Right Ventricular Inefficiency in Repaired Tetralogy of Fallot: Proof of Concept for Energy Calculations From Cardiac MRI Data

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Abstract—Repaired tetralogy of Fallot (rTOF) patients develop right ventricular (RV) dilatation and dysfunction. To prevent their demise, pulmonary valve replacement is necessary, though appropriate timing for it is challenged by a paucity of reliable diagnostic parameters. In this pilot study, we hypothesized that stroke work (SW) and energy calculations would delineate the inefficiency of RV performance in rTOF. RV SW was calculated for both an rTOF and a normal subject by utilizing RV pressure and volume measurements obtained during cardiac catheterization and MRI studies. Energy transfer rate and ratio were computed at the main pulmonary artery (PA). Compared to the normal RV, the rTOF RV had higher operating pressure, lower computed SW (0.078 J vs. 0.115 J for normal), and higher negative energy transfer at the PA (0.044 J vs. 0.002 J for normal). Furthermore, the energy transfer ratio was nearly twice as high for the normal RV (1.06) as for the rTOF RV (0.56). RV SW and energy transfer ratio delineate important operational efficiency differences in blood flow from the RV to the PA between rTOF and normal subjects. Our pilot data suggest that the rTOF RV is significantly less efficient than normal.

Keywords—Right ventricular stroke work, Tetralogy of Fallot, Pulmonary insufficiency, Phase contrast MRI.

INTRODUCTION

Tetralogy of Fallot (TOF), a common congenital heart defect, has been repaired in infants and small children for more than 50 years, with now an estimated 100,000 adult “repaired TOF” (rTOF) patients in North America alone. As a result, the long-term sequelae of the disease and its repair have become important clinical issues. Specifically, the loss of pulmonary valve (PV) function is one such accepted and often unavoidable sequela. The pathophysiology of rTOF with PV insufficiency (PI, Fig. 1a) consists of alterations in diastolic right ventricular (RV) loading conditions, triggering RV hypertrophy, and dilatation.2,9,18 In turn, RV dilatation can evolve into irreversible RV myocardial contractile dysfunction, and has been implicated in the development of fatal RV arrhythmias.18

To avoid this outcome, therapies are directed at the normalization of RV loading conditions via PV replacement (PVR), preferably performed prior to the onset of irreversible RV myocardial damage. In theory, with this operation, RV loading conditions are normalized, thereby decreasing/reversing the stimulus for RV dilatation and (hopefully) the incidence of symptoms (if present), arrhythmias, and/or sudden death. However, since prosthetic PVs require a re-operation and do not grow despite patient somatic growth, clinicians often try to defer this procedure as long as possible. However, if deferred too long, RV myocardial contractile dysfunction may become irreversible, despite the valve replacement.9,19,26,27

Unfortunately, the progression in RV dilatation to subsequent RV dysfunction in repaired rTOF patients with PI is difficult to determine clinically or with currently available clinical tests, such as echocardiography or standard cardiac MRI (CMR). For example, echocardiography, the mainstay of pediatric cardiac diagnoses and management for nearly three decades, is limited in its ability to characterize the RV. Well-documented limiting factors include the RV’s proximity in the near field, the often present poor acoustic/ultrasonic windows of post-operative adult patients, and the lack of a suitable geometric model of the RV from which to base calculations of RV volume and function. CMR, a burgeoning field increasingly employed to assess RV volume and function in rTOF

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patients, has nonetheless remained fairly descriptive, but not deterministic, in its ability to assess future RV health. It is thus paramount to characterize the RV in terms of its mechanics and energetics, which, in turn, will hopefully enable the identification of new indexes that are both useful and readily determined from available clinical information, in order to predict the onset of severe RV contractile dysfunction and thereby to define more suitable clinical windows for PVR in rTOF patients.

For some populations of congenital heart disease patients, such as the total cavopulmonary connection (aka Fontan), complex numerical analyses have been performed to better understand, characterize, and index the efficiency of post-operative physiology, and in some cases have been helpful in subsequent medical and/or surgical management. An example is the use of ventricular stroke work (SW) as a parameter to assess contractile function. Dasi et al. have proposed many energy-based indexes for Fontan physiology and other cardiovascular flow applications. Another computational approach has been described recently that uses a control volume technique to analyze the mechanism of energy losses in functional single ventricle patients after Fontan palliation. Recently, CMR-based flow simulations have been performed by Wong et al. and Morbiducci et al. to access blood flow patterns in heart, and by Funamoto et al. for cerebral aneurism that do not require pressure measurements.

In this pilot study, our working hypothesis is that SW and energy calculations will delineate the inefficiency of RV performance in rTOF. Our main contribution in this study is to compute energy values from clinically available data, i.e., assess work and energy using the non-synchronous measurement of pressure and volume.

**METHODS**

**Study Population**

Data were retrospectively analyzed from records of a small pilot group of three age-, size-, and gender-matched subjects who had undergone both clinical CMR and clinical cardiac catheterization within a span of 1 month at our center (Table 1). Further subject details are provided in Table 1. The Institutional Review Board of our hospital approved the study.

**Subject Data Stratification**

The subject data were stratified based on RV loading (abnormal or normal) and PV function (normal or abnormal), into three groups (Table 1): “Normal,” “rTOF,” and “Intermediate.” The “normal” subject had normal RV loading with normal PV function (as confirmed by exam and echocardiography). The “intermediate” subject had RV volume overload due to a large atrial septal defect and partial anomalous

**TABLE 1. Patient demographics and clinical data.**

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>BSA (m²)</th>
<th>Heart rate (bpm)</th>
<th>MRI-Cath.</th>
<th>MR-Cath.</th>
<th>Time gap (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: normal RV &amp; PV</td>
<td>4</td>
<td>1.11</td>
<td>20.3</td>
<td>0.78</td>
<td>85</td>
<td>79</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>rTOF: abnormal RV &amp; PV</td>
<td>5</td>
<td>1.07</td>
<td>16.9</td>
<td>0.72</td>
<td>102</td>
<td>100</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Intermediate: abnormal RV, normal PV</td>
<td>5</td>
<td>1.05</td>
<td>16.6</td>
<td>0.68</td>
<td>93</td>
<td>92</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 1.** Schematic diagram of the heart of (a) rTOF subject, (b) normal subject, and (c) intermediate subject. The rTOF subject (a) has defective PV and overloaded RV because of backflow. The normal subject (b) has functioning PV and normal RV. The intermediate subject (c) suffers from a partial anomalous PV return and thus has an overloaded RV but functioning PV.
pulmonary venous return, but had normal PV function (as confirmed by exam and echocardiography). The rTOF subject, 3 years status post-infantile transannular patch TOF repair, had RV volume overload due to a non-functional PV, with severe PI but no stenosis, as confirmed by echocardiography. None of the subjects showed more than mild tricuspid regurgitation on echocardiography, and all had normal right and left ventricular ejection fractions on clinical CMR.

**Data Acquisition**

**CMR Data**

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

**CMR Ventricular Volumetry and Global Functional Imaging**

Functional imaging for RV volume and function assessment was performed using retrospective electrocardiographic (ECG)-gating, segmented Steady State Free Precession (SSFP) technique after localized shimming and/or frequency adjusting. Subjects were breath-held as tolerated; for those subjects who could not adequately breath-hold, a free breathing technique with multiple signal averaging was used. Standard imaging included a short axis stack of cine SSFP images from cardiac base to apex; the short axis was prescribed as the perpendicular plane to the left ventricular long axis in two and four chamber views as previously described.21,28,33 Typical scan parameters included FOV = 32–38 cm, slice thickness = 5–6 mm, gap = 1–2 mm, NEX = 2 (breath hold; 4–5 for free breathing), TE/TR = 1.4/2.8, in-plane resolution = 1.2–2.2 mm. A minimum of 12 slices were performed, with 20 phases/slice. The typical temporal resolution of the cine SSFP images was 30–40 ms, adjusted according to the patient’s heart rate and ability to breath-hold. The RF flip angles were set between 50°/C176 and 70°/C176 dependent on the patient weight, height, and the SAR level.

**CMR Pulmonary Artery Flow Imaging**

Pulmonary artery (PA) flow imaging was performed using prospective ECG-gating, through-plane velocity-encoded phase contrast (PC) technique.7,10,14,22 Appropriate breath-holding procedures20 were followed as stated in the previous section. Typical scan parameters were similar to that described above. Velocity encoding limits were adjusted as needed for minimal peak to avoid aliasing of phase signal. PC imaging was performed at the mid-point of the main and each branch PA prescribed from preceding anatomical axial double inversion recovery images, with 18–22 phases at each site.

**Cardiac Catheterization**

Subjects underwent clinical cardiac catheterization using standard pediatric cardiac catheterization techniques while under general endotracheal anesthesia. Hemodynamic measurements were performed during the catheterization by advancement of a fluid-filled catheter (Cook Medical Inc., Bloomington, IN, USA) under fluoroscopic guidance into the RV and at least one of the followings: main (MPA), left (LPA), or right (RPA) PA. Pressure variation with time over the complete cardiac cycle at each site was recorded along with the ECG tracing on hard (paper) copy (Fig. 2).

**Data Analysis**

**CMR RV Volume Data**

Clinical CMR datasets were analyzed to compute RV volume vs. time curves via MRI planimetry techniques using semi-automated computer software (QMASS®, Medis Medical Imaging Systems, Inc., Leiden, Netherlands).

**PA Flow Analysis**

PC images were analyzed via standard CMR flow assessment techniques using semi-automated computer software (QFLOW®, Medis Medical Imaging Systems, Inc., Leiden, Netherlands). Data computed include peak velocity, area of flow, and flow rate (antegrade and retrograde) at each site.

**Co-Registration of the Catheterization and the CMR Data**

CMR and cardiac catheterization data were acquired at separate sessions. For our analyses, these datasets were adjusted to account for differences in heart rate between the sessions. This was performed digitally based on the resident ECG signal present in both the datasets (Fig. 2). This process required three steps for each subject. Initially, the hardcopy catheterization data (pressure vs. time curves from the RV, MPA, and branch PAs, and ECG vs. time) were manually digitized between two consecutive ECG R-waves, from which the heart rate interval was determined. Noise content (random white noise) was low in our subjects. Most pulses were repeatable and
not statistically different. A maximum of 3% variation was observed during time discretization between any pulse. The isolated pulses with high noise because of catheter movement were excluded by visual inspection of the pressure time plot. Next, the heart rate interval was measured from the digital CMR data (RV volume vs. time and PA flow vs. time), which by definition is recorded starting at the onset of the ECG R-wave. Finally, the CMR data were linearly scaled in the time domain to match the cardiac catheterization time period. All digital measurements and adjustments were performed via a customized MATLAB® (MATLAB, Inc., Waltham, MA, USA) software.

**Computational Methods**

**RV Pressure–Volume (P–V) Diagram**

The digitized, synchronized RV pressure and volume data were smoothed by fitting a Fourier series approximation, which was then used to construct a P–V diagram for RV.

**RV Stroke Work**

The RV SW, which supplies the necessary energy and momentum to the blood to be pushed into the branch PA, was estimated by computing the enclosed area within loop of the P–V diagram using
where \( p \) and \( V \) are the RV pressure and volume, respectively, and \( C \) the closed loop of the P–V diagram. The computational details of evaluating the cyclic integral over the P–V loop boundary, \( C \), in Eq. 1 are presented in the section “RV SW Computation” in Appendix. An in-house MATLAB script was developed to numerically compute the RV SW that (1) co-registered the pressure and volume data using ECG time points for two consecutive systoles, (2) fitted Fourier series to the pressure and the volume curves, and (3) computed the P–V SW using Eq. 7, which is the discrete form of Eq. 1 (see section “RV SW Computation” in Appendix). RV SW (Eq. 1) is based on the assumption of quasi-static variation of pressure with volume and does not take into account the inherent dynamic conditions in the RV.

**Total Energy at the MPA**

A transient pressure-flow energy calculation at the MPA was performed considering its ability to incorporate the dynamic conditions of blood velocity, flow rate, and MPA pressure.\(^{1,11,12}\) Considering the branch PA control volume shown in Fig. 1a, the rate of total energy transferred to the blood pool at the MPA can be expressed as

\[
\dot{E}_m = \left( p_m + \frac{1}{2} \rho v_m^2 \right) Q_m
\]

where \( Q_m \) is the MPA blood flow rate, \( p_m \) the pulsatile MPA pressure, \( \rho \) the density of blood, and \( v_m = \frac{Q_m}{A_m} \) is the pulsatile MPA velocity, with \( A_m \) the MPA cross-sectional area (see section “Derivation of the formulae for energy transfer rate at MPA” in Appendix for details). Time dependence of the quantities \( Q_m, p_m, \) and \( v_m \) in the above equation may be noted, which show that the rate of the transfer of energy by the RV to the blood pool never remains constant and varies over the cardiac cycle with the pulsatile variation of flow rate, pressure, and velocity. For PA, since the potential energy changes due to gravity are very small, Eq. 2 assumes that the main contribution to the energy at the MPA is from pressure-flow energy and kinetic energy only.

The net energy transferred to the blood pool at MPA (\( E_{\text{net}} \)) over the duration of cardiac period \( T \) is computed by integrating Eq. 2

\[
E_{\text{net}} = \int_0^T \dot{E}_m(\tau) \, d\tau
\]

over the period 0 to \( T \) seconds. Time averaged energy transfer rate over one cardiac cycle at MPA can be computed by

\[
\dot{E}_{\text{net}} = \frac{E_{\text{net}}}{T}.
\]

The SW and \( E_{\text{net}} \) are dimensional quantities and may be affected by many factors including but not limited to, age, physiology, BSA, etc. For rTOF subjects, SW might also be biased by high RV pressures inherent due to RV hypertrophy. An energy transfer ratio, \( e_{\text{mpa}} \), defined as \( e_{\text{mpa}} = E_{\text{net}}/\text{SW} \), can be used to evaluate RV inefficiency. The ratio \( e_{\text{mpa}} \) is strictly not a measure of RV efficiency because it does not directly account for complex energy components such as storage (due to elasticity of tissues) and losses (friction between blood and tissue); although a higher \( e_{\text{mpa}} \) value will indicate a more efficient RV. For our subjects, the pressure measurements were only available at the LPA. The quantities, \( v_m \) and \( Q_m \) in Eq. 2, were obtained from CMR measurements at the MPA. Thus, in order to compute the variation of \( \dot{E}_m \) with time over the cardiac cycle for our subjects using Eq. 2, \( p_m \) needed to be determined using a numerical calculation of the blood flow in the branch PA (Fig. 1a) employing computational fluid dynamics (CFD).

**Blood Flow Calculation in the Branch PA**

CFD\(^8\) was performed to obtain the MPA pulsatile pressure \( p_m \) to compute \( \dot{E}_m \) and \( E_{\text{net}} \) using Eq. 2. For the CFD analysis, a patient-specific three-dimensional (3D) geometric reconstruction of the respective branch PA anatomy at the beginning of systole was reconstructed from the individual CMR dataset (MIMICS\(^9\), Materialise, Inc., Leuven, Belgium). The surface of the reconstructed branch PA geometry created in MIMICS was then exported as a stereolithographic file of surface triangles to generate finite-element (FE) tetrahedral mesh in the blood flow domain (GAMBIT\(^\text{®} \), ANSYS, Inc., Canonsburg, PA, USA). A transient CFD analysis was performed in ADINA CFD\(^\text{®} \) (ADINA R&D, Inc., Watertown, MA, USA) after assigning material property to an FE mesh imported from GAMBIT, and setting up pulsatile boundary conditions at the MPA inlet and LPA and RPA outlet locations, respectively (Fig. 3).

All CFD models for our subjects were meshed with linear tetrahedral elements of mesh size 1 mm, resulting in typically 125–150 K elements (Fig. 3). A time step of magnitude 0.001 s was used for the transient analysis. The blood was considered to be shear thinning non-Newtonian fluid modeled using Carreau model\(^1\) with shear rate \( (\dot{\gamma}) \) dependent viscosity \( \mu \) given by
\[ l(t) = l_\infty + \left( l_0 - l_\infty \right) \left( 1 + A \dot{\gamma}^2 \right)^n \]  \hspace{1cm} (5)

where \( l_\infty = 0.345 \) poise, \( l_0 = 0.56 \) poise, \( A = 10.975 \) s\(^2\), \( n = 3.568 \), and \( \rho = 1.05 \) g/cc is the density of the blood and the shear rate \( \dot{\gamma} \) is in s\(^{-1}\).

The time-varying pulsatile velocity at the MPA and RPA, \( v_m \) and \( v_r \), respectively, was obtained from the CMR data for the individual subjects, whereas the LPA pressure \( p_l \) was directly measured using catheterization. The velocity boundary conditions, \( v_m \) and \( v_r \), were applied to the MPA inlet and the RPA outlet, respectively, and the pressure boundary condition \( p_l \) was applied to the LPA outlet.

Convergence of the CFD solution was verified by repeating the computations using a 220 K element model.\(^{23} \) The maximum difference in the MPA pressure value between the two runs was 2.2\%. A convergence criterion of 0.0001 for each degree of freedom was used for all the residuals in our numerical computation. The computations were performed for typically eight cardiac cycles. The LPA velocity predicted by the CFD model was validated against the measured LPA velocity \( v_l \) obtained from the CMR data to lie within 15\% error. The computed \( p_m \) was used in Eq. 2 to compute \( \dot{E}_m \).

The Reynolds number for our flow was in the laminar range (<2000). Thus, an unsteady laminar flow formulation was used. Considering such flows, we do not rule out possible local shear layer instabilities and organized vortical cells at the locations downstream of flow reversal. However, we will not categorize the flow in PA as turbulent which typically signifies random fluctuations.

**RESULTS**

The three subjects in our study had similar mean values for age (4.67 years), body surface area (0.73 m\(^2\)), and weight (19.2 kg), as shown in Table 1. To avoid complexity, the results for the intermediate subject are discussed in the Appendix section.

**RV Pressure and Volume Characteristics**

Plots of the variation of the RV pressure and volume over one cardiac cycle are shown in Fig. 4, with pressure and volume on the two opposite y-axes: Fig. 4a: the normal subject; and Fig. 4b, the rTOF subject. The peak end-diastolic RV volume of the rTOF subject (118.6 mL) is almost 40\% higher than that of the normal subject (84.4 mL), in spite of the two being comparable in terms of physiological characteristics such as age, BSA, and net stroke volume (SV; see Table 2), which illustrates the inherent RV volume overloading in rTOF with PI.

The RV pressure for the normal subject (Fig. 4a) ranges from a maximum value of 25 mmHg to a minimum value of 0.4 mmHg, whereas the values for the rTOF subject (Fig. 4b), RV pressure ranges from a maximum of 30 mmHg to a minimum of 2.0 mmHg. Despite the presence of the dysfunctional P–V, both the peak and mean RV pressures are higher in the rTOF subject as compared to the normal subject.

The volume vs. time relationship for the normal subject (Fig. 4a) shows that at the start of the systole (\( t = 0 \) s), the slope of the tangent to the RV volume vs. time curve is almost zero, whereas the RV pressure vs. time curve (Fig. 4a) shows a rapid build-up of the RV pressure. This rapid build-up of RV pressure while the RV volume change is minimal is the closest the RV comes to a true isovolumic contraction phase.\(^{29,30} \) During this “near-ivolumic” RV contraction phase, both the RV inlet and outlet valves, i.e., the tricuspid valve (TV) and the PV, respectively, are closed. As a result, the contraction of the RV does not significantly change the RV volume, since blood is essentially an incompressible fluid. This represents the right lower quadrant of the RV P–V curve in Fig. 5. In contrast, for the rTOF subject (Fig. 4b), the slope of the RV volume vs. time curve at the start of the systole (\( t = 0 \) s) is not horizontal but instead is distinctly downward. In other words, in the rTOF case, there is an immediate and significant drop in RV volume with the initiation of the contraction of the RV during the “near-isovolumic” contraction phase of the RV as described above. Thus, this data show that the rTOF subject (with abnormal RV and PV) has a much greater drop in volume during the
“near-isovolumic” contraction phase than does a normal subject.

**RV P–V Loops and RV SW Calculations**

Figure 5 shows the computed P–V loops for both the normal and the rTOF subject. The rTOF subject’s P–V loop is rightward and upward of the normal subject, consistent with the higher volume and pressure of the rTOF RV. In addition, the P–V curve of the normal subject (Fig. 5) has nearly vertical segments on the left and right, which correspond, respectively, to the isovolumic contraction and relaxation in the RV and thus indicate a much clearer isovolumic contraction and relaxation phase as compared to that of the rTOF subject.
The RV SW that pushes the blood into the PA is calculated by computing the area enclosed by the P–V loop (see section “RV SW computation” in Appendix). The values of the RV SW (absolute and normalized values) are shown in Table 2. The RV SW for the normal subject was 0.1149 J and that for the rTOF subject was 0.0782 J. For our subjects (with similar age, BSA, and SV), the absolute SW and the BSA-indexed SW values follow a similar trend (Table 2).

Total Energy Impacted at MPA

Figure 6 shows the variation of the rate of energy transferred to the blood computed using Eq. 2 at the MPA over one cardiac cycle. The differences in the duration for different subjects are due to small differences in their heart rates. The point, \( t = 0 \) s, in Fig. 6 corresponds to the start of the systole, i.e., the start of the isovolumic contraction phase of the RV. As shown...
in Fig. 6, the rate of energy transfer to the blood by the RV is not uniform over the entire cardiac cycle and increases with the contraction of the RV muscles during the systole and then decreases during diastole. The positive portion of the energy curve is associated with the net energy imparted to the blood pool, driving blood away from the RV and into the PA, whereas the negative portion is associated with the backflow of the blood from the PA back into the RV. The kinetic energy contribution to the total energy rate ($E_m$) at the MPA was insignificant compared to the pressure-flow component of the total energy transfer rate. For example, for the rTOF subject, the peak kinetic energy transfer rate was 0.013 J/s compared to the energy transfer rate due to pressure-flow work of 0.4 J/s (an order of magnitude difference). Therefore, the simplification of the velocity field with an average velocity vector did not significantly change the calculation of energy computed using Eq. 2.

With regard to the rate of energy transfer to the blood at MPA by the RV over one complete cardiac cycle (Fig. 6), the rTOF subject shows a significant negative contribution associated with the back-flow of blood from the PAs into the RV. The rate of forward energy transfer (Eq. 3) at the MPA for our normal subject was found to peak at 0.623 J/s, and that for the rTOF subject was 0.408 J/s. The backflow due to regurgitation in the rTOF subject has a negative energy transfer rate associated with it. For the rTOF subject, we note a very high negative rate of energy transfer, peaking at $-0.3653$ J/s, as opposed to $-0.0686$ J/s for our normal subject, attributable to the physiologic degree of PI present. The time averaged value of the energy transfer rate over one cardiac cycle ($\bar{E}_m$) was 0.07 J/s for the rTOF subject, compared to 0.17 J/s for the normal subject.

As mentioned above, the net energy transferred to the blood at the MPA over one cardiac cycle can be broken down into two groups: the energy transfer associated with the forward flow and that associated with the reverse flow. The forward and reverse flow net energies for our normal subject were 0.124 J (forward) and 0.002 J (reverse); the values for the rTOF subject were 0.085 J (forward) and 0.044 J (reverse). The net energy transferred at the MPA over one cardiac cycle, $E_{net}$ was computed to be 0.121 J for the normal subject and 0.044 J for the rTOF subject. The energy transfer ratio $e_{mpa}$ was 1.06 for the normal subject and 0.56 for the rTOF subject, indicating significant differences in efficiency for the rTOF RV compared to the normal RV.

**DISCUSSION**

This pilot study demonstrates that numerical methodology, coupled with CFD, can be employed with clinically acquired CMR data to characterize intravascular hemodynamics and energy efficiency in subjects with both normal and abnormal RV and PA pressure-flow physiology. Our observations suggest that parameters such as RV SW and energy transfer ratio ($e_{mpa}$) may be useful in assessing RV dysfunction in rTOF patients.

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

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

In normal PA physiology, the presence of the valve allows development of a larger pressure gradient under normal RV operating pressure than in rTOF pathophysiology, where generation of a significant pressure gradient requires increased RV operating pressures to maintain equivalent flow volumes. In rTOF physiology, the absence of a functioning PV prevents the development of a pressure gradient across the PV annular region, which thereby diminishes the work available for the RV to impart to the blood pool. Further detrimental to the RV is that, at ventricular end-systole, the absence of a valve allows blood to backflow into the RV, which causes the RV to be volume overloaded, thereby necessitating higher operating pressures. Furthermore, the presence of increased volume in the PAs serves as higher resistance to systolic flow in rTOF when compared to both normal RVs and volume overloaded RVs with normally functioning PVs (see section “Result for the intermediate case” in Appendix).

In addition to illustrating SW changes, the use of CFD in this study demonstrated that a normal subject
has no significant negative contribution to the total energy transfer, whereas a subject with rTOF has a significant negative contribution to the total energy transfer rate. This scenario is expected for the rTOF subject with the dysfunctional PV, since the abnormal PV lets the blood flow back into the RV, thereby reducing pump efficiency. We conclude that the total energy rate at the MPA may be a useful measure for evaluating the extent of deterioration of the RV.

**LIMITATIONS**

This proof of concept pilot study was limited by several factors. First, our sample size is too small to draw any general conclusion regarding the values of SW for the two physiology types: rTOF and normal. Despite such limitations, our study does indicate that energy values of SW and energy transfer ratio ($e_{mpa}$) can assess RV inefficiency for the two dissimilar subjects. Further studies are underway to validate this assessment utilizing larger statistical samples of patients.

Second, the use of cardiac catheterization data is a limitation. Implementation of our current methodology is impractical in current clinical management of rTOF patients because cardiac catheterization is no longer routinely performed for typical rTOF patients. The cardiac catheterization data were used in this proof of concept pilot study only to validate the energy-based approach.

Third, the catheterization and CMR data were not acquired simultaneously, requiring the use of the ECG wave form to synchronize “offline” the pressure and the flow or RV volume pulse. Simultaneous and synchronized MRI and pressure measurements are preferred options. Unfortunately, this scenario is not attainable in any clinical setting. Furthermore, this study was retrospective in nature. Therefore, for this pilot study we selected similarly aged and sized subjects whose MRI and catheterization data were acquired clinically as close as possible under comparable physiologic conditions (intubation and general anesthesia for both procedures in these subjects). The fact that heart rates were comparable for both procedures in each subject (refer Table 1) attests to the statement that the physiologic conditions for the subjects were comparable. The technique we used is one of the methods described to synchronize non-simultaneously acquired hemodynamic data provided that the heart rate is similar for each procedure.

Fourth, the assumptions of a spatially uniform (plug profile) velocity profile (although time varying) as a boundary condition, and rigid wall modeling may be simplistic idealizations. Our choice in the use of plug profile was based on the fact that the MPA location where we measured velocity, although downstream of the PV, was still very close to it. Consequently, there was inadequate length from the PV to our measurement site in the MPA for the flow to develop into a parabolic profile. Specifically, Grigoni et al.\(^17\) found fairly substantial variation in energy loss at low flow rate depending on which flow profile was used (plug vs. parabolic) in TCPC physiology. They reported only minimal variation in this parameter at higher flow rates similar to those in our data. We believe this further supports our use of the uniform profile for this pilot study. A novel alternate approach of using morphometry-based impedance boundary conditions,\(^35\) by solving one-dimensional blood flow equations at the boundary, can also be adopted for our problem. Use of a spatially varying velocity profiles and patient-specific geometric data incorporating arterial wall compliance effects\(^4,13\) is now being evaluated, which may provide more realistic energy result.

Lastly, this study does not focus on developing values to statistically compare the energy values among subjects with differing physiological characteristics, for which appropriate non-dimensional indices first need to be established.

**CONCLUSIONS**

In this study, we have demonstrated that CMR-based numerical and CFD methodology can be used to assess energy efficiency in the *in vivo* cardiovascular system. Our data suggest that energy-based parameters such as RV SW and energy transfer ratio ($e_{mpa}$) can distinguish RV inefficiency in normal and rTOF subjects. Similar CFD analysis of CMR data for greater number of subjects should validate the use of SW and $e_{mpa}$ as diagnostic indices to assess the state of deterioration of the PV in rTOF physiology.

**APPENDIX**

**RV SW Computation**

The Fourier series of the co-registered and synchronized RV pressure and volume curves (refer to the “Methods” section on co-registration of the catheterization and the CMR data) were sampled at a series of closely spaced consecutive time points, $t_1, t_2, ..., t_n$, over one cardiac period, $T$, progressing from $t = 0$ s to $t = T$ s. Thus, the P–V loop points evaluated at the sampled time points, $t_1, t_2, ..., t_n$, are ($p_1, V_1$), ($p_2, V_2$), ..., ($p_n, V_n$).

The SW given by Eq. 1, which is the area enclosed by the P–V loop, is computed by straightforward application of Gauss theorem, reducing Eq. 1 to
\[ SW = \oint_C pdV - \frac{1}{2} \oint_C (pdV - Vdp), \quad (6) \]

a cyclic integral over the closed path, \( C \), and then reducing the right-hand side of Eq. 6 to a summation over the closed path formed by the sampled P–V loop points, \((p_1, V_1), (p_2, V_2), \ldots, (p_n, V_n), (p_1, V_1)\) to

\[ SW = \left[ \sum_{i=1}^{n-1} \frac{1}{2} (p_i V_{i+1} - p_{i+1} V_i) \right] + \frac{1}{2} (p_n V_1 - p_1 V_n) \quad (7) \]

**Derivation of the Formulae for Energy Transfer Rate at MPA**

Equation 2 for the rate of energy transfer at MPA can be derived in a straightforward manner from basic fluid mechanics. In the analysis of CMR images, identifying the arterial wall location on the image plane at all the phases of MRI gives the distribution of blood velocity, \( \tilde{V}_m(\tilde{x}, t) \), at any point \( \tilde{x} \) inside the arterial section and at any instant of time \( t \). The arterial blood velocity distribution, \( \tilde{V}_m(\tilde{x}, t) \), varies both spatially and temporally. The rate of the total energy transferred to the blood at MPA \( (\dot{E}_m) \), neglecting potential energy changes because of gravity, is given by

\[ \dot{E}_m = \iiint_{A_m} \left( \rho_m + \frac{1}{2} \rho \tilde{V}_m^2 \right) \tilde{V}_m \cdot ndA_m \quad (8) \]

where the subscript \( m \) stands for the MPA location; \( A_m \) the MPA cross-sectional area; \( n \) the unit normal to the cross section; \( \rho_m \) the pulsatile MPA pressure; and \( \rho \) the density of the blood.

Equation 8 can be simplified to Eq. 2 by approximating the velocity distribution \( \tilde{V}_m(\tilde{x}, t) \) over the MPA cross section by an average MPA velocity vector with magnitude \( v_m \) given by

\[ v_m = \frac{Q_m}{A_m}, \quad (9) \]

is simply the volumetric flow rate at the MPA section.

**Result for the Intermediate Case**

The results for our intermediate subject with an atrial septal defect and partial anomalous pulmonary venous return abnormal and overloaded RV but a normal PV are presented in this section.

Figure 7 shows the RV pressure and volume variation with time. The peak pressure and peak volume are 26.6 mmHg and 111.8 mL, respectively, and fall somewhere between the rTOF and the normal subject (Table 1). The volume overloading is evident from the pressure–volume curve (Fig. 7) compared with that of rTOF and the normal subject (Figs. 4a and 4b). The extent of volume overloading is lower than our rTOF subject. As shown in Fig. 8, the P–V loop for the intermediate subject also falls in between the rTOF and the normal subject and hence the computed SW (0.8365 J) follows the same trend. Figure 8 shows that the intermediate subject has a volume overloaded RV with patterns of filling that mirror rTOF and yet operates at a relatively normal operating pressure (approx. 27 mmHg). As such, the increased pressure in

![FIGURE 7. Variation of RV pressure and volume with time for the intermediate subject. Our intermediate subject has overloaded RV but functioning PV.](image-url)
rTOF RV is the result of regurgitant backflow from the PA. Interestingly, the quadrant of this PV loop between end systole and end diastole does not remain isovolumic despite the fact that the higher confirmed competency of PV and TV. The reasons for these are unclear, though possibly secondary to delayed TV given the excess flow though it compared with flow through the mitral valve. In addition, other investigators have found that the RV is never truly isovolumic. More importantly, Fig. 8 shows despite operating with an abnormally higher volume than the normal subject RV, the intermediate subject RV does not operate at higher pressure than the normal subject RV. The variation of the energy transfer rate at the MPA for the intermediate subject (Fig. 9) also is in between the normal and the rTOF subject, with minimum and the maximum values at 0.033 and 0.482 J/s, respectively. The presence of the functioning PV prevents the backflow of the blood into the RV and thus the graph for energy rate has no negative contribution. The time-averaged energy transfer rate over one cardiac cycle ($\dot{E}_{net}$) was calculated to be 0.198 J/s. When compared with rTOF

FIGURE 8. RV PV diagram for our intermediate subject contrasted with those of our normal and rTOF subject. The SW value also falls in between the normal and the rTOF subject.

FIGURE 9. MPA power output for the intermediate subject. Comparison of total rate of power output at MPA for the normal, rTOF, and the intermediate subject.
subject, the normal subject RV operates at a lower pressure, and as such, we conclude that the increased pressure in the rTOF RV is necessary to overcome the energy losses resulting from the backflow and regurgitation because of the incompetent PV.

REFERENCES

4. Bazilevs, Y., M.-C. Hsu, D. J. Benson, S. Sankaran, and T. J. R. Hughes, and C. A. Taylor. A coupled momentum and pressure in the rTOF RV is necessary to overcome the pressure, and as such, we conclude that the increased pressure in the rTOF RV is necessary to overcome the energy losses resulting from the backflow and regurgitation because of the incompetent PV.

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