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

Moledina et al: Cardiac MRI in Paediatric Pulmonary Hypertension

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DOI: 10.1161/CIRCIMAGING.112.000082

Journal Subject Codes: 18 and 30
Abstract

Background—There are very few validated prognostic markers in pediatric pulmonary hypertension (PH). Cardiac magnetic resonance imaging (CMR) is a useful, non-invasive 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 PH (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 was obtained using retrospectively gated cine imaging (n=37) or real time imaging (n=63) depending on patient’s ability to breath-hold. During a median follow-up of 1.9 years, 11 patients died and 3 received lung transplantation. Of the CMR 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 standard deviation fall respectively, p<0.05). These results were reflected in good separation of tertile based Kaplan Meier survival curves for these variables.

Conclusions—CMR measures correlate with clinical status and prognosis in children with PH. CMR is feasible and may be useful in clinical decision making in pediatric PH.

Key Words: hypertension, pulmonary; magnetic resonance imaging; pediatric; prognosis; echocardiography
The ability to estimate prognosis plays a vital role in the management of children with pulmonary hypertension (PH). It not only determines initial medical therapy, but also escalation in treatment and consideration for lung transplantation. Whilst diagnosis of PH usually requires invasive measurement of pulmonary arterial (PA) pressure, prognosis is more related to invasive measures of cardiac function (e.g. reduced cardiac index and raised right atrial pressure)\(^1\). This suggests that non-invasive methods of assessing cardiac function may also be able to provide useful prognostic information in PH.

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\(^2\). 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\(^3\). 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 as 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\(^4\). Using these novel techniques it is now possible to properly assess the prognostic capabilities of CMR in children with PH, irrespective of disease state and dyspnea.

In the UK 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 large
representative population of children with PH.

Methods

Study Population

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

Patients underwent echocardiography (Vivid 7 GE Vingmed, Milwaukee, WI, USA) within twenty-four hours of CMR. The following parameters were assessed as previously described \(^6\): pulmonary artery systolic pressure, right atrial area indexed to body surface area (RAAi), mid right ventricular diameter indexed to body surface area (mRVDi) measured in the apical four chamber view and tricuspid plane systolic excursion (TAPSE).

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 lab (XMR) as previously
described (n=33). These patients had catheterization performed under general anesthetic. One patient had an MR scan for anatomical assessment of a cutaneous chest wall tumor under general anesthetic that was combined with CMR. All other patients (n=67) had unsedated CMR scans.

All images were obtained with a 1.5T 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 electrocardiogram 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 their breath. In patients over 7 years who could perform breath holds (n=37) and the one patient who had CMR together with tumor assessment under general anesthetic, retrospectively gated cine imaging was used. Each slice was acquired in a single 6-10 second breath hold as previously described. In all other unsedated patients (n=30) and patient undergoing combined CMR and catheterization (n=33), real-time radial k-t SENSE imaging was used (Figure 1.). This sequence has been previously described and validated on children with congenital heart disease. It provides high spatio-temporal resolution real-time imaging and permits data acquisition during free breathing.

Blood flow data was acquired using a velocity encoded phase contrast MR sequence as previously described. All flow data were acquired during free breathing; acquisition time was 1-3 minutes. Previous work has demonstrated inaccuracies in quantification of main pulmonary artery 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 as 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 software. The ventricular end diastolic volume (EDV) and end systolic volume (ESV) of both ventricles was 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 (RVM). Careful segmentation of the basal slices in conjunction with four 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. Ventricular stroke volume (SV) was the difference between the EDV and ESV, and ventricular ejection fraction (%) was (SV/EDV)×100.

Phase contrast MR data was segmented using a semi-automatic vessel edge detection algorithm with operator correction. 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:

- Pulmonary forward flow volume (PFFV) = RPA FFV + LPA FFV;
- Pulmonary backward flow volume (PBFV) = RPA BFV + LPA BFV;
- Net pulmonary flow volume (NPFV) = PFFV - PBFV;
- Pulmonary artery regurgitation fraction (PRF) = (PBFV/ PFFV)×100.
- Tricuspid valve regurgitation fraction (TRF) = (RVSV - PFFV/RVSV)×100 \(^{13}\).

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

**Statistical Analysis**

All volumetric data was indexed to body surface area. Data are presented as mean ± standard deviation (SD) or median and range as appropriate. Normal distribution of data was confirmed using D’Agostino-Pearson’s 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 Fisher’s exact test was used.

Baseline demographic, CMR parameters and use of pulmonary vasodilator therapy were compared between transplant free survivors and those who were transplanted or died. A two-sided t-test was used for normally distributed variables, Wilcoxon rank-sum test for skewed data and a Fisher’s exact test for categorical variables.

One-way ANOVA with calculation of eta squared (\(\eta^2\)) was performed to assess the relation of WHO functional class with CMR and echocardiographic parameters. Eta squared is a measure 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 relation between six minute walk distance and PA pressures and CMR/echocardiographic parameters was assessed using Pearson’s correlation test for normally distributed parameters and Spearman’s rank correlation test for non-normally distributed variables.

All patients were followed-up until death, transplantation or end of the study period (1\(^{st}\)
December 2012). Univariate Cox’s 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 transplant (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 brackets. The association of WHO functional class with survival was compared using the log-rank test for trend.

Results

Study Population

In total, 100 patients were assessed with a median age 10.4 years (range 0.5-17.6 years) and a female preponderance (n=61, 61%). Patient characteristics, CMR and echocardiographic derived parameters are summarized in Table 1. The majority of patients had idiopathic pulmonary arterial hypertension (IPAH, n=60), the remainder had either fully repaired congenital heart disease (CHD, 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, RVEF, LVEF, LVSVi or TR between groups. However, LVESVi was higher (p<0.01) in the repaired CHD group (28 mL/m$^2$) compared to IPAH (20 mL/m$^2$) and the miscellaneous group (20 mL/m$^2$). There was also more PR in the repaired CHD group (mean 9%) than in either IPAH or miscellaneous groups (1% and 2% respectively, p<0.01). TR was greatest in the IPAH group (6.5%) compared to the
miscellaneous group (5.7%) and CHD 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, 48 combination therapy). By the time of final follow-up 93 were still on therapy (5 CCB, 29 monotherapy, 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 for LVESVi) were significantly associated (p<0.05) with functional class. The strongest association (i.e. 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 mRVDi ($\eta^2=0.14$, p<0.01). All CMR parameters, except for RVEDVi, LVESVi, LVEF, PRF, significantly correlated (p<0.05) with 6-minute walk distance. The strongest correlations were once again with measures of RV function (RVEF, RVSVi). No echocardiographic parameters correlated with 6 minute walk distance. All CMR derived RV measures (except for RVSVi and LVEF) 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 for RVEDVi, LVESVi, PRF and TRF) significantly correlated with mean PA pressure, particularly measures of RV function. This was also seen with echocardiography, with TAPSE 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), 11 patients died and 3 received
bilateral lung transplantations. Overall 1, 2 & 3 year survival was 94 (87-97)%, 91 (82-95)% and 85 (74-92)% and transplant free survival was 93 (86-97)%, 87 (77-93)% and 81 (70-89)%. There was no significant difference in survival between the 3 diagnostic groups. Of the patients who died or were transplanted (poor outcome), 71% were on combination therapy at time of CMR assessment compared to 44% in 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 to those who survived 24% (p<0.01).

Univariate Analysis

Variables that correlated with survival and transplant 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 LVSVi had the greatest magnitude. Every standard deviation fall in RVEF and LVSVi led respectively to a 2.6-fold and 2.5-fold increase in risk of death. The only echocardiographic parameter that predicted survival was mRVDi, with every standard deviation increase being associated with a 2.2-fold increase in mortality. Neither estimated sPAP and invasively measured mean PA pressure (in those patient 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 a LVSVi <34mL/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, two and three-year survival in WHO functional class 3 was 85%(66-94), 81%(59-92) and 65%(38-83) respectively, while in class 4 it was 81%(42-95), 67%(28-89) and 51%(14-79). The difference in outcome in the different WHO functional classes reached statistical significance (p<0.01).

**Discussion**

This study represents the first time that the prognostic significance of CMR in pediatric PH has been demonstrated. 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 six-minute walk distance). This is in keeping with the fact that clinical state is closely related to cardiovascular function. Furthermore to our knowledge, we have shown for the first time that there 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 (e.g. due 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 does require formal testing. Of course to assess the long-term response to therapy it is vital that CMR measures not only reflect 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 \(^2\). Unfortunately, the results of adult studies are not necessarily transferable to children due to a different ventricular response to afterload, a greater prevalence of valvar regurgitation \(^15\), and a worse natural history in children \(^16\). 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 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 \(^2\). However, it should be noted that although LVSVi is prognostic, the hazard ratio for RVSVi did not reach statistical significance. The difference between RVSVi and LVSVi is primarily due to valvar regurgitation (either TR or PR) and this suggests that regurgitation is also an important factor in survival. Right ventricular 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 suggests that CMR could be used to predict outcome in children with PH. However, hazard ratios based on standard deviation 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. As these tertiles are associated with specific cut-off values, these ranges could be used to clinically categorize patients into risk groups and tailor therapy to their predicted outcome. This not only includes medical therapy, but also lung transplantation as 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. This is because it is widely available, 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 size were prognostic, while TAPSE was not. In this study, we were not suitably powered to evaluate any superiority of CMR over echocardiography. Nevertheless, the increased risk of death associated with SD decreases RVEF and LVSVi was greater than the risk associated with SD increases in RAAi or mRVDi. The reasons for this may relate to operator dependence and difficulty assessing the complex three-dimensional (3D) structure of the RV using simple 2D techniques.

Echocardiography does have one 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, as without it more than 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 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 limitation 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 greatest hazard ratios, suggesting that they were the most predictive CMR measures evaluated in this study. Nevertheless, in order to truly demonstrate superiority it will be necessary to perform a larger prospective study. Such a study could also 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 as 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 in order 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 will be important area of study for future work. It should also be noted that six-minute walk distance was not predictive of outcome; this finding may be related to greater variability when performing this test in children.

Conclusion

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 do believe that these results will demonstrate that CMR can be a useful adjunct in pediatric PH. Furthermore, CMR may also offer useful endpoints for the clinical trials that are vital in improving prognosis in pediatric PH. In conclusion, CMR is both a feasible and may aid clinical decision making in pediatric PH.

Sources of Funding

SM was funded by – The pulmonary hypertension association UK - grant no. PHA001
VM is funded by the British Heart Foundation (BHF) – grant no.FS/08/012/24454
AMT is funded by the National Institute of Health Research (NIHR), UK – grant no. SRF/08/01/018,

Disclosures

ISN has received lecture, consultant fees and educational and research support from Actelion, Pfizer, GlaxoSmithKlein and Lilly. SGH has has served on advisory boards for Actelion,
Encysive, Pfizer and GlaxoSmithKline, and has received grant support from Actelion, Encysive and GlaxoSmithKline.

References


Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>All patients (n=100)</th>
<th>Transplant free survivors (n=86)</th>
<th>Transplanted or died (n=14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</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>Female (n,%)</td>
<td>61 (61%)</td>
<td>52 (60%)</td>
<td>9 (64%)</td>
<td>1.00*</td>
</tr>
<tr>
<td>WHO (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>RSVVi (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>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 (cm/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 (standard deviation) except for age, which is median (range). Comparisons made using two sided t-test, * Fisher’s exact test, § Wilcoxon rank-sum test. Six minute walk distance (6-mwd), Right ventricular end diastolic volume index (RVEDVi), Right ventricular end systolic volume index (RVESVi), Right ventricular stroke volume index (RSVVi), Right ventricular ejection fraction (RVEF), Right ventricular mass index (RVMi), Left ventricular end diastolic volume index (LVEDVi), Left ventricular end systolic volume index (LVESVi), Left ventricular stroke volume index (LVSVi), Left ventricular ejection fraction (LVEF), Pulmonary regurgitation fraction (PRF), Tricuspid regurgitation fraction (TRF), Right atrial area index (RAAi), mid right ventricle diameter index (mRVDi), Tricuspid annular plane systolic excursion (TAPSE)
Table 2. Clinical and hemodynamic correlates

<table>
<thead>
<tr>
<th>WHO functional class</th>
<th>6-min walk distance (%) predicted</th>
<th>Estimated PA systolic pressure</th>
<th>Invasive mean PAP (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(η²) p r p</td>
<td>r p</td>
<td>r p</td>
</tr>
<tr>
<td>RVEDVi</td>
<td>0.18 &lt;0.01 -0.13 0.32</td>
<td>0.29 &lt;0.01</td>
<td>0.16 0.36</td>
</tr>
<tr>
<td>RVESVi</td>
<td>0.31 &lt;0.01 -0.28 0.03</td>
<td>0.36 &lt;0.01</td>
<td>0.46 &lt;0.01</td>
</tr>
<tr>
<td>RVSVi</td>
<td>0.16 &lt;0.01 0.46 &lt;0.01</td>
<td>-0.17 0.12</td>
<td>-0.53 &lt;0.01</td>
</tr>
<tr>
<td>RVEF</td>
<td>0.58 &lt;0.01 0.52 &lt;0.01</td>
<td>-0.41 &lt;0.01</td>
<td>-0.6 &lt;0.01</td>
</tr>
<tr>
<td>RVMi</td>
<td>0.26 &lt;0.01 -0.40 &lt;0.01</td>
<td>0.42 &lt;0.01</td>
<td>0.46 &lt;0.01</td>
</tr>
<tr>
<td>LVEDVi</td>
<td>0.16 &lt;0.01 0.29 0.02</td>
<td>-0.17 0.13</td>
<td>-0.43 0.01</td>
</tr>
<tr>
<td>LVESVi</td>
<td>0.08 0.05 0.40 0.08</td>
<td>0.49 0.29</td>
<td>0.29 0.1</td>
</tr>
<tr>
<td>LVSVi</td>
<td>0.21 &lt;0.01 0.39 &lt;0.01</td>
<td>-0.31 &lt;0.01</td>
<td>-0.47 &lt;0.01</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.11 0.01 0.16 0.24</td>
<td>-0.03 0.81</td>
<td>-0.12 0.51</td>
</tr>
<tr>
<td>PRF</td>
<td>NP</td>
<td>&lt;0.01 -0.10</td>
<td>0.42 0.10</td>
</tr>
<tr>
<td>TRF (MRI)</td>
<td>NP</td>
<td>&lt;0.01 -0.42</td>
<td>&lt;0.01 0.36</td>
</tr>
<tr>
<td>RAAi</td>
<td>0.11 0.02 -0.11 0.39</td>
<td>0.35 &lt;0.01</td>
<td>0.03 0.88</td>
</tr>
<tr>
<td>mRVDi</td>
<td>0.11 0.02 -0.11 0.42</td>
<td>0.22 0.05</td>
<td>-0.01 0.94</td>
</tr>
<tr>
<td>TAPSE z-score</td>
<td>0.08 0.05 0.21 0.11</td>
<td>-0.09 0.41</td>
<td>-0.38 0.03</td>
</tr>
</tbody>
</table>

(NP) = non-parametric Kruskal Wallis test. Right ventricular end diastolic volume index (RVEDVi), Right ventricular end systolic volume index (RVESVi), Right ventricular stroke volume index (RVSVi), Right ventricular ejection fraction (RVEF), Right ventricular myocardial mass index (RVMi), Left ventricular end diastolic volume index (LVEDVi), Left ventricular end systolic volume index (LVESVi), Left ventricular stroke volume index (LVSVi), Left ventricular ejection fraction (LVEF), Peak right atrial pressure (PRAA), Mean right ventricular diastolic pressure (mRVDi), Tricuspid annular plane systolic excursion (TAPSE z-score).
ejection fraction (RVEF), Right ventricular mass index (RVMi), Left ventricular end diastolic volume index (LVEDVi), Left ventricular end systolic volume index (LVESVi), Left ventricular stroke volume index (LVSVi), Left ventricular ejection fraction (LVEF), Pulmonary regurgitation fraction (PRF), Tricuspid regurgitation fraction (TRF), Right atrial area index (RAAi), mid right ventricle diameter index (mRVDi), Tricuspid annular plane systolic excursion (TAPSE).
Table 3. Univariate Cox proportional analysis Hazard ratio (HR) per SD increase in parameter being tested

<table>
<thead>
<tr>
<th></th>
<th>Death (n=11)</th>
<th>Death or transplant (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
</tr>
<tr>
<td>6-mwd (% predicted)(n=59)</td>
<td>0.67 (0.25-1.80)</td>
<td>0.42</td>
</tr>
<tr>
<td>HR(% max)</td>
<td>1.80 (1.34-2.44)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVEDVi</td>
<td>1.78 (1.23-2.80)</td>
<td>0.01</td>
</tr>
<tr>
<td>RVESVi</td>
<td>1.95 (1.27-2.99)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVSVi</td>
<td>0.55 (0.29-1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>RVEF</td>
<td>0.39 (0.23-0.68)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVMi</td>
<td>1.99 (1.24-3.20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDVi</td>
<td>0.69 (0.36-1.31)</td>
<td>0.26</td>
</tr>
<tr>
<td>LVESVi</td>
<td>1.14 (0.67-1.94)</td>
<td>0.62</td>
</tr>
<tr>
<td>LVSVi</td>
<td>0.40 (0.20-0.82)</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.65 (0.39-1.10)</td>
<td>0.10</td>
</tr>
<tr>
<td>PRF</td>
<td>1.36 (0.96-1.93)</td>
<td>0.08</td>
</tr>
<tr>
<td>TRF</td>
<td>1.68 (1.10-2.55)</td>
<td>0.02</td>
</tr>
<tr>
<td>RAAi</td>
<td>1.84 (1.11-3.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>mRVDi</td>
<td>2.23 (1.45-3.42)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TAPSE (z)</td>
<td>0.88 (0.69-1.11)</td>
<td>0.28</td>
</tr>
<tr>
<td>Est sPAP</td>
<td>1.25 (0.71-2.21)</td>
<td>0.44</td>
</tr>
<tr>
<td>mPAP (n=33)</td>
<td>1.60 (0.56-4.42)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

(95% Confidence interval). Right ventricular end diastolic volume index (RVEDVi), Right ventricular end systolic volume index (RVESVi), Right ventricular stroke volume index (RVSVi), Right ventricular ejection fraction (RVEF), Right ventricular mass index (RVMi), Left ventricular end diastolic volume index (LVEDVi), Left ventricular end systolic volume index (LVESVi), Left ventricular stroke volume index (LVSVi), Left ventricular ejection fraction (LVEF), Pulmonary regurgitation fraction (PRF), Tricuspid regurgitation fraction (TRF), Right atrial area index (RAAi), mid right ventricle diameter index (mRVDi), Tricuspid annular plane systolic excursion (TAPSE), Doppler derived estimated pulmonary artery systolic pressure (est sPAP), invasively measured mean pulmonary artery pressure (mPAP).
Figure Legends

Figure 1. Representative examples of A) retropectively gated cine image (breath hold), and B) real time (free breathing) from short axis in a 12-year old and 8-year old child respectively.

Figure 2. Kaplan-Meier survival curves for: A) WHO function class and cardiac MRI and echocardiographic variables by tertile. B) right ventricular end diastolic volume index, C) right ventricular end systolic volume index, D) right ventricular ejection fraction, E) left ventricular stroke volume index, F) right ventricular mass index, G) tricuspid regurgitation fraction, H) mid right ventricular diameter and I) right atrial area index.
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Circ Cardiovasc Imaging. published online April 9, 2013;
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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