Prognostic Significance of Cardiac Magnetic Resonance Imaging in Children With Pulmonary Hypertension

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Background—There are very few validated prognostic markers in pediatric pulmonary hypertension. Cardiac MRI is a useful, noninvasive method for determining prognosis in adults. The present study is the first to assess its prognostic value in children.

Methods and Results—A total of 100 children with pulmonary hypertension (median, 10.4 years; range, 0.5–17.6 years) were evaluated (idiopathic, n=60; repaired congenital heart disease, n=22; miscellaneous, n=18). In all patients, ventricular volumes and great vessel flow were measured. Volumetric data were obtained using retrospectively gated cine imaging (n=37) or real-time imaging (n=63), depending on the patient’s ability to hold his or her breath. During a median follow-up of 1.9 years, 11 patients died and 3 received lung transplantation. Of the cardiac MR parameters measured, right ventricular ejection fraction and left ventricular stroke volume index were most strongly predictive of survival on univariate analysis (2.6- and 2.5-fold increase in mortality for every 1-SD decrease, respectively; P<0.05). These results were reflected in good separation of tertile-based Kaplan-Meier survival curves for these variables.

Conclusions—Cardiac MR measures correlate with clinical status and prognosis in children with pulmonary hypertension. Cardiac MR is feasible and may be useful in clinical decision making in pediatric pulmonary hypertension. (Circ Cardiovasc Imaging. 2013;6:407-414)

Key Words: echocardiography ▪ hypertension ▪ MRI ▪ pediatric ▪ prognosis ▪ pulmonary

The ability to estimate prognosis plays a vital role in the management of children with pulmonary hypertension (PH). It determines not only initial medical therapy but also escalation in treatment and consideration for lung transplantation. Although diagnosis of PH usually requires invasive measurement of pulmonary arterial (PA) pressure, prognosis is more related to invasive measures of cardiac function (eg, reduced cardiac index and raised right atrial pressure). This suggests that noninvasive methods of assessing cardiac function also may be able to provide useful prognostic information in PH.

Clinical Perspective on p 414

Cardiac magnetic resonance (CMR) is a highly reproducible method of assessing cardiovascular function and has been shown to be a powerful predictor of outcome in adult PH. This has led to its incorporation into the clinical management of adult PH, as well as its use as an end point in clinical trials. However, there are significant differences between pediatric and adult PH, and the findings of adult studies are not necessarily applicable to children. Thus, for CMR to be used in children, it is necessary to specifically assess the predictive power of CMR in the pediatric population. Unfortunately, traditional CMR requires breath holding, which many children with PH find difficult to perform. Real-time CMR performed during free breathing may offer a solution to this problem because it allows imaging in the vast majority of children. Furthermore, this technique has been shown to accurately measure ventricular function (including right ventricular function) in pediatric patients. With these novel techniques, it is now possible to properly assess the prognostic capabilities of CMR in children with PH, regardless of disease state and dyspnea.

In the United Kingdom, there is a single national referral center for pediatric PH with centralized CMR assessment that includes the ability to perform real-time CMR. The main aim of this study was to evaluate the clinical and prognostic significance of CMR measures of cardiac function in a large representative population of children with PH.

Study Population

The study population included all children with a history of PH (defined as a measure mean PA pressure >25 mmHg [n=93] or estimated systolic PA pressure >50 mmHg [n=7]), biventricular hearts, and no ventricular or arterial level shunts referred for clinical CMR assessment between August 2007 and December 2012. CMR referral...
criteria are as follows: (1) right ventricular (RV) assessment after initial diagnosis of PH, (2) clinical worsening, and (3) assessment on PH specific therapy. All patients underwent assessment of World Health Organization (WHO) functional status and patients >5 years of age with the cognitive ability to do so performed a 6-minute walk test (result expressed as a percentage of predicted distance) within 24 hours of CMR scanning. Patients were followed up in the outpatient setting at 3- to 6-month intervals.

Patients underwent echocardiography (Vivid 7 GE Vingmed, Milwaukee, WI) within 24 hours of CMR. The following parameters were assessed as previously described: PA systolic pressure, right atrial (RA) area indexed to body surface area, mid-RV diameter indexed to body surface area measured in the apical 4-chamber view, and tricuspid annular plane systolic excursion.

CMR Image Acquisition

In patients who were having cardiac catheterization as part of their clinical assessment, CMR was incorporated into their catheterization in an MR/catheter hybrid laboratory as previously described (n=33).5 These patients had catheterization performed under general anesthesia. One patient had an MR scan for anatomic assessment of a cutaneous chest wall tumor under general anesthesia that was combined with CMR. All other patients (n=67) had unsedated CMR scans.

All images were obtained with a 1.5-T MR scanner (Avanto, Siemens, Erlangen, Germany) using a 12-element phased-array coil for signal reception and the body coil for signal transmission. A vector ECG system was used for cardiac gating. The CMR scan time was between 15 and 30 minutes.

Left ventricular (LV) and RV volumes were measured from contiguous short-axis cines covering both ventricles (7–13 slices, depending on the size of the child). CMR protocols were modified, depending on the patient’s age and ability to hold his or her breath. In patients >7 years of age who could perform breath holds (n=37) and the 1 patient who had CMR together with tumor assessment under general anesthesia, retrospectively gated cine imaging was used. Each slice was acquired in a single 6- to 10-second breath hold as previously described.6 In all other unsedated patients (n=30) and patients undergoing combined CMR and catheterization (n=33), real-time radial k-t sensitivity encoding imaging was used (Figure 1). This sequence has been previously described and validated on children with congenital heart disease.7 It provides high spatiotemporal resolution real-time imaging and permits data acquisition during free breathing.

Blood flow data were acquired using a velocity-encoded phase-contrast MR sequence as previously described.8 All flow data were acquired during free breathing; acquisition time was 1 to 3 minutes. Previous work has demonstrated inaccuracies in quantification of main PA blood flow, possibly related to pulmonary trunk dilation and vortical flows. To overcome this problem, pulmonary blood flow was measured by summing the flow in the right pulmonary artery (RPA) and left pulmonary artery (LPA). This approach is based on the assumption that flow can be more accurately quantified in the less dilated branches. However, it should be noted that this approach might slightly overestimate pulmonary regurgitation because it measures regurgitation into the pulmonary trunk rather than regurgitation across the pulmonary valve. Blood flow was also measured in the ascending aorta.

CMR Image Analysis

All image processing was performed using in-house plug-ins for the open-source OsiriX DICOM (digital imaging and communications in medicine) software.4,10,11 The ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) of both ventricles were measured by manual segmentation of the endocardial borders in the short-axis data. Segmentation of the epicardial border of the RV at end systole allowed calculation of RV free-wall mass. Careful segmentation of the basal slices in conjunction with 4-chamber and RV long-axis views was performed to overcome problems with delineating the tricuspid valve. This approach has been shown to be robust in several pediatric populations with RV disease.8,12 Ventricular stroke volume (SV) was the difference between the EDV and ESV, and ventricular ejection fraction (%) was (SV/EDV)×100.

Phase-contrast MR data were segmented using a semiautomated vessel edge detection algorithm with operator correction.10 Metrics that were directly measured in all vessels were forward-flow volume (FFV) and backward-flow volume (BFV); all other metrics were calculated as follows:

1. Pulmonary forward flow volume (PFFV)=RPA FFV+LPA FFV.
2. Pulmonary backward flow volume (PBFV)=RPA BFV+LPA BFV.
3. Net pulmonary flow volume (NPFV)=PFFV−PBFV.
4. Pulmonary artery regurgitation fraction (PRF)=(PBFV/PFFV)×100, and
5. Tricuspid valve regurgitation fraction (TRF)=(RVSV−PFFV/RVSV)×100.13

In the patients who underwent combined MR and catheterization, pulmonary vascular resistance index was calculated by dividing the transpulmonary pressure gradient by indexed pulmonary blood flow.

Statistical Analysis

All volumetric data were indexed to body surface area. Data are presented as mean±SD or median and range as appropriate. Normal distribution of data was confirmed using D’Agostino-Pearson omnibus normality test. One-way ANOVA was performed to determine differences in CMR and demographic parameters between diagnostic groups for continuous variables. For categorical variables, the Fisher exact test was used.

Baseline demographic, CMR parameters, and use of pulmonary vasodilator therapy were compared between transplant-free survivors and those who received transplantation or died. A 2-sided t test was used for normally distributed variables, a Wilcoxon rank-sum test for skewed data, and a Fisher exact test for categorical variables.

One-way ANOVA with calculation of η² was performed to assess the relation of WHO functional class with CMR and echocardiographic

Figure 1. Representative examples of (A) retrospectively gated cine image (breath hold), and (B) real time (free breathing) from short axis in a 12-year-old and an 8-year-old child, respectively.
parameters. $\eta^2$ is a measure of proportion of the variance in a given variable explained by another variable and is analogous to $r^2$. For ordinal variables, the Kruskal-Wallis test was used. The linear relations between 6-minute walk distance and PA pressures and CMR/echocardiographic parameters were assessed using Pearson correlation test for normally distributed parameters and Spearman rank correlation test for nonnormally distributed variables.

All patients were followed up until death, transplantation, or end of the study period (December 1, 2012). Univariate Cox proportional hazards analysis was used to assess the prognostic significance of CMR and echocardiographic variables. The primary outcome was survival, and the secondary outcome was survival without transplantation. Patients were censored at the end of the study period or at time of transplantation (for survival model).

For variables that were significantly associated with survival on univariate analysis, Kaplan-Meier survival curves were constructed with the population divided into 3 equal-sized groups using tertile-based ranges. Estimates of survival from the Kaplan-Meier graphs include confidence intervals in parentheses. The association of WHO functional class with survival was compared using the log-rank test for trend.

## Results

### Study Population

In total, 100 patients with a median age of 10.4 years (range, 0.5–17.6 years) and a female preponderance (n=61; 61%) were assessed. Patient characteristics, CMR, and echocardiographic-derived parameters are summarized in Table 1. The majority of patients had idiopathic pulmonary arterial hypertension (n=60); the remainder had either fully repaired congenital heart disease (n=22) or other miscellaneous causes of PH (n=18). There were no statistically significant clinical or demographic differences between the diagnostic groups. In addition, there were no statistically significant differences in RV volumes, RV ejection fraction (RVEF), LV ejection fraction, LV systolic volume index, or tricuspid regurgitation between groups. However, LVESV index was higher ($P<0.01$) in the repaired congenital heart disease group (28 mL/m²) compared with the idiopathic pulmonary arterial hypertension group (20 mL/m²) and the miscellaneous group (20 mL/m²). There also was more pulmonary regurgitation in the repaired congenital heart disease group (mean 9%) than in either the idiopathic pulmonary arterial hypertension or miscellaneous group (1% and 2%, respectively; $P<0.01$). Tricuspid regurgitation was greatest in the idiopathic pulmonary arterial hypertension group (6.5%) compared with the miscellaneous group (5.7%) and congenital heart disease group (3.8%; $P=0.02$).

Eighty-six patients were receiving PH therapy at the time of CMR study (4 calcium channel blockers, 34 monotherapy, and 48 combination therapy). By the time of final follow-up, 93 were still on therapy (5 calcium channel blockers, 29 monotherapy, and 64 combination therapy).

### Clinical and Hemodynamic Correlations

Correlations between PH severity and CMR and echocardiographic parameters are shown in Table 2. All CMR parameters (except LVESV index) were significantly associated ($P<0.05$) with functional class. The strongest association (ie, largest $\eta^2$) was with RVEF ($\eta^2=0.58$; $P<0.01$). The only echocardiographic parameters that were associated with functional class were RA size ($\eta^2=0.11$; $P=0.02$) and mid-RV

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>All Patients (n=100)</th>
<th>Transplantation-Free Survivors (n=86)</th>
<th>Transplanted or Died (n=14)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>10.4 (0.5–17.6)</td>
<td>10.4 (0.5–17.6)</td>
<td>11.0 (0.8–17.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>61 (61%)</td>
<td>52 (60%)</td>
<td>9 (64%)</td>
<td>1.00*</td>
</tr>
<tr>
<td>WHO class 1/2/3/4</td>
<td>20/39/29/12</td>
<td>20/39/21/6</td>
<td>0/0/8/6</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>6-mwd, % predicted</td>
<td>62 (SD 15)</td>
<td>63 (15)</td>
<td>54 (6)</td>
<td>0.26</td>
</tr>
<tr>
<td>RVEDVi, mL/m²</td>
<td>100 (38)</td>
<td>92 (34)</td>
<td>122 (52)</td>
<td>0.01</td>
</tr>
<tr>
<td>RVESVi, mL/m²</td>
<td>53 (37)</td>
<td>48 (33)</td>
<td>83 (47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVSVi, mL/m²</td>
<td>43 (13)</td>
<td>44 (12)</td>
<td>39 (14)</td>
<td>0.19</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>48 (15)</td>
<td>51 (14)</td>
<td>35 (13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVMI, g/m²</td>
<td>73 (40)</td>
<td>68 (34)</td>
<td>102 (58)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDVi, mL/m²</td>
<td>60 (17)</td>
<td>61 (17)</td>
<td>56 (19)</td>
<td>0.40</td>
</tr>
<tr>
<td>LVESVi, mL/m²</td>
<td>22 (10)</td>
<td>21 (9)</td>
<td>23 (13)</td>
<td>0.55</td>
</tr>
<tr>
<td>LVSVi, mL/m²</td>
<td>38 (12)</td>
<td>40 (12)</td>
<td>32 (8)</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>65 (8)</td>
<td>65 (8)</td>
<td>61 (9)</td>
<td>0.09</td>
</tr>
<tr>
<td>PRF, %</td>
<td>2.7 (8.8)</td>
<td>2 (8)</td>
<td>6 (14)</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>TRF, %</td>
<td>6 (9)</td>
<td>4 (8)</td>
<td>14 (11)</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>RAAi, cm²/m²</td>
<td>13.4 (4.6)</td>
<td>13 (4)</td>
<td>15 (6)</td>
<td>0.07</td>
</tr>
<tr>
<td>mRVDi, cm²/m²</td>
<td>4.0 (1.7)</td>
<td>4 (1)</td>
<td>5 (2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TAPSE, Z score</td>
<td>−2.4 (2.8)</td>
<td>−2.2 (2.9)</td>
<td>−3.5 (2.2)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Values represent mean (SD) except for age, which is median (range). Comparisons made using 2-sided t test. LVEDVi indicates left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; mRVDi, mid right ventricular diameter index; PRF, pulmonary regurgitation fraction; RAAi, right atrial area index; RVEDVi, right ventricular end-diastolic volume index; RVESVi, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; RVMI, right ventricular mass index; RVSVi, right ventricular stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TRF, tricuspid regurgitation fraction; WHO, World Health Organization; and 6-mwd, 6-minute walk distance.

*Fisher exact test. † Wilcoxon rank-sum test.
diameter indexed to body surface area ($\eta^2=0.14$; $P<0.01$). All CMR parameters, except RVEDV index, LVESV index, LV ejection fraction, and PRF, significantly correlated ($P<0.05$) with 6-minute walk distance. The strongest correlations were once again with measures of RV function (RVEF, RV stroke volume index). No echocardiographic parameters correlated with 6-minute walk distance. All CMR-derived RV measures (except RV stroke volume index and LV ejection fraction) correlated with tricuspid Doppler-derived estimated systolic PA pressures. The only echocardiographic parameter that correlated with estimated PA pressure was RA size. In the subset of patients who underwent combined CMR and catheterization, all CMR parameters (except RV end-diastolic volume index, LVESV index, PRF, and TRF) significantly correlated with mean PA pressure, particularly measures of RV function. This was also seen with echocardiography, with tricuspid annular plane systolic excursion being the only parameter that correlated with mean PA pressure.

**Overall Survival Data**

Over a median follow-up period of 23.3 months (range, 0–84.6 months), 11 patients died and 3 received bilateral lung transplants. Overall 1-, 2-, and 3-year survival was 94% (87–97), 91% (82–95), and 85% (74–92); transplantation-free survival was 93% (86–97), 87% (77–93), and 81% (70–89). There was no significant difference in survival among the 3 diagnostic groups. Of the patients who died or were transplanted (poor outcome), 71% were on combination therapy at the time of CMR assessment compared with 44% of patients who survived ($P=0.08$). At final follow-up, 79% of those with poor outcome were treated with combination therapy versus 62% who survived ($P=0.37$). Patients who experienced poor outcome were more likely to have been treated with prostacyclin therapy (64%) compared with those who survived (24%; $P<0.01$).

**Univariate Analysis**

Variables that correlated with survival and transplantation-free survival on univariate analysis are summarized in Table 3. Resting heart rate predicted survival; however, 6-minute walk distance did not predict survival. Several CMR parameters predicted survival (Table 3), of which RVEF and left ventricular stroke volume index (LVSVi) had the greatest magnitude. Every 1-SD decrease in RVEF and LVSVi led to a 2.6-fold and 2.5-fold increase, respectively, in risk of death. The only echocardiographic parameter that predicted survival was mid-RV diameter indexed to body surface area, with every 1-SD increase being associated with a 2.2-fold increase in mortality. Neither estimated PA systolic pressure or invasively measured mean PA pressure (in those patients who underwent CMR and catheterization) predicted survival.

**Kaplan-Meier Survival Analysis**

Kaplan-Meier curves of significantly predictive variables on univariate analysis and WHO functional class are presented in Figure 2. Of note, patients with an RVEF <44% (lowest tertile) had a 1-, 2-, and 3-year survival of 87% (69–95), 78% (56–90), and 65% (40–82), respectively. Similarly, patients with an LVSVi <34 mL/m² (lowest tertile) had a 1-, 2-, and 3-year survival of 90% (73–97), 81% (61–92), and 69% (43–85), respectively. There were no deaths in WHO functional classes 1 or 2. One-, 2-, and 3-year survival in WHO functional class 3 was 85% (66–94), 81% (59–92), and 65% (38–83), respectively, whereas in class 4 it was 81% (42–95),...
Table 3. Univariate Cox Proportional Analysis HR Per 1-SD Increase in Parameter Being Tested

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Death (n=11)</th>
<th>Death or Transplantation (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mwd, % predicted (n=59)</td>
<td>0.67 (0.25–1.80)</td>
<td>0.58 (0.25–1.37)</td>
</tr>
<tr>
<td>HR, % max</td>
<td>1.80 (1.34–2.44)</td>
<td>1.70 (1.27–2.28)</td>
</tr>
<tr>
<td>RVEDVi</td>
<td>1.78 (1.23–2.80)</td>
<td>1.85 (1.25–2.74)</td>
</tr>
<tr>
<td>RVESVi</td>
<td>1.95 (1.27–2.99)</td>
<td>1.96 (1.35–2.86)</td>
</tr>
<tr>
<td>RVSVi</td>
<td>0.67 (0.25–1.80)</td>
<td>0.42 (0.26–0.68)</td>
</tr>
<tr>
<td>RVEF</td>
<td>0.55 (0.29–1.04)</td>
<td>0.67 (0.38–1.16)</td>
</tr>
<tr>
<td>RVMi</td>
<td>0.39 (0.23–0.68)</td>
<td>0.42 (0.26–0.68)</td>
</tr>
<tr>
<td>LVEDVi</td>
<td>1.99 (1.24–3.20)</td>
<td>2.00 (1.32–3.04)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.69 (0.36–1.31)</td>
<td>0.73 (0.42–1.28)</td>
</tr>
<tr>
<td>LVESVi</td>
<td>1.14 (0.67–1.94)</td>
<td>1.13 (0.70–1.82)</td>
</tr>
<tr>
<td>LVSVi</td>
<td>0.40 (0.20–0.82)</td>
<td>0.46 (0.25–0.85)</td>
</tr>
<tr>
<td>PRF</td>
<td>0.65 (0.39–1.10)</td>
<td>0.67 (0.42–1.06)</td>
</tr>
<tr>
<td>TRF</td>
<td>1.36 (0.96–1.93)</td>
<td>1.30 (0.93–1.82)</td>
</tr>
<tr>
<td>RAAi</td>
<td>1.68 (1.10–2.55)</td>
<td>1.81 (1.26–2.60)</td>
</tr>
<tr>
<td>mRVDi</td>
<td>2.23 (1.45–3.42)</td>
<td>1.97 (1.32–2.94)</td>
</tr>
<tr>
<td>TAPSE, Z score</td>
<td>0.88 (0.69–1.11)</td>
<td>0.87 (0.70–1.08)</td>
</tr>
<tr>
<td>Est sPAP</td>
<td>1.25 (0.71–2.21)</td>
<td>1.51 (0.91–2.51)</td>
</tr>
<tr>
<td>mPAP, n=33</td>
<td>1.60 (0.56–4.42)</td>
<td>1.82 (0.69–4.87)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; Est sPAP, Doppler-derived estimated pulmonary artery systolic pressure; HR, hazard ratio; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; mPAP, mean pulmonary artery pressure; mRVDi, mid right ventricle diameter index; PRF, pulmonary regurgitation fraction; RAAi, right atrial area index; RVEDVi, right ventricular end-diastolic volume index; RVESVi, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; RVMi, right ventricular mass index; RVSVi, right ventricular stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TRF, tricuspid regurgitation fraction; and 6-mwd, 6-minute walk distance.

67% (28–89), and 51% (14–79). The difference in outcome in the different WHO functional classes reached statistical significance (P<0.01).

**Discussion**

The prognostic significance of CMR in pediatric PH has been demonstrated for the first time in this study. The main finding of the study is that several CMR parameters, particularly measures of RV function, correlate with disease severity and are predictive of mortality. This suggests that CMR can be used successfully to assess severity and prognosis in children with PH. Furthermore, we were able to demonstrate the feasibility of using real-time sequences to acquire this data, making CMR more applicable to this patient group.

In pediatric PH, we have shown that almost all CMR parameters correlate with clinical measures of disease severity (WHO functional class and 6-minute walk distance). This is in keeping with the fact that clinical state is closely related to cardiovascular function. Furthermore, to the best of our knowledge, we have shown for the first time that there is a strong correlation between RV function measured using CMR and both estimated and invasively measured PA pressure. This implies that CMR could be used to evaluate changes in RV function that are a consequence of the alterations in afterload (eg, attributable to disease progression or medical therapy). In the adult literature, the role of CMR in monitoring response to therapy and disease progression has already been demonstrated. 

Our results suggest that it might also be useful in children, although this assertion requires formal testing. Of course, to assess the long-term response of therapy, it is vital that CMR measures reflect not only severity but also outcome.

In adult PH, CMR measures of RV dilation, poor LV filling, and reduced RVSV have been shown to independently predict mortality. Unfortunately, the results of adult studies are not necessarily transferable to children because of different ventricular response to afterload, a greater prevalence of valvular regurgitation, and a worse natural history in children. Thus, it is vital that the prognostic capabilities of CMR are specifically tested in pediatric PH.

In this study, we have shown that several CMR variables predict increased mortality in pediatric PH. The CMR parameters most associated with an increased risk of death or transplantation were RVEF and LVSVi. In fact, a 1-SD decrease in these measures resulted in a 2.6- and 2.5-fold increased risk of death, respectively. This implies that RV function is the primary determinant of outcome in this population, which is in broad agreement with the previous adult study. However, it should be noted that although LVSVi is prognostic, the hazard ratio for RV stroke volume index did not reach statistical significance. The difference between RV stroke volume index and LVSVi is due primarily to valvular regurgitation (either tricuspid regurgitation or pulmonary regurgitation), and this suggests that regurgitation is also an important factor in survival. RV mass was also prognostic, possibly because it is a marker of increased RV afterload as demonstrated by its correlation with PA pressure. However, neither estimated nor measured PA pressures predicted outcome in this study, and
this means that other factors that correlate with hypertrophy (such as length of illness) may also be important.

Overall, the prognostic data suggest that CMR could be used to predict outcome in children with PH. However, hazard ratios based on 1-SD differences in CMR variables are difficult to use in the clinical environment. Consequently, we used Kaplan-Meier analysis to predict 1-, 2-, and 3-year survival in groups divided into tertiles. In keeping with previous analyses, being in the lowest tertile of RVEF or LVSVi was associated with a significantly poorer outcome. Because these tertiles are associated with specific cutoff values, these ranges could be used to clinically categorize patients into risk groups and to tailor therapy to their predicted outcome. This includes not only medical therapy but also lung transplantation because timing must take into consideration the risk of death while on the waiting list for transplantation.

Of course, traditionally, echocardiography would be used to perform the functions that we are suggesting for CMR because it is widely available, is easy to perform, and provides measures of RV size and function, as well as estimated PA pressure. However, in our study, we found that the echocardiographic measures did not correlate strongly or consistently with clinical or hemodynamic severity. Furthermore, only RV and RA sizes were prognostic, whereas tricuspid annular plane systolic excursion was not. This study was not suitably powered to evaluate any superiority of CMR over echocardiography. Nevertheless, the increased risk of death associated with 1-SD decreases in RVEF or LVSVi was greater than the risk associated with 1-SD increases in RA area indexed to body surface area or mid RV diameter indexed to body surface area. The reasons for this may relate to operator dependence and difficulty assessing the complex 3-dimensional structure of the RV using simple 2-dimensional techniques.

Echocardiography has 1 great advantage over conventional CMR, which is that it can be performed on almost any patients without the need for breath holds. In this study, real-time CMR was used to assess ventricular function in children who were unable to perform breath holds. This was vital in this study because without it >40% of the unsedated children in our population could not have been scanned. In particular, real-time CMR allowed assessment of younger children without general anesthesia, essentially making CMR a safe procedure in this population. It should be noted that patients who underwent CMR and catheterization in the same sitting did undergo general anesthesia. However, this was done for the catheterization and was not necessary for the CMR, which could have been performed during free breathing in an awake state.

Figure 2. Kaplan-Meier survival curves. A, World Health Organization (WHO) function class and cardiac MRI and echocardiographic variables by tertile. B, Right ventricular end-diastolic volume index (RVEDVi). C, Right ventricular end-systolic volume index (RVESVi). D, Right ventricular ejection fraction (RVEF). E, Left ventricular stroke volume index (LVSVi). F, Right ventricular mass index (RVMi). G, Tricuspid regurgitation (TR) fraction. H, Mid right ventricular diameter index (mRVDi). I, Right atrial area index (RAAi).
child. Thus, with real-time CMR, it is possible to acquire data with the predictive power of conventional CMR and the ease of use of echocardiography.

**Limitations**

The main limitations of this study was its retrospective nature and the low event rate for the given population, which prevented multivariate statistical analysis and development of a composite predictive score. However, using univariate analysis, we were able to show that RVEF and LVSVi had the greatest hazard ratios, suggesting that they were the most predictive CMR measures evaluated in this study. Nevertheless, to truly demonstrate superiority, it will be necessary to perform a larger prospective study. Such a study also could allow evaluation of the prognostic significance of less frequently used CMR measures such as PA velocity–based metrics, septal curvature, late gadolinium enhancement, and diastolic indices. These were not tested in this study because we were trying to restrict variables to those commonly acquired in clinical CMR departments. In addition, a larger study may allow the development of a composite predictive score that incorporates several CMR (and clinical) parameters to improve prognostic accuracy.

Another limitation was the fact that the majority of patients were already being treated at the time of CMR, and further treatment decisions were made with knowledge of the CMR findings. Thus, patients with worse CMR parameters were treated more aggressively, which should have improved outcome. Nevertheless, CMR still proved significantly prognostic, suggesting that these data are important even after treatment optimization. A further limitation is that we were unpowered to assess any age-related differences in the prognostic abilities of CMR variables. This is an important area of study for future work. It should also be noted that 6-minute walk distance was not predictive of outcome; this finding may be related to greater variability when this test is performed in children.

**Conclusions**

This study has demonstrated for the first time that CMR measures correlate strongly with clinical status and prognosis in children with PH. Although CMR is not a replacement for invasive catheterization, we believe that these results will demonstrate that CMR can be a useful adjunct in pediatric PH. Furthermore, CMR may also offer useful end points for the clinical trials that are vital in improving prognosis in pediatric PH. CMR is feasible and may aid clinical decision making in pediatric PH.

**Disclosures**

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**References**


CLINICAL PERSPECTIVE

Prognosis in pediatric pulmonary hypertension is heavily influenced by right ventricular function. Cardiovascular magnetic resonance (CMR) is now considered the reference standard method of assessing the right ventricle. With the advent of new real-time sequences, CMR is now feasible in the majority of children with pulmonary hypertension (PH). The aim of this study was to assess the use of CMR measures of right ventricular function to predict outcome in pediatric PH. We were able to demonstrate that CMR measures, particularly right ventricular ejection fraction and left ventricular stroke volume, correlate with prognosis and clinical status in children with PH. This suggests that these measures could be used to guide treatment. For instance, a decrease in right ventricular ejection fraction could be used to trigger treatment escalation or listing for lung transplantation. Furthermore, CMR may offer novel end points for the clinical trials of new therapies in pediatric PH. Therefore, in the era of goal-driven treatment strategies, we believe that these results demonstrate that CMR can be a useful adjunct in the management of children with PH.
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