Pulmonary Arterial Hypertension

Prognostic Value of Cardiovascular Magnetic Resonance Imaging Measurements Corrected for Age and Sex in Idiopathic Pulmonary Arterial Hypertension

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Background—There are limited data on the prognostic value of cardiovascular magnetic resonance measurements in idiopathic pulmonary arterial hypertension, with no studies investigating the impact of correction of cardiovascular magnetic resonance indices for age and sex on prognostic value.

Methods and Results—Consecutive patients with idiopathic pulmonary arterial hypertension underwent cardiovascular magnetic resonance imaging at 1.5T. Steady-state free precession cardiac volumes and mass measurements were corrected for age, sex, and body surface area according to reference data and prognostic significance assessed. A total of 80 patients with idiopathic pulmonary arterial hypertension were identified, and 23 patients died during the mean follow-up of 32±14 months. Corrected for age, sex, and body surface area, right ventricular end-systolic volume (P=0.004) strongly predicted mortality, independent of World Health Organization functional class, mean right atrial pressure, cardiac index, and mixed venous oxygen saturations.

Conclusions—Consideration should be given to correcting cardiovascular magnetic resonance measurements for age, sex, and body surface area, particularly given the changing demographics of patients with idiopathic pulmonary arterial hypertension. Corrected right ventricular end-systolic volume is a strong prognostic marker in idiopathic pulmonary arterial hypertension, independent of invasively derived measurements, mean right atrial pressure cardiac index, and mixed venous oxygen saturations. (Circ Cardiovasc Imaging. 2014;7:100-106.)

Key Words: heart ventricles ■ hypertension, pulmonary ■ magnetic resonance imaging ■ prognosis

Received April 6, 2013; accepted November 8, 2013.
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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org
DOI: 10.1161/CIRCIMAGING.113.000338
Methods

Patients

Consecutive treatment-naïve patients with IPAH who underwent MRI and right heart catheterization (RHC), within 48 hours, were identified from a database of a large volume, nationally designated, pulmonary hypertension referral center from January 1, 2008, to November 2011. A census was performed on December 17, 2012, providing a minimum of 1 year follow-up from scan date. Patients referred with suspected pulmonary hypertension underwent systematic evaluation as previously described in the Assessing the Spectrum of Pulmonary Hypertension Identified At a Referral Centre (ASPIRE) registry, including lung function, exercise testing, high resolution computed tomography and computed tomographic pulmonary angiography, CMR and MR angiography, and RHC. This study was approved by our institutional review committee, and informed consent was waived for this retrospective study.

CMR Image Acquisition

CMR imaging was performed using an 8-channel cardiac coil on a GE HDx (GE Healthcare, Milwaukee, WI) whole body scanner at 1.5T. Short-axis cine images were acquired using a cardiac gated multislice balanced steady-state free precession sequence (20 frames per cardiac cycle; field of view, 48; matrix, 256×256; bandwidth, 125 KHz/pixel; repetition time/echo time, 3.7/1.6 ms). A stack of images in the short-axis plane with slice thickness of 8 mm (2-mm interslice gap) were acquired fully covering both ventricles from base to apex. End-systole was considered to be the smallest cavity area. End-diastole was defined as the first cine phase of the R-wave triggered acquisition. Patients were in the supine position with a surface coil and with retrospective ECG gating.

Image Analysis

Image analysis was performed on a GE Advantage Workstation 4.1 with the observer blinded to the patient clinical information and cardiac catheter parameters. Right and left endocardial and epicardial surfaces were manually traced from the stack of short-axis cine images using our MR workstation software to obtain RV end-diastolic (RVEDV) and end-systolic (RVESV) and LV end-diastolic (LVEDV) and end-systolic volumes (LVESV). From end-diastolic volume and end-systolic volumes, RV and LV ejection fraction (RVEF and LVEF) and RV and LV stroke volume (RVSV and LVSV) were calculated. Cardiac volumes but not RVEF and LVEF were indexed for BSA. For calculation of ventricular mass, the interventricular septum was considered as part of the LV. The RV myocardial volume was calculated by multiplying the area of the RV wall on each slice by the interslice distance. The product of the sum total of myocardial slice volumes for the RV and the density of myocardium (1.05 g/cm3) gave an estimate of RV mass. Ventricular mass index (VMI) was defined as RV mass divided by LV mass, as previously described.

RHC

RHC was performed using a balloon-tipped 7.5 Fr thermodilution catheter (Becton-Dickinson, Franklin Lakes, NJ). RHC was usually performed via the internal jugular vein using a Swan-Ganz catheter. Features at RHC required to define IPAH were mean pulmonary arterial pressure (mPAP) ≥25 mm Hg at rest with a pulmonary capillary wedge pressure (PCWP) of ≤15 mm Hg. Pulmonary vascular resistance index (PVRI) was determined as follows: PVRI=(80×(mPAP–PCWP)/cardiac index (CI)).

Statistics

CMR volumetric measurements indexed for BSA were corrected for age and sex and presented as percentage (%) predicted. To establish predicted values for corrected cardiac volumes, regression equations were generated for age and sex from healthy volunteers on previously published reference data, for example, corrected RVEDVI (%)=RVEDVI/predicted RVEDVI×100. The interval from evaluation with CMR until all-cause death or census was considered as the follow-up period. Log-log plots were produced for each variable to assess proportional hazards; continuous variables were dichotomized, with an even number of deaths in each group for this analysis. The prognostic value of CMR-derived volumetric measurements, phase contrast indices, invasive hemodynamic measurements, mPAP, mean right atrial pressure (mRAP), cardiac output, PVRI, mixed venous oxygen saturation (mVO2), and patient age, sex, and World Health Organisation (WHO) functional class (dichotomized into WHO groups II and II versus WHO group IV) were assessed using univariate Cox proportional hazards regression analysis. Bivariate analysis was performed for RV indices significant at univariate analysis (P<0.2), on significant covariates, and a regression of CMR indices on outcome adjusting for both age and sex was performed. Kaplan–Meier analysis was used to assess the prognostic value of CMR volumetric measurements using median threshold values. CMR variable rescaling was performed for secondary Cox proportional hazards analysis to improve ease of interpretation of Hazard ratios. Rescaling was performed by dividing individual CMR values by the standard deviation of the variable. A P value ≤0.05 was considered statistically significant; the P values are 2-sided. Statistical analysis was performed using SPSS 19 (SPSS, Chicago, IL), and for presentation of the data, GraphPad Prism 5.05 (GraphPad Software, San Diego, CA) software was used.

Table 1. Demographics, Right Heart Catheter, and Cardiac MRI Value for Survivors and Nonsurvivors

<table>
<thead>
<tr>
<th>All patients</th>
<th>N=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>59±17</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>48/32</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>IV (18), III (48), II (14)</td>
</tr>
<tr>
<td>RHC</td>
<td></td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>53±11</td>
</tr>
<tr>
<td>mRAP, mm Hg</td>
<td>11±5</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>10±3</td>
</tr>
<tr>
<td>PVRI, dyn.s.cm–5.m2</td>
<td>1449±599</td>
</tr>
<tr>
<td>CI, L/min per m2</td>
<td>2.6±0.8</td>
</tr>
<tr>
<td>Mixed venous O2, %</td>
<td>62±8.7</td>
</tr>
<tr>
<td>CMR phase contrast</td>
<td></td>
</tr>
<tr>
<td>PA stroke volume index, mL/m2</td>
<td>35±15</td>
</tr>
<tr>
<td>PA cardiac index, L/min per m2</td>
<td>2.7±1.1</td>
</tr>
<tr>
<td>Corrected cardiac MR</td>
<td></td>
</tr>
<tr>
<td>RVEDV index, %</td>
<td>136±40</td>
</tr>
<tr>
<td>RVESV index, %</td>
<td>301±121</td>
</tr>
<tr>
<td>RVEF, %†</td>
<td>45±20</td>
</tr>
<tr>
<td>RVSV index, %</td>
<td>61±38</td>
</tr>
<tr>
<td>LVEDV index, %</td>
<td>63±17</td>
</tr>
<tr>
<td>LVESV index, %</td>
<td>74±28</td>
</tr>
<tr>
<td>LVEF, %†</td>
<td>92±15</td>
</tr>
<tr>
<td>LVSV index, %</td>
<td>58±18</td>
</tr>
<tr>
<td>VMI, (ratio)†</td>
<td>0.9±0.3</td>
</tr>
</tbody>
</table>

*Cardiac magnetic resonance (CMR) measurements are presented corrected for age, sex, and body surface area (BSA). CI indicates cardiac index; LVEDV, left ventricular (LV) end-diastolic volume; LV EF, LV ejection fraction; LVSV, LV end-systolic volume; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RHC, right heart catheterization; RV, right ventricle; RV EF, RV ejection fraction; RVSV, RV end-systolic volume; RVSV, RV stroke volume; VMI, ventricular mass index; and WHWHO, World Health Organisation.†% predicted by age, sex. For example, RVEDV index predicted by age and sex/RVEDVI×100.
Results

Patients
A total of 109 patients were identified fitting the diagnostic criteria for IPAH: 81 patients had undergone RHC and MRI within 48 hours, and 1 patient was excluded because the imaging was of nondiagnostic quality and precluded volumetric analysis. Thus, 80 patients with IPAH were included in the study. During a mean follow-up of 32 months (standard deviation 14 months), 23 patients died. Baseline hemodynamic, demographic, and CMR data for all patients, survivors, and nonsurvivors are shown in Table 1.

Cox Proportional Hazards Survival Analysis

Demographics and Hemodynamics
Age, WHO functional class, right atrial pressure, cardiac index, and mixed venous oxygen saturation were all univariate predictors of mortality (Table 2).

CMR Indices Indexed for BSA. Table 3 presents Cox proportional hazards regression analysis results for scaled CMR indices. RVESVI and RVEDVI did not predict mortality when uncorrected for age and sex, $P=0.140$ and $P=0.259$, respectively. In addition, RVEF when uncorrected did not significantly predict an adverse outcome ($P=0.336$). LVSVI was the only CMR measurement without correction for age and sex that predicted adverse outcome ($P=0.023$) at univariate analysis. We performed a regression of CMR indices indexed for BSA on outcome, adjusting for age and sex, and found RVESVI and LVSVI to be a significant predictor of adverse outcome ($P=0.040$) and ($P=0.023$), respectively.

CMR Indices Corrected for Age, Sex, and BSA. RVESV when corrected was a CMR predictor of mortality ($P=0.004$). Corrected measurements of RVEDV ($P=0.078$) and RVEF ($P=0.187$) did not predict adverse outcome. Ventricular mass index was not of prognostic significance ($P=0.960$). Corrected LVSV was the only LV measurement that predicted an adverse outcome ($P=0.048$).

At bivariate analysis, corrected RVESV was associated with mortality independent of WHO functional class ($P=0.001$), mRAP (0.041), CI ($P=0.042$), and mixed venous oxygen saturations (mV02; $P=0.018$) (see Table 4).

Table 3. Cox Proportional Hazards Analysis Is Presented for scaled CMR Volumes Indexed for BSA, Corrected for BSA, Age, and Sex

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>$P$ Value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDV 1.213 (0.868 to 1.695)</td>
<td>0.259</td>
<td>1.318 (0.969 to 1.791)</td>
</tr>
<tr>
<td>RVESV 1.315 (0.914 to 1.893)</td>
<td>0.140</td>
<td>1.551 (1.152 to 2.087)</td>
</tr>
<tr>
<td>RVEF* 0.823 (0.554 to 1.224)</td>
<td>0.336</td>
<td>0.783 (0.511 to 1.140)</td>
</tr>
<tr>
<td>RVSV 0.847 (0.060 to 11.858)</td>
<td>0.902</td>
<td>0.999 (0.676 to 1.476)</td>
</tr>
<tr>
<td>LVEDV 0.694 (0.431 to 1.118)</td>
<td>0.133</td>
<td>0.828 (0.532 to 1.288)</td>
</tr>
<tr>
<td>LVE SV 1.024 (0.680 to 1.540)</td>
<td>0.911</td>
<td>1.231 (0.837 to 1.811)</td>
</tr>
<tr>
<td>LVEF* 0.813 (0.549 to 1.205)</td>
<td>0.302</td>
<td>0.766 (0.519 to 1.132)</td>
</tr>
<tr>
<td>LVSV 0.588 (0.369 to 0.936)</td>
<td>0.025</td>
<td>0.631 (0.400 to 0.995)</td>
</tr>
</tbody>
</table>

Scaling was performed by dividing the mean by the SD for each metric. BSA indicates body surface area, HR, hazard ratio; LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; LVSV, LV stroke volume; mRAP, mean right arterial pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right arterial pressure; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RHC, right heart catheterization; RVEDV, RV end-diastolic volume; RVEF, RV ejection fraction; RVESV, RV end-systolic volume; RVSV, RV stroke volume; VMI, ventricular mass index; and WHO, World Health Organisation.

*RVEF, LVEF, and VMI are not indexed for BSA.
Kaplan–Meier plots for CMR measurements corrected for age, sex, and BSA and simply indexed for BSA are presented in Figures 1–4. Corrected RVESV above the median value of 292% predicted was associated with significantly worse outcome (P=0.002). When indexed for BSA, RVESV did not predict mortality at Kaplan–Meier analysis (P=0.257). Corrected LV stroke volume less than the median value of 56% predicted was strongly linked to adverse outcome (P=0.007). However, LVEDV and LVESV measurements did not significantly predict adverse outcome (P=0.083 and P=0.356, respectively). Ventricular mass index was not associated with adverse outcome (P=0.952).

**Discussion**

This study has shown that correction of CMR parameters for age and sex impacts on the prognostic value of RV and LV metrics. We have demonstrated that RVESV corrected for age, sex, and BSA is strongly associated with adverse outcome in newly diagnosed patients with IPAH. We have also shown that the prognostic significance of corrected RVESV is independent of invasive predictors of outcome, namely, mRAP, CI, and mVO2.

Van Wolferen et al9 studied the prognostic value of CMR measurements indexed for BSA in 64 patients with IPAH. They found baseline RVEDV and progressive RV enlargement were associated with an adverse outcome. Our study has corrected CMR measures for age and sex as recommended by Maceira et al11 and demonstrates that corrected RVESV is a stronger predictor of adverse outcome than RVEDV. Increased RVESV implies enlargement of the RV in combination with a loss of systolic function and may explain the greater prognostic significance of RVESV over RVEDV. Our findings are reflected in work by van de Veerdonk et al,20 in which RVESV but not RVEDV measurements significantly predicted mortality at baseline in patients with PAH. These studies highlight the adverse prognostic impact of RV volumetric measurements in patients with PAH. Correction for age and sex when interpreting CMR volumetric measurements may be particularly important because the average age of patients with IPAH is significantly higher than in previous studies, and a reduction in cardiac volumes with advancing years may act to minimize the prognostic value of this measure.21

Several studies have highlighted the prognostic value of cardiac output and stroke volume in the evaluation of patients with pulmonary arterial hypertension.9,22–25The present study highlights the importance of making volumetric estimates of stroke volume from the left rather than RV (Figure 4). Previous investigators have already suggested that left-sided estimates of stroke volume are mandatory,26 although this is the first article to directly compare RV and LV volumetric measurements of stroke volume. Using RV volumetry to estimate cardiac output has been shown previously to be a poor marker of the forward flow from the RV in pulmonary hypertension possibly reflecting difficulties in accurate border detection and RV trabeculations, although the loss of forward contribution to cardiac output may also be important.

Low LVEDV as a predictor of mortality at Kaplan–Meier analysis was of borderline statistical significance (P=0.083). Previous studies have shown that low LVEDV is a predictor of

![CMR indices corrected for body surface area only](image1)

![CMR indices corrected for age, gender and body surface area](image2)

**Table 4. Bivariate Cox Proportional Hazards Regression Analysis of Scaled and Corrected RVESV on Covariates**

<table>
<thead>
<tr>
<th>Bivariate Analysis</th>
<th>Hazard Ratio of RVESV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO functional class</td>
<td>1.513 (1.074 to 2.132)</td>
<td>0.018</td>
</tr>
<tr>
<td>mRAP</td>
<td>1.438 (1.014 to 2.037)</td>
<td>0.041</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>1.417 (1.013 to 1.984)</td>
<td>0.042</td>
</tr>
<tr>
<td>mVO2</td>
<td>1.492 (1.084 to 2.053)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

mRAP indicates mean right arterial pressure; mVO2, mixed venous oxygen saturations; RVESV, right ventricular end-systolic volume; and WHO, World Health Organisation.

[Figure 1. Kaplan–Meier plots showing the prognostic value of cardiovascular magnetic resonance right ventricular volume indices indexed for body surface area (BSA) alone (left) and corrected for age, sex, and BSA (right).]
adverse outcome in IPAH and PAH cohorts; the likely mechanistic explanations include underfilling of the LV because of reduced blood flow or compression of the LV cavity because of RV pressure overload.9

van de Veerdonk et al.20 has shown that baseline measurement of RVEF predicts mortality in a heterogeneous group of patients with PAH, and an improvement in RVEF at follow-up has been associated with better outcome independent of PVR. In contrast, van Wolferen et al.9 did not demonstrate any prognostic value of RVEF at baseline in IPAH. In our study, RVEF when corrected for age and sex did not reach statistical significance ($P=0.09$). This possibly reflects the sample size and also the differing populations of patients included in studies.

The mechanisms underlying the impact of increasing age and sex on the outcome of patients with PAH and specifically how this may relate to RV modeling are not clear. An animal study has shown that the LV of female rats adapts more favorably to volume overload than males. In contrast to males, in female rats, volume overload leads to concentric LV hypertrophy, yet there is minimal ventricular dilatation and no change in myocardial compliance, with females showing less frequent progression to heart failure. The ability of female rats to develop appropriate concentric hypertrophy is sufficient to maintain a stable compensated state preventing the development of ventricular dilatation and congestive heart failure.27 Whether this is the case in the RV is not known but clearly remains a possibility. Interestingly,
in patients with IPAH, females are at a higher risk of developing pulmonary hypertension, but women seem to have better RV function and improved survival compared with men with IPAH. Ventetuolo et al.,28 in a large study of patients with no known cardiovascular disease, have shown that higher levels of estradiol are associated with better RV systolic function in postmenopausal women using hormone therapy. In addition, higher levels of androgens are associated with greater RV mass and larger RV volumes in men and postmenopausal women. There are little data in the published literature on the impact of age on RV function, but one may postulate that the ventricle may have a reduced ability to remodel in the setting of an increase in RV afterload.

In stratifying patients within a population for disease severity, adjusting for important variables such as age and sex may be helpful in more accurately identifying patients with a poor prognosis who may benefit from more intensive therapy at the time of diagnosis. In addition, it may be helpful in making outcome comparisons between different pulmonary hypertension centers where patient demographics may vary. However, the use of the presented corrected MR volumetric measurements will be minimized when using MRI to follow up treatment response in an individual patient.

Limitations
The major limitation of this work is the comparison to data from a reference normal population and the relatively small number of subjects (n=120) from which the regression equations were derived to allow correction for age and sex. However, in our view, the study by Maceira et al.11 as a comparative cohort provides the most well-defined normal population in which we were able to derive regression equations to adjust for age and sex. The absence of other comparable normal populations that have measured MR variables using the same methodology as we have, particularly with regard to the inclusion or exclusion of trabeculae in RV mass and volume measurements, means that our reference equation is based on a small albeit well-defined reference population structure. More work to establish a larger cohort of normals to improve the confidence of correction is required. Validation of our observations in prospective studies at other centers would be helpful. Given the small number of deaths, we have used a bivariate rather than a multivariate Cox proportional hazards model. All data in this study were from the baseline assessment of patients with IPAH. Further work studying MRI predictors at follow-up would be of value in future studies.

Conclusions
In patients with IPAH, corrected RVESV predicts mortality more strongly than RVEDV and has prognostic value independent of mRAP, CI, and mVO2. Adjusting volumetric cardiac magnetic resonance measurements for patient age, sex, and BSA should be considered given the changing demographics and increasing age at diagnosis of patients with IPAH.

Sources of Funding
A.J. Swift, R. Condliffe, C. Elliot, J.M. Wild, and D.G. Kiely have received funding from the National Institute for Health Research via its Biomedical Research Units funding scheme. J.M. Wild is also funded by the Engineering and Physical Sciences Research Council. D. Capener receives funding from Bayer Schering, S. Rajaram from Pfizer, and J. Hurdman from Actelion Pharmaceuticals.

Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Cardiac volumes, indexed to body surface, have been shown to have prognostic value in patients with pulmonary hypertension. However, these volumes not only vary with body size but also with age and sex. In this study, we demonstrate that transformation of magnetic resonance imaging variables using a normal reference population influences their clinical significance. Corrected right ventricular end-systolic volume is a strong predictor of outcome in patients with idiopathic pulmonary arterial hypertension independent of invasive hemodynamic indices. Correcting volumetric cardiac magnetic resonance measurements for patient age, sex, and body surface area should be considered in patients with idiopathic pulmonary hypertension.
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Circ Cardiovasc Imaging. 2014;7:100-106; originally published online November 25, 2013; doi: 10.1161/CIRCIMAGING.113.000338
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

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