characterize the hemodynamic state of RV. Quantification of the hemodynamic insufficiency in the RV-PA in terms of $e_{MPA}$ accounts for both volume and pressure increases in the RV, as well as changes in flow in PA. It is because the $e_{MPA}$ is defined (Eq. 3.10) as the ratio of the net energy transferred to the MPA($E_{net}$) and RV stroke work (SW), and it takes into account RV pressure and volume, as well as MPA pressure and flow rate. Present limitation of the $e_{MPA}$ is that it requires invasive cardiac catheterization for pressure measurement which is generally not a standard of care procedure for a typical rTOF patient. However, as will be discussed in next chapter, with the ongoing advancement of 4D PC-MRI based non-invasive pressure estimation (Ebbers et al., 2001, Tyszka et al., 2000), $e_{MPA}$ can also be obtained non-invasively. Further, both RV SW and BSA-indexed RV SW (SW$_1$) are not dimensionless physical quantity, whereas, $e_{MPA}$ is a dimensionless quantity. A higher value of $e_{MPA}$ will indicate a more efficient RV.

From an energy point of view, the $e_{MPA}$ accounts for pressure-flow and kinetic energy of the blood at MPA along with stroke work performed by the RV. Therefore, the $e_{MPA}$ may be useful to quantify the state of the RV-PA hemodynamics in terms of energy transition between the RV and PA. Specifically, as seen from the Table 5.3 and Fig. 5.1, the $e_{MPA}$ of the patient group (0.56 ± 0.33) was significantly lower (2.8 times; $p<0.01$) than that of the control group.
(1.56 ± 0.85), despite the fact that RV SW$_1$ of the patient group (0.21 ± 0.10 J/m$^2$) was significantly higher (2.3 times; p<0.02) as compared to that of the control group (0.09 ± 0.04 J/m$^2$). These results show that the RV, in the presence of PA regurgitation and PA obstruction, is under an overloading condition, to maintain equivalent blood flow towards the PA. Based on our $e_{MPA}$ measurement, the RV performance in patients was less efficient compared to that of normal subjects. The lower $e_{MPA}$ value of the patient group can be attributed to the combined effect of lower $E_{net}$, caused by both PA regurgitation and PA obstruction, and higher RV stroke work, caused by relatively higher RV pressure and volume overloading.

The $e_{MPA}$ does not measure all the RV complex energy components or losses. For example, the calculation of RV SW assumes a quasi-static variation of RV pressure and volume and thus it does not account for the dynamic conditions in the RV, such as transient blood velocity and flow rate. In addition, the energy dissipated by friction as the blood flows through the RVOT (or a conduit for a majority of patients) was not included in the RV SW calculation. Thus, RV SW could underestimate the energy that the RV possibly generates. Likewise, $E_{net}$ does not take into consideration complex energy storage by elasticity of tissues, as well as the friction loss between the blood and tissues. This could explain the mean $e_{MPA}$ of the control group being greater than 1 (Table 5.3).

In this study, spatially averaged velocity values from PC MRI measurement were used to calculate the total energy transferred at the MPA ($E_{net}$). We found that the kinetic energy contribution to the total energy ($E_{net}$) associated with the blood flow velocity at the MPA was insignificant compared to the contribution from the pressure-flow energy. For example, the
mean kinetic energy for the patient group was 0.014 J compared with the mean pressure-flow
energy of 0.112 J; whereas for the control group the mean kinetic energy was 0.023 J compared
with the mean pressure-flow energy of 0.167 J. Therefore, the contribution of the kinetic energy
was one order of magnitude lower than that of the pressure-flow energy. This significant
difference between the kinetic energy to pressure-flow energy is attributed to the pressure change
that occurs between the RV and MPA (or PA conduit) due to appreciable change in area.
Therefore, the contribution of the kinetic energy towards the total energy in general is
insignificant.

Calculation of energy based indices requires simultaneous measurements of pressure and
volume or flow rate. However, this is a limitation because simultaneous measurement of MRI
and catheterization is not trivial under the clinical settings. Our approach to synchronize
pressure and volume or flow measurements by ECG gating as reported by (Das et al., 2010), is
thus far the best alternative.

We do not expect our results to be significantly affected by variation in heart rate during
CMR and catheterization. This is because most subjects (10 out of 14) had a gap of at most one
month between CMR and catheterization. Only one subject had a gap of seven months, whereas
the remaining three subjects had a gap of no more than 3 months. As shown in Table 5.1, the
mean heart rate change between CMR and catheterization was 2.4 % for the control group and
5.2 % for the patient group. Therefore, the RV-PA physiologic conditions for both the groups
were comparable during CMR and catheterization measurements. Further, we do not observe
any significant RV remodelling during such a short time span.
5.6 Conclusions

We have calculated energy-based endpoints characterizing the efficiency of energy transfer between the RV and MPA, $e_{MPA}$, using measured RV volume and pressure, as well as MPA pressure and flow rate for human subjects. Our data showed that the RV of patients was volume and pressure overloaded and the RV was less efficient due to a combination of pulmonary regurgitation and obstruction. Thus, we believe that the $e_{MPA}$ can provide comprehensive hemodynamic assessment in terms of RV performance and its efficiency since the $e_{MPA}$ accounts for the RV pressure and volume, as well as the MPA pressure and flow rate. Furthermore, it correlates well with the RV pressure and volume data for the patients in this study. Considering this, we conclude that the $e_{MPA}$ may be useful to assess the progression of the RV myocardial dysfunction of repaired CHD patients during a long term clinical follow-up.

The energy-based endpoints we discussed through chapter 4 and 5, RV SW$_1$ and $e_{MPA}$, were computed using data currently available under the clinical settings. RV volume and MPA blood flow were measured using cardiac MRI, and RV and MPA pressure were obtained from catheterization. As discussed, this would be a limiting condition for those energy endpoints since it is applicable to only patients who have RV and MPA pressure data from catheterization. Therefore, we attempted to compute an energy-based endpoint non-invasively using a novel algorithm with non-invasive 4D phase contrast (PC) MRI, which will be presented in next chapter, to extend its applicability.
Chapter 6  Non-invasive Evaluation of Energy Loss in the Pulmonary Arteries using 4D Phase Contrast MR Measurement

6.1  Introduction

As mentioned earlier, energy-based endpoints require invasive pressure measurement, i.e., cardiac catheterization, which limits the applicability of energy-based endpoints in practice to only those patients who underwent catheterization. Thus, there is a need for non-invasive methodology to assess pressure information in the heart, in order to compute an energy-based endpoint non-invasively.

With recent development of MR scanner and sequence, flow sensitive 4D PC MRI, i.e. three directional velocity encoding over the cardiac cycle, has demonstrated its efficacy in both quantifying and visualizing complex 3D flow fields for repaired and native CHD (Markl et al., 2011). The 4D PC MRI data has isotropic spatial resolution, allowing analysis of flow in any region included in a large volume of interest. Therefore, the pressure information can be estimated non-invasively for any of the heart’s conduits and chambers by using the time varying 3D velocity vector field derived from 4D PC MRI data (Ebbers et al., 2001, Markl et al., 2011).

In this research, 4D PC MRI data was analyzed to assess the hemodynamics of PAs in CHD patients who have had surgical intervention. In addition, using a novel algorithm with the 4D velocity fields, the pressure drop and energy loss in the branch PAs was computed non-invasively. The average pressure drop and energy loss in the branch PAs for the CHD patients were compared to those for normal subjects. It is expected that energy loss in the branch PAs
provides new hemodynamic data that could be included in the longitudinal monitoring of patients with post-surgical RV-PA residual lesions. This may allow cardiologists to assess the progression of the disease, which may, in turn, lead to improving the timing of intervention procedure and thus, better management of patient outcome.

6.2 Study Population

Table 6.1 shows the demographic and clinical information of all subjects in the study. Normal volunteers and CHD patients, who had undergone 4D PC MRI at the Cincinnati Children’s Hospital Medical Center from 2011 to 2012, were registered for the study. Five subjects had normal RV-PA physiology and seven subjects had abnormal RV-PA physiology from repaired CHD.

Out of five subjects with normal RV-PA physiology, two subjects were excluded from the study since one had insufficient data for the LPA and the other had aortic lesion. As a result, three normal subjects were considered as the control group. The control group had normal RV and functioning pulmonary valve without any obstruction seen in the PAs and pulmonary valve itself. The control group consisted of two males and one female and had the average age of 25.3 ± 4.2 years, weight 65.7 ± 4.3 kg, and heart rate 76.0 ± 2.5 beats/min.

Out of seven subjects, four subjects were excluded from the study since two had insufficient LPA data and one had abnormal RPA flow, i.e., the superior vena cava connected to the RPA distal. The remaining one had residual ventricular septal defect causing the blood
leaking from the RV into the left ventricle. Consequently, the remaining three subjects having abnormal RV-PA physiology were registered as the patient group. The patient group had the average age of $17.3 \pm 0.9$ years, weight $82.0 \pm 23.9$ kg, and heart rate $77.7 \pm 2.4$ beats/min.

Among three in the patient group, two subjects were repaired TOF patients who had a conduit replacing RV-PA homograft resulting in mild to moderate pulmonary regurgitation and the dilated MPA. The remaining patient had aortic valve disease and underwent the Ross procedure, which requires aortic autograft with pulmonary valve homograft, resulting in also moderate pulmonary regurgitation and MPA dilation. The demographic data for the controls and patients in the study was comparable ($p>0.05$; Table 6.1).

**Table 6.1.** Demographic and clinical information of the subjects in the study. The mean $\pm$ SE (standard error) values are shown in table.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Weight (kg)</th>
<th>Heart rate (bpm)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25.3 ± 4.2</td>
<td>2/1</td>
<td>65.7 ± 4.3</td>
<td>76.0 ± 2.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient</td>
<td>17.3 ± 0.9</td>
<td>3/0</td>
<td>82.0 ± 23.9</td>
<td>77.7 ± 2.4</td>
<td>TOF (PR, MPA dilation)/Ross (PR, MPA dilation, and RPA stenosis)</td>
</tr>
<tr>
<td>$p$ value</td>
<td>&gt; 0.2</td>
<td>-</td>
<td>&gt; 0.5</td>
<td>&gt; 0.7</td>
<td></td>
</tr>
</tbody>
</table>

Note: TOF, tetralogy of Fallot; PR, pulmonary regurgitation; MPA, main pulmonary artery; RPA, right pulmonary artery; Ross, Ross procedure
6.3 Data Acquisition

4D PC MRI was performed on a 3.0 Tesla MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands) during spontaneous breathing without sedation. The three directional velocity encoded images were acquired covering the ventricles, atria, and PAs. The parameters, shown in Table 6.2, were: 24 to 36 slices for the control subjects and 35 to 40 slices for the patients, spatial resolution = 128 × 128 for all subjects, pixel size = 2.5 mm × 2.5 mm for the controls and 2.34 mm × 2.34 mm for the patients, slice gap = 2.5 mm, repetition time (TR) = 3.8 ms, echo time (TE) = 1.8 ms, and flip angle = 5° for all subjects. The velocity encoding (VENC) for all three directions, anterior to posterior ($u_x$), foot to head ($u_y$), and right to left ($u_z$), was 200 cm/s for the controls. The VENC varied from 300 cm/s to 580 cm/s for the patients.

Table 6.2. Detail of 4D PC MRI acquisition parameters

<table>
<thead>
<tr>
<th></th>
<th>Control (n=3)</th>
<th>Patient (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Slice</td>
<td>24–36</td>
<td>35–40</td>
</tr>
<tr>
<td>Spatial resolution</td>
<td></td>
<td>128 × 128</td>
</tr>
<tr>
<td>Pixel size (mm²)</td>
<td>2.5× 2.5</td>
<td>2.34 × 2.34</td>
</tr>
<tr>
<td>Gap (mm)</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Repetition time, TR (ms)</td>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td>Echo time, TE (ms)</td>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td>Flip angle (°)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>VENC (cm/s)</td>
<td>200</td>
<td>300–580</td>
</tr>
</tbody>
</table>
6.4 Results

Table 6.3 shows the peak blood velocity, average blood flow over the cardiac cycle, and regurgitation fraction at the PAs for both the patients and control subjects. The flow rates versus time curves for each PA for all subjects are presented in Fig. 6.1. The pressure drop and energy loss in the branch PAs are given in Table 6.4 and 6.5, respectively. The pressure drop and energy loss in the branch PAs versus time curves for all subjects are shown in Fig. 6.2 and 6.3, respectively.

6.4.1 The Peak Velocity, Average Blood Flow, and Regurgitation Fraction

The peak blood velocity, average blood flow over the cardiac cycle, and regurgitation fraction of the PAs for all subjects in the study were shown in Table 6.3. As expected the peak velocity at the PAs was higher in all patients than controls, however, the difference in the LPA peak velocity between the two groups was only statistically significant (81.9 ± 5.6 cm/s and 148.9 ± 16.1 cm/s, for the controls and patients, respectively; \( p < 0.02 \)). The peak velocity at the MPA and RPA was not significantly different due to the large variation in the data.

Although the MPA systolic flow rates of all patients were considerably larger than the controls (Fig. 6.1), the average blood flow over the cardiac cycle in the MPA was not significantly different (89.5 ± 3.6 ml/s and 94.0 ± 11.2 ml/s, for the controls and patients, respectively; \( p > 0.05 \)) between the two groups. This is because the regurgitant (reverse) flow occurred during the diastole phase in the MPA, causing the reduction in the time averaged forward flow to the branch PAs. Similar observation was noted at the branch PAs, the RPA and
LPA. As expected, the patients had significantly larger regurgitation fraction in all PAs compared to the controls.

**Table 6.3.** The peak velocity, average blood flow, and regurgitation fraction of the PAs for the subjects in the study. The mean ± SE (standard error) values are shown in table.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak velocity (cm/s)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA</td>
<td>84.3 ± 8.7</td>
<td>140.0 ± 23.2</td>
<td>&lt; 0.09</td>
</tr>
<tr>
<td>RPA</td>
<td>86.0 ± 3.7</td>
<td>131.1 ± 31.1</td>
<td>&lt; 0.3</td>
</tr>
<tr>
<td>LPA</td>
<td>81.9 ± 5.6</td>
<td>148.9 ± 16.1</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td><strong>Average Blood flow (ml/s)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA</td>
<td>89.5 ± 3.6</td>
<td>94.0 ± 11.2</td>
<td>&lt; 0.9</td>
</tr>
<tr>
<td>RPA</td>
<td>44.6 ± 2.0</td>
<td>9.6 ± 9.6</td>
<td>&lt; 0.8</td>
</tr>
<tr>
<td>LPA</td>
<td>41.5 ± 7.4</td>
<td>45.6 ± 0.5</td>
<td>&lt; 0.7</td>
</tr>
<tr>
<td><strong>Regurgitation fraction (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA</td>
<td>1.3 ± 0.6</td>
<td>35.7 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RPA</td>
<td>0.4 ± 0.4</td>
<td>21.6 ± 7.7</td>
<td>0.05</td>
</tr>
<tr>
<td>LPA</td>
<td>3.0 ± 1.7</td>
<td>36.1 ± 6.9</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Note: Regurgitation fraction (%) = (reverse flow volume/forward flow volume) ×100
Figure 6.1. The blood flow rate versus time curves for the all subjects, three controls (A-C) and three patients (D-F).
6.4.2 The Average Pressure Drop and Peak Pressure Drop

The average pressure drop and the peak pressure drop over the cardiac cycle are presented in Table 6.4. Figure 6.2 shows the pressure drop versus time curves in the branch PAs for all subjects. The pressure drop for the controls were lesser compared to the patients; thus, the enlarged view of plot of the pressure drop curve for each control subject is provided for better readability.

The average pressure drop in both the LPA and RPA of the patients (-0.4 ± 0.1 mmHg/s and -1.0 ± 0.5 mmHg/s, respectively) was order of magnitude larger than that of the control subjects (-0.05 ± 0.01 mmHg/s and -0.09 ± 0.02 mmHg/s, respectively).

The peak pressure in both branch PAs of the patients (-2.1 ± 0.4 mmHg and -3.6 ± 1.7 mmHg, for the LPA and RPA, respectively) was also order of magnitude larger than that of the control subjects (-0.3 ± 0.07 mmHg and -0.4 ± 0.09 mmHg, for the LPA and RPA, respectively). The average pressure drop and peak pressure drop in the LPA were significantly different (p<0.05) between the two groups. The pressure drop in the RPA was not significantly different due to the large variation in the data.

<table>
<thead>
<tr>
<th>Table 6.4. The average pressure drop and peak pressure drop in the branch PAs over the cardiac cycle for the subjects in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ave. dP (mmHg/s)</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>LPA</td>
</tr>
<tr>
<td>RPA</td>
</tr>
<tr>
<td><strong>Peak dP (mmHg)</strong></td>
</tr>
<tr>
<td>LPA</td>
</tr>
<tr>
<td>RPA</td>
</tr>
</tbody>
</table>
Figure 6.2. The pressure drop in the branch PAs versus time curves for the all subjects, three controls (A-C) and three patients (D-F).
6.4.3 The Average Energy Losses; Total, Major, and Minor Energy Loss

The average energy losses in the branch PAs, total (= major loss + minor loss), major loss (the pressure-flow and kinetic losses), and minor loss (due to flow separation in the MPA bifurcation) over the cardiac cycle are presented in Table 6.5. Figure 6.3 shows the total energy loss over the cardiac cycle in the branch PAs for all subjects. Similar to the pressure drop curves for the controls, the enlarged images of the relevant part of the total energy loss curves for the controls are provided.

The total loss in the LPA of the patients (-17.5 ± 5.4 mJ/s) was significantly different ($p = 0.05$) from that of the controls (-2.6 ± 0.8 mJ/s). Although, the total loss in the RPA (-47.9 ± 29.8 mJ/s) of the patients was one order of magnitude larger than that of the controls (-3.0 ± 1.5 mJ/s), the difference was not significant ($p = 0.2$) due to the large variation. As a result, the total energy loss in the branch PAs was marginally different ($p = 0.16$) between the two groups. Similar to the total energy loss, the major loss in the LPA of the patients (-17.4 ± 5.3 mJ/s) was significantly larger than that of the controls (-2.6 ± 0.8 mJ/s). However, the major loss in the RPA was not significantly different between the two groups. That led the major loss in the branch PAs between the two groups became marginally different ($p = 0.16$). The minor loss in the branch PAs for patients was larger than the controls, but was not significantly different between the two groups. The contribution of the minor loss to the total energy loss was minimal for both the groups (less than 4%).
Table 6.5. The average energy losses, total energy loss (= major + minor), major loss (the pressure-flow and kinetic losses), and minor loss, over the cardiac cycle in the branch PAs for the subjects in the study

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total $E_{\text{loss}}$ (mJ/s)</td>
<td>-2.6 ± 0.8</td>
<td>-17.5 ± 5.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Major $E_{\text{loss}}$ (mJ/s)</td>
<td>-2.6 ± 0.8</td>
<td>-17.4 ± 5.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Minor $E_{\text{loss}}$ (mJ/s)</td>
<td>-0.04 ± 0.02</td>
<td>-0.1 ± 0.1</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>RPA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total $E_{\text{loss}}$ (mJ/s)</td>
<td>-3.0 ± 1.5</td>
<td>-47.9 ± 29.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Major $E_{\text{loss}}$ (mJ/s)</td>
<td>-3.0 ± 1.5</td>
<td>-47.7 ± 29.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Minor $E_{\text{loss}}$ (mJ/s)</td>
<td>-0.06 ± 0.03</td>
<td>-0.2 ± 0.1</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Branch PAs (=RPA+LPA)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total $E_{\text{loss}}$ (mJ/s)</td>
<td>-5.7 ± 2.2</td>
<td>-65.4 ± 35.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Major $E_{\text{loss}}$ (mJ/s)</td>
<td>-5.6 ± 2.1</td>
<td>-65.1 ± 34.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Minor $E_{\text{loss}}$ (mJ/s)</td>
<td>-0.1 ± 0.05</td>
<td>-0.3 ± 0.2</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Figure 6.3. The total energy loss in the branch PAs versus time curves for the all subjects, three controls (A-C) and three patients (D-F).
6.5 The Comparison of Pressure Drop and Energy Loss in the Branch PAs

As mentioned earlier (Section 3.3.4 in Chapter 3), the validation of our results with physiologic pressure drop and energy loss in the LPA and RPA was not possible since catheterization was not performed for the subjects in this study. Alternatively, the pressure drop and energy loss in the branch PA were calculated for two subjects from our previous study (Lee et al., 2012), who underwent catheterization and 2D cardiac MRI in their PAs separately, and were indirectly compared to our results from 4D PC MRI study presented in this chapter. The both subjects in the previous study had only LPA pressure data measured by catheterization. The CHD patient in previous study had severe pulmonary regurgitation and moderate stenosis in the LPA, and the normal subject had normal RV-PA physiology. Both are comparable to the subjects in this study. As shown in Table 6.6, the average pressure drop and energy loss in the branch PA from this study were in a similar range with the physiologic pressure drop and energy loss values calculated from clinical data. Although the patient in this study had lower pressure drop in the RPA (−1.0 ± 0.5 mmHg/s) than the patient’s LPA in the previous study (−3.7 mmHg/s), the total energy loss in the RPA (−47.9 ± 29.8 mJ/s) was higher than that in the LPA (−41.9 mJ/s) because the kinetic energy loss was large due to either PA stenosis, imbalanced PA flows, or both.
Table 6.6. Comparison of average pressure drop and total energy loss in the branch PA in this study with those computed from cardiac MRI and invasive catheterization data in the previous study (Lee et. al., 2012)

<table>
<thead>
<tr>
<th></th>
<th>Normal 4D PC MRI</th>
<th>Patient 4D PC MRI</th>
<th>Normal Lee et.al.</th>
<th>Patient Lee et.al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$dP$ [mmHg/s]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPA</td>
<td>$-0.05 \pm 0.01$</td>
<td>$-0.12$</td>
<td>$-0.4 \pm 0.1$</td>
<td>$-3.7$</td>
</tr>
<tr>
<td>RPA</td>
<td>$-0.09 \pm 0.02$</td>
<td>N/A</td>
<td>$-1.0 \pm 0.5$</td>
<td>N/A</td>
</tr>
<tr>
<td>Energy loss [mJ/s]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPA</td>
<td>$-2.6 \pm 0.8$</td>
<td>$-3.7$</td>
<td>$-16.3 \pm 6.1$</td>
<td>$-41.9$</td>
</tr>
<tr>
<td>RPA</td>
<td>$-3.1 \pm 1.5$</td>
<td>N/A</td>
<td>$-47.9 \pm 29.8$</td>
<td>N/A</td>
</tr>
</tbody>
</table>

6.6 Discussion

CHD lesions requiring catheterization or surgical intervention result in hemodynamically significant sequelae that needs life-long monitoring (Murphy et al., 1993, Pigula et al., 1999, Oosterhof et al., 2006). For example, TOF repair involves patch, often crossing the pulmonary valve annulus, to enlarge the RVOT, narrowed pulmonary annulus, and proximal pulmonary artery. Similarly, the Ross procedure (aortic valve replacement with pulmonary autograft to correct aortic valve stenosis) requires a PV homograft. For both cases mentioned above, the pulmonary valve is removed or surgically compromised resulting in progressive pulmonary insufficiency. Two of the patients registered for this study had undergone TOF repair and one was status-post the Ross procedure. As one might expect, they showed different degrees of pulmonary regurgitation as shown in Fig. 6.1D to 6.1F.

In Fig. 6.1D to 6.1F, all patients in the study had unequal flow distribution to the branch PAs. This is often observed in CHD patients with TOF status-post repair, and is a combination of intrinsic narrowing of PA and its morphological changes. Similarly, in the Ross procedure,
the pulmonary homograft can distort the branch PA, particularly if it was performed before the patient’s linear growth has completed.

**Figure 6.4.** 3D gadolinium-enhanced magnetic resonance angiography (Gd-MRA) of PA for A) patient 1, B) patient 2, and C) patient 3.
The temporal course of systolic flow can be altered secondary to stenosis in the PAs. In patient 1 the systolic flow in the RPA was phase-shifted (Fig. 6.1D) due to the stenosis in the RPA (Fig. 6.4A). The flow in the RPA gradually increased till the late systole. The peak RPA flow occurred at the late systole phase and some regurgitant flow was observed in the RPA (8.0 %). In contrast, the peak LPA blood flow occurred at the early systole and large regurgitation was shown during the diastole phase (49.8 %). Varied flow dynamics and differential regurgitation can result in progressive pulmonary artery remodeling, often times detrimental to the long-term repair.

In addition, the change in anatomical configuration of the pulmonary bifurcation from the repairs can cause the irregular blood flow in the branch PAs. Being able to analyze these patterns is a unique feature of 4D PC MRI data. As noticed, the patient 1 had eccentric flow distribution in the RPA where the blood flow got trapped and recirculated in the dilated RVOT before it flowed through the RPA (Fig. 6.4A). Also, the patient 3 had swirling flow along the RPA wall with smaller volume of blood flow compared to the LPA (Fig. 6.5). These can alter wall shear stress distribution in the PAs, especially, within bifurcation and along the bends. Further, the patients had higher peak velocity in the PAs (Table 6.3) than the controls, which can also adversely affect wall shear stress distribution in the PAs. It is known that abnormality in wall shear stress distribution directly affects the formation of the stenosis and its growth (LaDisa et al., 2011, Meierhofer et al., 2012).
Figure 6.5. 3D image of the PA for the patient 3 showing swirling blood flow along the arterial wall at the RPA.
In Table 6.4 and 6.5, as predicted, the pressure drop and energy loss in the branch PAs for the control subjects was minimal. However, the difference in those values between the controls and patients was statistically significant only in the LPA due to the large variation in the pressure drop data of patients. In spite of that, as we have shown previously, the pressure drop and energy loss are efficient indicators for obstruction severity and abnormal RV-PA physiology.

For example, among all patients the patient 1 showed the largest pressure drop and energy loss in both the branch PAs (-2.0 mmHg/s and -106.8 mJ/s for pressure drop and energy loss in the RPA, -0.6 mmHg/s and -28.3 mJ/s for pressure drop and energy loss in the LPA, respectively). As seen in Fig. 6.4A, the patient 1 had severe stenosis at the RPA origin and shortened LPA, resulting in the MPA-LPA dilation, which affected the blood flow towards the LPA. In comparison, the patient 3 had mild stenosis in the RPA and dilated LPA (Fig. 6.4C) and showed smaller pressure drop and energy loss in the PAs than those for the patient 1, but larger compared to those for the patient 2, who had no obstruction in the PAs (Fig. 6.4B). It can be noted that the patient 3 had swirling flow along the arterial wall of the RPA (Fig. 6.5) causing larger kinetic energy loss. As a result, the total energy loss in the RPA (-25.5 mJ/s) was larger than the patient 2 (-11.3 mJ/s) although the level of pressure drop in the branch PAs was not different (Fig. 6.3F).

Simultaneous measurement of in-vivo pressure and cardiac MRI is not trivial under the current clinical setting; thus, physiological pressure data was not available for all subjects in this study to validate our results. Therefore, as shown in our pilot study (Lee et al., 2012), the average pressure drop and energy loss computed from 4D PC MRI data were indirectly...
compared with those calculated from cardiac MRI (blood flow and velocity) and invasive catheterization (pressure) data available in Lee et al. The normal subject in Lee et al. had normal RV-PA physiology with no obstruction seen, and the patient in Lee et al. had severe pulmonary regurgitation and moderate LPA stenosis that is comparable to the patient 1 and 3 in this study. Thus, the pressure drop and energy loss in the LPA from Lee et al. can be compared with those in the RPA from the present study. Invasive catheterization data for the RPA was not available for both normal and patient subjects in Lee et al. As shown in Table 6, the level of pressure drop and total energy loss computed from 4D PC MRI data was in a similar range with those calculated from cardiac MRI and catheterization data in the previous study.

Although the average RPA energy loss for the patients was one order of magnitude larger compared to the controls, the difference between the two groups was not significantly different ($p>0.05$). It is caused by the large variation in the RPA energy loss values for the patients as shown in Fig. 6.6. The controls have a minimal energy loss in the RPA; however, the patient 1 had such a large RPA energy loss due to the severe obstruction in the RPA compared to other patients. It is expected that the $p$ value of the energy loss in the branch PAs between the two groups would decrease as the patient pool becomes larger. Also, more conservative validation needs to be performed to confirm the results in this study. This can be achieved by conducting a) the computational fluid dynamics (CFD) analysis using cardiac MRI data, which is the part of our on-going study, or b) using simultaneous measurement of in-vivo pressure and 4D PC MRI in human or an animal model.
Figure 6.6. The average total energy loss in the branch PAs for controls and the total energy loss for each patient in the study showing the large variation of the RPA energy loss for the patients.

The measured three directional velocities from 4D PC MR images directly affects the accuracy of the pressure drop and energy loss computation in the PAs (Eq. 3.11 and 3.17). To increase the quality of 4D PC MR images, initial noise corrections were performed to remove background noise and eddy current distortion on the MRI scanner. The correction algorithm for velocity aliasing was then applied to the measured velocity data after they were pulled out from the scanner (Bock et al., 2007). However, inherent noise components, resulting from systolic translational motion is still a limitation of 4D PC MR images (Andersen et al., 1996). This noise increases in magnitude near the vessel wall. Thus, the streamlines passing through the predominant portion PA flow were chosen in calculating the pressure drop in the branch PAs (Fig. 3.10).
The standards of care imaging modalities are echocardiography and 2D PC MRI. However, both modalities are limited by single directional velocity measurement from 2D cross sectional planes chosen prior to interrogation. Thus, it may be insufficient to characterize the complex flow and resulting hemodynamics of CHD patients, since blood flow is, typically, patient specific and is inherently complex with 3D variation. Therefore, the altered local blood flow in even large vessels may be impossible to capture using current modalities. Also, the 4D PC data sets can be used to generate pressure fields not otherwise visible.

Using 4D PC MRI allows the ability to visualize complex 3D flows in reconstructed PA anatomy. More importantly, it allows the calculation of pressure drop and energy loss in the PAs using fundamental fluid mechanics principles, previously only accessible by cardiac catheterization. Together with all hemodynamic information from 4D PC MRI, the comprehensive assessment on local hemodynamic changes can be obtained in any cardiac region of interest. This can be beneficial for since all hemodynamics and functional data we discussed here were derived from the same 4D PC MRI.

6.6 Conclusions

We have computed the hemodynamics in the PAs, i.e. blood flow, peak velocity, pressure drop, and energy loss, using 4D PC MRI data. Altered hemodynamic changes of repaired CHD patients were evaluated non-invasively. The elevated peak velocity and systolic blood flow, the large pressure drop and the energy loss in the branch PAs were observed for CHD patients compared to controls. We believe that the non-invasively obtained energy loss values, avoiding
catheterization, can be useful in delineating the progression of the disease in a longitudinal care for CHD patients, which can lead to improvement on surgical reintervention planning.
Chapter 7  Evaluation of Hemodynamics and Energy Loss in the Pulmonary Arteries using 4D Phase Contrast MRI: CFD Analysis

7.1  Introduction

As discussed in chapter 6, 4D PC MRI has a great potential to eliminate the need of invasive catheterization, providing the pressure information in the PAs. With those data from 4D PC MRI, energy loss in the branch PAs can be computed non-invasively, for evaluating hemodynamic conditions in the PAs in detail. In order to validate the pressure drop and energy loss values computed from 4D PC MRI, simultaneous measurements of 4D PC MRI and catheterization need to be carried out, which is not trivial under the clinical setting. Thus, in this study, we have tested a new methodology, described in the section 3.5 in Chapter 3, for performing computational fluid mechanics (CFD) analysis using 4D PC MRI data, to verify hemodynamics and energy loss values obtained from 4D PC MRI.

7.2  Demographic Data of the Subject

A subject with normal RV-PA physiology was considered for this initial study as shown in Table 7.1: a normal male volunteer with age of 29 years, weight of 70 kg, and heart rate of 79 beats/min. The subject had normal pulmonary valve function, and no stenosis was observed in the PAs.
Table 7.1. Demographic of the subject in the study

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Heart rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>Male</td>
<td>70</td>
<td>79</td>
</tr>
</tbody>
</table>

Subject with normal RV-PA physiology

7.3 Data Acquisition

4D PC MRI was performed for the subject using a 3.0 Tesla MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands). As listed in Table 7.2, MR acquisition parameters used were: 24 phases per each one of 24 slices, spatial resolution = 128 × 128, pixel size = 2.5 mm × 2.5 mm, slice gap = 2.5 mm, acquisition volume = 32.0 cm × 32.0 cm × 6.0 cm, velocity encoding (VENC) = 200 cm/s, TR = 3.79 ms, TE = 1.81 ms, and flip angle = 5°. Initial data corrections for background noise and eddy current distortion were applied to 4D PC MR images.

Table 7.2. Detail of 4D PC MRI acquisition parameters

<table>
<thead>
<tr>
<th>Normal subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Phase</td>
</tr>
<tr>
<td>No. Slice</td>
</tr>
<tr>
<td>Spatial resolution</td>
</tr>
<tr>
<td>Pixel size (mm)</td>
</tr>
<tr>
<td>gap (mm)</td>
</tr>
<tr>
<td>Acquisition volume (cm³)</td>
</tr>
<tr>
<td>VENC (cm/s)</td>
</tr>
<tr>
<td>Repetition time, TR (ms)</td>
</tr>
<tr>
<td>Echo time, TE (ms)</td>
</tr>
<tr>
<td>Flip angle (°)</td>
</tr>
</tbody>
</table>
7.4 Results

Figure 7.1A shows the 3D PA reconstruction used for the numerical computation and respective velocity vectors on each PA plane at the systolic phase (t = 0.096s). The time varying flow rate at the PAs was computed by integrating the velocity vector over the arterial cross section at each time point as shown in Fig. 7.1B. The flow rate at each PA computed from the numerical computation was compared to the flow rate obtained directly from the 4D PC MRI measurements (Fig. 7.2). The flow rates from the numerical computation and 4D PC MRI measurements are referred to as ‘CFD’ and ‘4DMRI’, respectively.
Figure 7.1. A) A reconstructed 3D PA geometry with velocity vectors on each PA plane obtained from the numerical computation. B) The time varying flow rate profiles at the PAs obtained from the numerical computation. The MPA flow was equal to the summation of RPA and LPA flows ($Q_{\text{MPA}} = Q_{\text{LPA}} + Q_{\text{RPA}}$).
7.4.1 The Average Flow Rate in the PAs

In Fig. 7.2A the average flow rate in the MPA over the cardiac cycle was 89.4 ml/s and 88.6 ml/s, from the numerical computation and 4D MRI measurement, respectively. The difference was 1.0 % (\(=\frac{[89.4-88.6]}{89.4}\times100\)). Similarly, the difference in the average flow in the LPA was also 1.9 %; 51.1 ml/s and 50.1 ml/s, from the numerical computation and 4D MRI measurement, respectively (Fig. 7.2B). The difference in the flow at the MPA and LPA was minimal since those were applied as boundary conditions for the numerical computation. On the other hand, the difference in the average flow in the RPA was 13.3 %; 38.3 ml/s and 44.2 ml/s, from the numerical computation and 4D MRI, respectively (Fig. 7.2C). The error in the average RPA flow rate between two methodologies was larger than others. This is mainly caused by the flow imbalance that existed in the measured flow rates from 4D PC MRI (\(Q_{\text{MPA}} = 88.6 \text{ ml/s}\) and \(Q_{\text{RPA}} + Q_{\text{LPA}} = 94.4 \text{ ml/s}\); Fig. 7.3). The difference between \(Q_{\text{MPA}}\) and \(Q_{\text{RPA}} + Q_{\text{LPA}}\) was 6.1 %. The more details are provided in the discussion section.
Figure 7.2. The flow rate comparison between CFD and 4D MRI measurement; A) MPA showing 1.0 % of error in the time averaged flow rate, B) LPA 1.9 % of error, and C) RPA 13.3 % of error.
7.4.2 The Average Pressure Drop and Energy Loss in the Branch PAs

The average pressure drop and energy loss in the branch PAs over the cardiac cycle computed using CFD were shown in Table 7.3. The pressure drop computed directly from 4D PC MRI was -0.13 mmHg/s and -0.04 mmHg/s for the RPA and LPA, respectively. Whereas, the pressure drop obtained from CFD was -1.3 mmHg/s and -0.7 mmHg/s, for the RPA and LPA, respectively. The energy loss in the branch PAs computed from 4D PC MRI was -5.5 mJ/s and -2.9 mJ/s for the RPA and LPA, respectively. However, the energy loss in the branch PAs obtained from CFD was -44.1 mJ/s and -20.8 mJ/s, for the RPA and LPA, respectively.

Table 7.3. The comparison of average pressure drop and energy loss in the branch PAs between 4D PC MRI study and CFD

<table>
<thead>
<tr>
<th></th>
<th>4D PC MRI</th>
<th>CFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ave. pressure drop</td>
<td>RPA</td>
<td>-0.13</td>
</tr>
<tr>
<td>(mmHg/s)</td>
<td>LPA</td>
<td>-0.04</td>
</tr>
<tr>
<td>Ave. energy loss</td>
<td>RPA</td>
<td>-5.5</td>
</tr>
<tr>
<td>(mJ/s)</td>
<td>LPA</td>
<td>-2.9</td>
</tr>
</tbody>
</table>
7.5 Discussion

As we discussed earlier in chapter 6, in order to validate the flow rate, pressure drop, and energy loss in the branch PAs computed from 4D PC MRI, simultaneously measured physiological data from catheterization is needed. However, it is not trivial to perform 4D PC MRI and catheterization simultaneously under the clinical setting. Further, only CHD patients who have RV or PA hypertension issue generally undergo catheterization to check the pressure level of RV and PA. Therefore, the pressure information was not available for the subjects in the study presented in Chapter 6. As a result, we indirectly compared our results from 4D PC MRI with the physiological data from subjects in our previous study (Lee et. al, 2012), as shown in Chapter 6 (Table 6.6).

The CFD analysis using 4D PC MRI data can be an alternative to validate the pressure drop and energy loss values directly obtained from 4D PC MRI. With image enhancement techniques introduced in Chapter 3, such as linear interpolation, edge sharpening, and filtering, a patient specific 3D PA geometry can be obtained from 4D PC MRI data. Further, blood flow data at the PAs, which can be used as boundary conditions and validation data in the numerical computation, also can be measured using the same 4D PC MRI data.

In Fig. 7.2 the PA flow rates over the cardiac cycle calculated from the CFD analysis were compared with that obtained from 4D PC MRI. The variation in the average MPA and LPA flow rates between the two techniques was small, 1.0 % and 1.9 %, for the MPA and LPA, respectively. However, the difference in the RPA flow was larger (13.3 %) than others. As stated earlier, those errors in the average flow rate from CFD are due to inherent flow imbalance
from 4D PC MR measurement. In Fig. 7.3 the time averaged flow at the MPA over the cardiac cycle from 4D MRI measurements was 88.6 ml/s and the summation of the time averaged flow at the LPA and RPA was 94.4 ml/s. The difference between the two was 7.5 %. For the numerical computation, the summation of flow in the RPA and LPA (outlets) equals to flow in the MPA (inlet) conserving the continuity principle. Since the MPA and LPA flows were constrained as input boundary conditions, the RPA flow was reduced to satisfy the continuity, that caused large flow imbalance between the branch PAs (Fig. 7.1), which also influenced larger RPA pressure drop in the numerical computation (Table 7.3).

![Graph showing flow rates vs time](image)

**Figure 7.3.** The flow rate at the PAs obtained from 4D MRI measurements versus time curves. The difference in the flow rates between the MPA and RPA+LPA was 7.5 %.

Secondly, the 3D PA geometry for the numerical computation was reconstructed using 4D PC MR images with spatial resolution of 2.5 mm³. Although enhanced image had better spatial resolution (0.63mm × 0.63mm × 1.25mm), the techniques used for enhancement, linear
interpolation, edge sharpening, and filtering, induced some burring in the images, especially, near the arterial boundary. This also caused underestimation of the original PA volume while contouring PA region in 3D geometry reconstruction process.

Those limitations discussed above can cause overestimation of pressure drop in the branch PAs in the numerical computation. As shown in Table 7.3, the pressure drop computed using CFD was larger than that obtained directly from 4D PC MRI. Consequently, the energy loss in the branch PAs computed from CFD was order of magnitude larger compared to that from 4D PC MRI. The issues discussed above were caused by low quality of 4D PC MR images for 3D geometry reconstruction. Thus, alternatively, we can use separately acquired cardiac MR images for more accurate 3D PA geometry reconstruction. The additional PA reconstruction from the separate cardiac images can be co-registered with 4D PC MRI data for carrying out further CFD analysis, presented in Chapter 3, to compute pressure drop and energy loss.

There are other factors that can be attributed to the large difference in the average pressure drop and energy loss values between two methodologies. For instance, simplified uniform velocity profiles applied to the numerical model as boundary conditions may be one factor, which can be expected to generate larger pressure drop compared to the parabolic or realistic velocity profiles. With the use of Womersley velocity profiles (Das et al. 2011), which more realistic compared to the parabolic velocity profile, as boundary conditions, the level of pressure drop can be reduced in the numerical computation. Other factor can be due to the reduced size of the PA reconstructed geometry caused by smaller magnitude of phase values close to the arterial boundary in 4D PC MR images, and surface smoothening during PA
reconstruction process in order to remove excessive roughness in an initial 3D PA volume reconstructed from enhanced 4D PC MR images. This caused underestimation of PA volume, which led to larger pressure drop in the numerical computation. The finer spatial resolution of 4D PC MRI is needed to overcome the issues on PA geometry reconstruction process. Alternative MR image data can be used to reconstruct the PA geometry. The geometry obtained from MR image (instead of the magnitude image of 4D PC MRI) is expected to be more accurate.

Despite these limitations mentioned above, CFD analysis can be a useful alternative to verify the pressure drop and energy loss endpoint computed from 4D PC MRI. With future development on MR sequences, better 4D PC MR acquisition can be obtained with finer spatial resolution within shorter scan time. This can significantly improve the quality of 4D PC MR images that would allow us to perform better CFD analysis.
Chapter 8  Summary and Future Work

8.1  Summary of the Research

This section provides a summary of the results of this dissertation. The task 1-1 (RV SW₁) and 1-2 (e₉MPA), which are discussed in Chapters 4 and 5, respectively, have been accomplished. Regarding the task 2-1 (energy loss in the branch PAs; Chapter 6), a unique non-invasive methodology was developed to compute the pressure drop and energy loss in the branch PAs by using 4D PC MRI. For the task 2-2, the methodology for CFD analysis to validate the pressure drop and energy loss in the branch PAs computed from 4D PC MRI was tested. A brief summary of specific aims and their subtasks are given in the following sections.

8.1.1  Task 1 of Specific Aim 1: Right Ventricular Stroke Work Index

The right ventricular stroke work indexed to BSA (RV SW₁) was calculated by co-registration of non-simultaneously measured RV volume and pressure data using ECG gating for a group of rTOF patients and control subjects. Statistical analysis confirmed that the mean of RV SW₁ of the patient group was significantly higher than that of the control group (p < 0.05). This shows that the RV of rTOF patients with TOF pathophysiology requires more work to displace blood into the lungs for oxygenation than that of controls with normal physiology. Furthermore, RV SW₁ correlated well with both RV volume and pressure data: RV EDV₁ and ESV₁, RV ESP and EDP, respectively, whereas, RV volume and pressure indices did not show
significant correlations. Importantly, RV SW$_1$ had better correlations with ejection fraction and regurgitation fraction than RV EDV$_1$ and ESP.

8.1.2 Task 2 of Specific Aim 1: Energy Transfer Ratio between the RV and the MPA

The energy transfer ratio between the RV and the MPA, $e_{MPA} (= E_{net}/RV$ SW), was computed for a group of patients and control subjects. Statistical analysis confirmed that the mean of $e_{MPA}$ for the patients with altered RV-PA physiology was significantly lower than that for the control subjects with normal RV-PA physiology ($p<0.05$), despite the fact that RV SW for the patients was significantly higher than for the control subjects. Thus, compared to that of the control subjects, the RV of the patients was less efficient due to abnormal RV-PA physiology, including pulmonary regurgitation and obstruction.

The $e_{MPA}$ provided comprehensive RV-PA hemodynamics in terms of RV performance and its efficiency since the $e_{MPA}$ accounts for RV pressure and volume data, as well as the MPA pressure and flow rate data. As discussed above, it differentiated the abnormal RV-PA physiology of patients from the normal physiology with statistical significance ($p<0.05$). Additionally, it correlated with RV pressure and volume indices, RV EDV$_1$ and ESP.

8.1.3 Task 1 of Specific Aim 2: Non-invasive Computation of Pressure Drop and Energy Loss in the Branch PAs
The pressure drop and energy loss in the branch PAs for the subjects (three controls and three patients) were computed directly from 4D PC MRI measurements. The average pressure drop in both the RPA and LPA for the patient group was order of magnitude larger than the control group. The average total energy loss in the RPA and LPA for the patient group was also order of magnitude larger than the control group.

Although the computed pressure drop and total energy loss in the branch PAs for the patients were considerably larger than those for the controls in the study, the level of pressure drop and total energy loss varied depending on the severity of disease of each patient. This showed that the pressure drop and energy loss can be good indicators for assessing RV-PA abnormal physiology. Therefore, we believe the non-invasively computed pressure drop and energy loss using 4D PC MRI measurements may help in monitoring the PA patho-physiology status of the repaired CHD patients.

8.1.4 Task 2 of Specific Aim 2: CFD Analysis to Compute Hemodynamics and Energy Loss in the Branch PAs using 4D PC MRI

The methodology for numerical computation to calculate PA hemodynamics and energy loss in the branch PAs using 4D PC MRI was tested. It included image enhancement techniques to increase the quality of 4D PC MR images which enabled us to obtain better 3D PA geometry reconstruction.

The numerically computed flow rate at each PA, pressure drop, and energy loss in the branch PAs were compared with those computed directly from 4D PC MRI. Due to various
factors, such as PA flow imbalance from 4D PC MRI and inherent noise in PC MR images causing underestimation of real PA volume during 3D geometry reconstruction, the difference in the pressure drop and energy loss values between two techniques was large.

8.2 Recommendations for Future Work

1) As discussed in Chapter 7, the accuracy of pressure drop and energy loss values computed from 4D PC MRI depends on the quality of 4D PC MR images. Due to coarser spatial resolution of 4D PC MR images (2.5 mm²) compared to cardiac MR images (~ 1mm²), inherent error exists in PA reconstruction and flow rates obtained from 4D PC MRI that can cause larger error in the numerical computation. At this juncture, it is difficult to eliminate them by using post-processing including image enhancement techniques as explained in Chapter 3.

In order to circumvent the issue described above, alternatively, we can use another set of cardiac MR images to reconstruct accurate 3D PA geometry. The 3D PA geometry reconstruction from separate cardiac MRI can be co-registered with 4D PC MRI data, in order to perform the same procedures, described in Chapter 3, for computing the pressure drop. Next, with the accurate PA geometry, instead of simplified uniform velocity profile, the parabolic or Womersley velocity profiles can be applied to a numerical model as boundary conditions to see if pressure drop and energy loss values can be further improved.

2) The current 4D PC MRI protocol covering the entire cardiac volume takes 10 ~ 20 mins to be completed for human subject, which is much longer than typical cardiac MRI (seconds to few minutes). Although it is obvious that smaller spatial resolution would give better
outcome in flow measurement and PA reconstruction, it is difficult to reduce the current spatial resolution of images since smaller spatial resolution results in longer scan time. Therefore, current MR acquisition can be optimized in order to obtain better resolution of images within reasonable scan time in human.

For the purpose of optimization of MR acquisition, an engineered animal model, such as porcine or sheep, can be used. Using an animal model, both scan time and the severity of disease can be controlled in order to acquire better resolution of images with different level of disease. Further, simultaneous in-vivo pressure measurement can be performed with animal model using MR-compatible catheterization apparatus, which is difficult to perform under the current clinical setting with human subject. Therefore, animal model can help in optimizing MR sequences that can lead better quality of 4D PC MR images. Also, the pressure drop and energy endpoints directly computed from 4D PC MRI can be validated with those obtained from catheterization data.
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