Pulmonary Arterial Hypertension

Changes in Right Ventricular Function Measured by Cardiac Magnetic Resonance Imaging in Patients Receiving Pulmonary Arterial Hypertension–Targeted Therapy
The EURO-MR Study

Andrew J. Peacock, MD; Stephen Crawley, MB, ChB; Lindsey McLure, MB, ChB; Kevin G. Blyth, MD; Carmine Dario Vizza, MD; Roberto Foscia, MD, PhD; Marco Francone, MD, PhD; Ilaria Iacucci, MD; Horst Olschewski, MD; Gabor Kovacs, MD; Anton vonk Noordegraaf, MD; J. Tim Marcus, PhD; Marielle C. van de Veerdonk, MD; Frank P.T. Oosterveer, MD

Background—Most measures that predict survival in pulmonary hypertension (PH) relate directly to, or correlate with, right ventricular (RV) function. Direct assessment of RV function using noninvasive techniques such as cardiac MRI may therefore be an appropriate way of determining response to therapy and monitoring disease progression in PH.

Methods and Results—In this pan-European study, 91 patients with PH (mean pulmonary arterial pressure 46±15 mm Hg) underwent clinical and cardiac MRI assessments at baseline and after 12 months of disease-targeted therapy (predominantly endothelin receptor antagonists [47.3%] or phosphodiesterase type-5 inhibitors [25.3%]). At month 12, functional class had improved in 21 patients, was unchanged in 63 patients, and had deteriorated in 7 patients. Significant improvements were achieved in RV and left ventricular ejection fraction (P<0.001 and P=0.0007, respectively), RV stroke volume index (P<0.0001), and left ventricular end-diastolic volume index (P=0.0015). Increases in 6-minute walk distance were significant (P<0.0001) and correlated with change in RV ejection fraction and left ventricular end-diastolic volume, although correlation coefficients were low (r=0.28, P=0.01 and r=0.26, P=0.02, respectively).

Conclusions—On-treatment changes in cardiac MRI–derived variables from left and right sides of the heart reflected changes in functional class and survival in patients with PH. Direct measurement of RV function using cardiac MRI can fully assess potential benefits of treatment in PH. (Circ Cardiovasc Imaging. 2014;7:107-114.)

Key Words: magnetic resonance imaging • hypertension, pulmonary • right ventricle

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological state defined as increased mean pulmonary artery pressure ≥25 mm Hg at rest (assessed by right heart catheterization [RHC]).1 PH can be precapillary (pulmonary wedge pressure ≤15 mm Hg, normal or reduced cardiac output) where the changes occur in the pulmonary arterial circulation or postcapillary (pulmonary wedge pressure >15 mm Hg) where the left ventricle (LV) or the mitral valve is likely to be involved.

Clinical Perspective on p 114

In precapillary PH, increased pressure in the pulmonary arteries overloads the right ventricle (RV), causing hypertrophy and failure.2–4 Most measures that predict survival in PH relate directly to RV function (eg, right atrial pressure and cardiac index) or correlate with measures related to RV function (eg, exercise capacity and functional class [FC]).5–7 Until recently, little was known about the RV; however, improved imaging techniques have allowed prognostic factors beyond the traditional variables of 6-minute walk distance (6MWD) and FC to be studied to identify factors more directly linked to RV function.

During the past 2 decades, several treatments targeting the pathophysiological mechanisms of pulmonary arterial hypertension (PAH) have been introduced.1 These agents have been approved largely based on improved hemodynamic variables
on RHC or improved exercise capacity (increase in 6MWD) in randomized controlled trials. Consequently, disease progression and treatment efficacy in the clinic are frequently assessed using 6MWD or RHC. Recent interest in the RV and its response to change in afterload has raised the possibility that direct assessment of RV function may be a more appropriate way of determining response to therapy and monitoring disease progression.

Noninvasive cardiac MRI (CMRI) provides a comprehensive picture of RV structure and function because it has unparalleled resolution, is reproducible, can provide 3-dimensional images, has the ability to depict soft tissues, and can be conducted in patients not suitable for echocardiography. CMRI also has benefits over RHC and is considered to be the gold standard for assessment of RV volume, mass, and function. However, uptake of CMRI in clinical practice has been limited, and although this may be partly attributable to cost, lack of published data showing its use in patients with PH, especially in those receiving treatment, may also contribute. This pan-European study of patients with PH evaluated RV function using CMRI during treatment of patients with PH.

**Methods**

As part of the EU Framework 6 Pulmotension initiative, the prospective, longitudinal European Magnetic Resonance Imaging Study in PAH study was conducted in 4 European centers: Scottish Pulmonary Vascular Unit, Glasgow, United Kingdom; Medical University Graz, Austria; Sapienza University of Rome, Rome, Italy; and Department of Pulmonary Medicine, VU University Medical Center, Amsterdam, The Netherlands. The aim of this initiative was to determine RV function changes during disease-specific therapy. The initiative complied with the widely recognized guidelines for conducting studies in humans. The study was approved by an institutional review committee, and all subjects provided written, informed consent.

Between June 2003 and May 2010, patients with suspected PH were referred to their local PH center for evaluation. Patients underwent clinical assessment, including New York Heart Association (NYHA) FC, RHC, 6MWD, and CMRI. PH was diagnosed and classified according to current guidelines and, if appropriate, disease-targeted therapy was initiated.

The initial therapy used was left to the discretion of the local PH physician. The 12-month follow-up evaluation assessment included 6MWD and CMRI. Patients from the Glasgow center also had a planned assessment (6MWD and CMRI) after 4 months of treatment.

Patients in World Health Organization (WHO) group 1, WHO group 3, or WHO group 4, if ineligible for surgery, were included in the study. Patients excluded from the analysis included those unable to attend or who declined follow-up evaluation; those who were not commenced on disease-targeted therapy after initial evaluation; those with no evidence of PH at RHC; those with PH associated with left heart disease; and those previously treated with disease-targeted therapy.

**Clinical Assessment**

The 6-minute walk test was performed at each center according to the American Thoracic Society guidelines. RHC was performed at each center according to international recommendations. This typically involved the use of a 7F triple-channel thermodilution Swan-Ganz catheter (Baxter Healthcare; Irvine, CA). All measurements were recorded with the patient in a supine position, at rest, and breathing room air. Hemodynamic variables, including pulmonary artery pressure and pulmonary artery occlusion pressure, were recorded from the traces. Cardiac output was determined using thermodilution, allowing the calculation of pulmonary vascular resistance (mean pulmonary artery pressure–pulmonary artery occlusion pressure/cardiac output).

**Statistical Analysis**

For all variables, a normal distribution was verified using histograms and Kolmogorov–Smirnov tests. For demographic, hemodynamic, and CMR variables, mean±SD were calculated. For the entire cohort, comparison between baseline and 12-month follow-up was performed using the paired t test. A repeated measure 1-way ANOVA was used to compare the mean values in the smaller Glasgow subgroup. A significance level of 5% was used in all tests. All calculations were performed using GRAPHPAD Prism (Version 5.00; GraphPad Software Inc; La Jolla, CA). All values in the subsequent results and discussion sections are presented as mean±SD unless otherwise stated.

**Results**

RHC was conducted in 107 patients with suspected PH, which was confirmed in 91 patients (Glasgow: 35; Amsterdam: 26; Rome: 17; and Graz: 13); these patients underwent assessment at baseline and after 12 months of disease-targeted therapy. Baseline characteristics for the entire cohort and by study center are summarized in Table 1. Most patients (n=71) were in WHO group 1 and had significant PH at baseline RHC. Baseline characteristics of the subgroups are provided in the Data Supplement. Medical therapy initiated at baseline is shown in Table 1. There was a significant increase in 6MWD after 12 months of disease-targeted therapy (381±127 m at baseline, 443±124 m at month 12; P<0.0001). At the 12-month follow-up, 5, 46, 36, and 4 patients were in NYHA FC I, II, III, and IV, respectively. FC
improved in 21 patients, was unchanged in 63 patients, and deteriorated in 7 patients.

**CMRI Assessment**

CMRI characteristics at baseline and after 12 months of disease-targeted therapy in the whole group (n=91) are summarized in Table 2 and provided for each study center in the Data Supplement. After 12 months of therapy, there were significant increases in RVEF (40.5±16.0% at baseline, 45.2±14.7% at month 12; \(P<0.001\)) and RV stroke volumes index (31.0±8.4 mL/m² at baseline, 35.9±9.3 mL/m² at month 12; \(P=0.001\)). Significant improvements were also noted in LVEDV index (48.4±12.9 mL/m² at baseline, 52.5±14.1 mL/m² at month 12; \(P=0.0015\)) and LVEF (66.7±11.7% at baseline, 70.3±9.8% at month 12; \(P=0.0007\)). Overall, there was no improvement or deterioration in the degree of RV dilatation (RVEDV index) or RV hypertrophy (ventricular mass index). Similar results were obtained from subanalyses of patients with PAH or when data were stratified according to baseline PAH therapy (Table 3).

**Glasgow Subgroup Analysis**

The improvements in clinical and CMRI characteristics measured at 12 months were present at 4 months in the Glasgow subgroup (Table 4). 6MWD increased significantly throughout the study (Figure 1; \(P<0.0001\)). There were also early improvements in RVEF and stroke volume index that were preserved at 12 months (Table 4). A similar pattern of improvement was observed in LVEDV
There was no overall improvement or deterioration in RV hypertrophy or RV dilatation. Analysis of interobserver variability in a subgroup of patients from the Glasgow center demonstrated lower interobserver variability for LV measures than for those in the RV (Table III in the Data Supplement). Intraobserver variability was low for volume measurements (EDV, stroke volume, and EF) but higher for mass measurements (Table IV in the Data Supplement). Variability was lower for the LV than for the RV.

### Table 3. Baseline and 12-Month Cardiac MR Variables of the Entire Cohort Group

<table>
<thead>
<tr>
<th>CMRI Variable</th>
<th>Baseline (n=91)</th>
<th>12 mo (n=91)</th>
<th>Mean Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right ventricle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV index, mL/m²</td>
<td>83.5±25.8</td>
<td>86.0±28.8</td>
<td>2.5±18.9</td>
<td>0.22</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>31.0±8.4</td>
<td>35.9±9.3</td>
<td>4.9±10.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.29±0.63</td>
<td>2.62±0.66</td>
<td>0.33±0.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>40.5±16.0</td>
<td>45.2±14.7</td>
<td>4.6±10.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mass index, g/m²</td>
<td>51.6±20.5</td>
<td>52.0±19.4</td>
<td>0.4±10.1</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Left ventricle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV index, mL/m²</td>
<td>48.4±12.9</td>
<td>52.5±14.1</td>
<td>4.1±11.8</td>
<td>0.0015</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>32.3±10.0</td>
<td>36.5±10.2</td>
<td>4.3±10.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.36±0.63</td>
<td>2.66±0.67</td>
<td>0.30±0.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>66.7±11.7</td>
<td>70.3±9.8</td>
<td>3.6±9.8</td>
<td>0.0007</td>
</tr>
<tr>
<td>Mass index, g/m²</td>
<td>50.4±12.0</td>
<td>51.5±12.7</td>
<td>1.2±6.8</td>
<td>0.11</td>
</tr>
<tr>
<td>Ventricular mass index, g/m²</td>
<td>1.04±0.37</td>
<td>1.03±0.36</td>
<td>–0.01±0.21</td>
<td>0.97</td>
</tr>
</tbody>
</table>

All data expressed as mean±SD. CMRI indicates cardiac MRI; EDV, end-diastolic volume.

By guest on October 23, 2017 http://circimaging.ahajournals.org/ Downloaded from
Association of CMRI Variables With 6MWD

Significant correlations were seen between change in 6MWD and change in RV and LVEDV, although correlation coefficients were low (Figure 2).

Discussion

This is the first multicenter study to prospectively assess the use of CMRI before and during PAH disease-specific therapy. It demonstrated that both left-sided and right-sided variables should be included when assessing cardiac function in patients with precapillary PH. In the current analysis, stroke volume index, cardiac index, and EF were associated with response when measured in either the left or the right heart. LVEDV was also associated with therapeutic response. In the past, there has been evidence that the initial benefits achieved with some disease-targeted therapies are not maintained during long-term treatment; however, the data from the Glasgow cohort demonstrate that the improvement in stroke volume index, cardiac index, and EF at month 4 was still present at month 12.

The current study is the most comprehensive to date, investigating the use of CMRI during treatment of patients with PH, and supports the data from several smaller trials studying changes in CMRI-derived variables during treatment. The Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study demonstrated that RV mass decreased significantly from baseline after 16 weeks of sildenafil treatment (n=13; \( P = 0.015 \)); although this was not observed in the 12 patients receiving bosentan, for whom there was no significant difference between treatments (\( P = 0.142 \)). Similarly, addition of sildenafil to background bosentan therapy reduced RV mass, which may be explained either by reduced RV wall stress or by an intrinsic effect on the heart. In a small single-center study, a trend toward a treatment (bosentan)-related effect on stroke volume index was seen, and there was no effect on RVEF, LVEDV, or RVEDV. This study highlighted the need for further investigation of CMRI variables associated with RV function and how they relate to variables such as 6MWD. It has also been shown previously that epoprostenol therapy lowered pulmonary vascular resistance but did not affect RV dilatation or hypertrophy.

A key advantage of this multicenter analysis was that it provided an opportunity to study the consistency of the findings in several subanalyses. Although the number of patients in each center was small and the analysis was not powered for comparison, at the majority of centers, there was a trend toward improvement or at least no deterioration in the CMRI variables significantly associated with therapeutic response in the main analysis. Similarly, when stratified for baseline PAH

### Table 4. Baseline and On-Treatment Cardiac MRI Variables in Patients With Data Available at Baseline, Month 4, and Month 12 (Glasgow Subgroup)

<table>
<thead>
<tr>
<th>CMRI Variable</th>
<th>Baseline (n=27)</th>
<th>4 mo (n=27)</th>
<th>Mean Change (Baseline to 4 mo)</th>
<th>12 mo (n=27)</th>
<th>Mean Change (Baseline to 12 mo)</th>
<th>( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV index, mL/m²</td>
<td>88.3±24.3</td>
<td>87.5±23.8</td>
<td>−0.8±12.9</td>
<td>90.1±27.3</td>
<td>2.3±18.6</td>
<td>0.61</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>27.2±7.7</td>
<td>34.7±10.7</td>
<td>7.4±8.7</td>
<td>36.0±7.5</td>
<td>8.7±8.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.00±0.41</td>
<td>2.43±0.7</td>
<td>0.43±0.67</td>
<td>2.58±0.51</td>
<td>0.59±0.68</td>
<td>0.0002</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>34.4±16.7</td>
<td>42.1±15.3</td>
<td>7.7±9.3</td>
<td>43.4±15.0</td>
<td>9.1±10.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mass index, g/m²</td>
<td>60.1±24.4</td>
<td>56.8±22.3</td>
<td>−3.3±7.6</td>
<td>58.4±21.0</td>
<td>−1.7±12.5</td>
<td>0.28</td>
</tr>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV index, mL/m²</td>
<td>45.3±10.8</td>
<td>53.8±14.9</td>
<td>8.4±10.6</td>
<td>53.4±12.9</td>
<td>8.1±10.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>28.0±8.9</td>
<td>36.6±9.5</td>
<td>8.6±8.4</td>
<td>36.7±9.8</td>
<td>8.8±9.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.04±0.48</td>
<td>2.58±0.68</td>
<td>0.54±0.61</td>
<td>2.62±0.59</td>
<td>0.58±0.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>61.4±12.7</td>
<td>68.6±7.3</td>
<td>7.2±10.8</td>
<td>69.2±10.8</td>
<td>7.7±11.4</td>
<td>0.0004</td>
</tr>
<tr>
<td>Mass index, g/m²</td>
<td>52.1±8.8</td>
<td>2.9±6.4</td>
<td>0.8±6.3</td>
<td>53.8±10.5</td>
<td>1.7±8.3</td>
<td>0.47</td>
</tr>
<tr>
<td>Ventricular mass index</td>
<td>1.16±0.43</td>
<td>1.07±0.39</td>
<td>−0.09±0.20</td>
<td>1.10±0.39</td>
<td>−0.05±0.27</td>
<td>0.16</td>
</tr>
</tbody>
</table>

All data are expressed as mean±SD. Comparison from 1-way ANOVA. CMRI indicates cardiac MRI; and EDV, end-diastolic volume.

*\( P \) values relate to the trend from baseline to month 4 and month 12.
therapy, the same variables were identified, and despite the small numbers, statistical significance was achieved. These findings demonstrate the wide applicability of CMRI for following up patients with PH.

Several therapeutic options are now available for management of patients with PAH, and prescription patterns vary between countries. In this analysis, identification of patients suitable for therapy was at the discretion of the physician, which can be seen as both a strength and limitation of the study. Because the results obtained reflect real clinical practice, the findings are likely to be pertinent for other treatment centers and may also provide insight into different treating practices. However, differences between treatments cannot be determined because the study was not designed to collect data on changes in therapy during the study duration, which is a limitation. However, the consistency of the findings when stratified by baseline PAH-specific therapy suggests that although acting via different pathways, the net effect of these treatments on pulmonary vasculature and RV function will be similar.

The use of 6MWD as a surrogate marker of outcome (in particular, mortality and morbidity) has been questioned in several recent studies. To meet the criteria as a surrogate, it needs to provide a reliable replacement for the outcome measure. A recent pooled analysis of data from 10 randomized controlled trials of PAH-specific therapies showed that although the change in 6MWD from baseline to week 12 was a mediator of the relationship between treatment and the development of a clinical event, it accounted for <25% of the total relationship. The findings of our analysis confirmed that the correlations between 6MWD and CMRI variables were weak.

It is well established that RV function is associated with outcome in patients with PAH. Factors relating to the dynamic function of the right heart (in particular, stroke volume and EF) seem to be the most linked to outcome. However, some left heart variables are known to better correlate with overall cardiac function than RV function in patients with PH. For example, LV end-diastolic volume is more closely related to stroke volume than RVEDV. This is supported by data from echocardiography studies in patients with PH that demonstrated that eccentricity index, which include LV size, is closely associated with outcome in PAH, whereas RVEDV is not.

Several groups have also demonstrated that poor LV output in PH is related to poor filling of the LV. This underfilling of the LV, a consequence of poor filling on the left side because of prolonged RV contraction time, contributes to decreased SV. For this reason, it is likely that LVEDV may be a particularly important variable because it reflects both SV and increased RV contraction time. These findings highlight the importance of LV volume measurements in patients with PH.

Echocardiography is the most frequently used noninvasive technique used to assess RV function and provides a comprehensive assessment of right heart performance. The evaluation is based on the assessment of tricuspid annular plane systolic excursion, LV eccentricity index, and degree of tricuspid regurgitation. However, well-described limitations of echocardiography include the inability to accurately estimate RV mass or volume as a result of the complex geometry of the RV. Radionuclide imaging, RHC, or measuring levels of N-terminal B-type natriuretic peptide, possibly as a marker of intravascular overload rather than a direct marker of RV function, all provide ways of measuring RV function but are either invasive or less comprehensive than CMR or both. CMRI is superior to radionuclide imaging because it does not require ionizing radiation and superior to electrocardiography because it is more sensitive. There is also some evidence to suggest that N-terminal B-type natriuretic peptide measurements reflect changes in CMRI-determined RV structure and function in patients with PH, but the potential of this noninvasive marker as a surrogate for outcome remains to be demonstrated.

The study had some limitations. The number of patients was low compared with the time span of enrollment, and this is because only a proportion of consecutive patients underwent CMRI, which could have been a result of either concerns of the patient about claustrophobia or technical problems. The inclusion criteria allowed a heterogeneous population of patients with PH to be enrolled, and, unlike previous studies, it was not restricted to patients with PAH. Although disease-specific therapy is only recommended in management guidelines for PAH, in clinical practice, these treatments are also used in WHO groups 3, 4, and 5. There was also the potential for analysis of the CMRI scans to vary between the centers; however, containing the reading of the scans to a single laboratory with a small number of observers ensured that a uniform technique for measurements and reporting was used. As demonstrated in the small subanalysis, both interobserver and intraobserver variability were low, although variability was higher in RV analyses than in those involving the LV. This reflects planimetry of the RV being more challenging than planimetry of the LV. Other variables that may be important prognostically and therapeutically were not included in the current analysis. These include pulmonary artery stiffness, pulmonary perfusion, and RV arterial coupling. Clearly, these are important variables and, as measurement techniques improve, will become part of the armory of CMRI-derived measurements used to study patients with PAH. Although it would have been valuable to determine the relationship between the CMRI variables and patient outcome, outcome data were not collected in
this study, and retrospective analysis is therefore not feasible. Future studies are required to determine whether the CMRI variables identified are associated with patient outcome.

In conclusion, this multicenter study demonstrated that the detailed CMRI assessments at baseline and during follow-up conducted in this patient cohort provide valuable information about response to PAH-specific therapy. The robust and noninvasive nature of CMRI means that the results of this study should be considered when designing future studies in PH so that CMRI variables are included as indicators of therapeutic response.

Acknowledgments
Medical writing support was provided by Liesje Quine, PhD, Elements Communications Ltd, Westerham, Kent, United Kingdom and funded by Actelion United Kingdom.

Sources of Funding
The EURO-MR study was funded by a grant from EU Framework 6 ‘Pulmotension’ initiative.

Disclosures
Dr Peacock has received honoraria for speaking at meetings (nonpromotional) from Actelion, Eli Lilly, GSK, Novartis, Pfizer, and United Therapeutics; assistance with travel to conferences from Actelion, Eli Lilly, GSK, Novartis, Pfizer, and United Therapeutics; and sits on Advisory Boards for Actelion, Eli Lilly, GSK, Novartis, and Pfizer. S. Crawley has received honoraria for speaking at meetings (nonpromotional) from Actelion; and assistance with travel to conferences from Actelion, GSK, and Pfizer. Dr Vizza has received fees for serving as a speaker, consultant, and an advisory board member from the following companies: Actelion, Dompè, GSK, and Pfizer. Dr Vizza has received fees for serving as a speaker and consultant from Dompé and Ialfarmacco. The other authors have no conflicts to report.

References
Right ventricular function has been shown to play a key role in the survival of patients with pulmonary arterial hypertension (PAH). However, little information is available about the impact that PAH-specific therapy has on right ventricular function. Although cardiac MRI provides a comprehensive picture of right ventricular structure and function, its use in clinical practice is limited, which may result, at least in part, from the lack of published data on patients with PAH. The multicentre pan-European study described here is the most comprehensive to date, investigating the use of cardiac MRI during treatment of patients with PH. It demonstrates that cardiac MRI variables (stroke volume index, cardiac index, and ejection fraction) are significantly associated with response to PAH-specific therapy. The study describes the detailed assessments required at baseline and during follow-up in this cohort of patients. We think that these data should be considered when designing future trials of PAH-specific therapy so that cardiac MRI variables are included as a marker of therapeutic response.
Changes in Right Ventricular Function Measured by Cardiac Magnetic Resonance Imaging in Patients Receiving Pulmonary Arterial Hypertension–Targeted Therapy: The EURO-MR Study

Andrew J. Peacock, Stephen Crawley, Lindsey McLure, Kevin G. Blyth, Carmine Dario Vizza, Roberto Pocchia, Marco Francone, Ilaria Iacucci, Horst Olschewski, Gabor Kovacs, Anton vonk Noordegraaf, J. Tim Marcus, Marielle C. van de Veerdom and Frank P.T. Oosterveer

Circ Cardiovasc Imaging. 2014;7:107-114; originally published online October 30, 2013;
doi: 10.1161/CIRCIMAGING.113.000629

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/7/1/107

An erratum has been published regarding this article. Please see the attached page for:
/content/10/2/e000015.full.pdf

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2013/10/30/CIRCIMAGING.113.000629.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/

The author Kevin Blyth’s name should read Kevin G. Blyth.

This correction has been made to the current online version of the article, which is available at http://circimaging.ahajournals.org/content/7/1/107.
Supplemental Material

Peacock et al. Changes in Right Ventricular Function Measured by Cardiac Magnetic Resonance Imaging in Patients Receiving Pulmonary Arterial Hypertension-targeted Therapy: The EURO-MR Study
Supplemental results

Table S1 - Patient characteristics of PAH patient subgroup

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>71</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>49 ± 15</td>
</tr>
<tr>
<td>Female : Male</td>
<td>52 : 19</td>
</tr>
<tr>
<td>Body Surface Area, mean ± SD, m²</td>
<td>1.80 ± 0.24</td>
</tr>
<tr>
<td>Aetiology PH</td>
<td></td>
</tr>
<tr>
<td>WHO Group 1</td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>42</td>
</tr>
<tr>
<td>PAH-CTD</td>
<td>15</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>4</td>
</tr>
<tr>
<td>Portopulmonary</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>26</td>
</tr>
<tr>
<td>III</td>
<td>41</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
</tr>
<tr>
<td>Initial Medication</td>
<td></td>
</tr>
<tr>
<td>Endothelin Receptor Antagonist</td>
<td>34</td>
</tr>
<tr>
<td>Phosphodiesterase-5 Inhibitor</td>
<td>16</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>8</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>4</td>
</tr>
<tr>
<td>Prostanoid</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
</tr>
<tr>
<td>Baseline Haemodynamics</td>
<td></td>
</tr>
<tr>
<td>Mean PAP, mean ± SD, mmHg</td>
<td>46 ± 15</td>
</tr>
<tr>
<td>PVR, Wood Units</td>
<td>10.0 ± 6.7</td>
</tr>
<tr>
<td>Cardiac Index, L/min/m²</td>
<td>2.5 ± 0.9</td>
</tr>
<tr>
<td>6MWT, mean ± SD, m</td>
<td>390 ± 121</td>
</tr>
</tbody>
</table>

6MWT = 6-min walk test; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; WHO = World Health Organization.
Table S2. Baseline and Month 12 CMRI variables by study center

<table>
<thead>
<tr>
<th></th>
<th>Glasgow (n=35)</th>
<th>Amsterdam (n=26)</th>
<th>Rome (n=17)</th>
<th>Graz (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Months</td>
<td>Baseline</td>
<td>12 Months</td>
</tr>
<tr>
<td><strong>Right ventricle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV index (ml/m²)</td>
<td>86 ± 23</td>
<td>90 ± 29</td>
<td>84 ± 29</td>
<td>83 ± 28</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>29 ± 8</td>
<td>37 ± 8*</td>
<td>32 ± 8</td>
<td>34 ± 8</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.1 ± 0.4</td>
<td>2.6 ± 0.5*</td>
<td>2.6 ± 0.7</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>37 ± 17</td>
<td>45 ± 15*</td>
<td>42 ± 15</td>
<td>43 ± 15</td>
</tr>
<tr>
<td>Mass index (g/m²)</td>
<td>55 ± 23</td>
<td>55 ± 21</td>
<td>49 ± 20</td>
<td>50 ± 18</td>
</tr>
<tr>
<td><strong>Left ventricle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV index (ml/m²)</td>
<td>47 ± 11</td>
<td>54 ± 13*</td>
<td>47 ± 14</td>
<td>48 ± 14</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>30 ± 9</td>
<td>37 ± 9*</td>
<td>33 ± 10</td>
<td>34 ± 10</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.1 ± 0.5</td>
<td>2.6 ± 0.5</td>
<td>2.6 ± 0.7</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>63 ± 12</td>
<td>69 ± 10*</td>
<td>71 ± 9</td>
<td>73 ± 9</td>
</tr>
<tr>
<td>Mass index (g/m²)</td>
<td>51 ± 9</td>
<td>53 ± 10</td>
<td>47 ± 10</td>
<td>46 ± 11</td>
</tr>
</tbody>
</table>

* P<0.01 from baseline to Month 12
Table S3. Inter-observer variability data collected from 24 patients who completed the EURO-MR study at the Glasgow center.

<table>
<thead>
<tr>
<th></th>
<th>Mean difference ± SD</th>
<th>Paired t-test (observer 1 vs. observer 2)</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction (%)</td>
<td>-1.7 ± 7.4</td>
<td>0.27</td>
<td>0.81</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>1.2 ± 9.5</td>
<td>0.56</td>
<td>0.96</td>
</tr>
<tr>
<td>LV stroke volume (mL)</td>
<td>-0.3 ± 7.1</td>
<td>0.82</td>
<td>0.97</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>-8.2 ± 17.7</td>
<td>0.04</td>
<td>0.83</td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>0.8 ± 5.2</td>
<td>0.45</td>
<td>0.94</td>
</tr>
<tr>
<td>RV end-diastolic volume (mL)</td>
<td>-11.6 ± 17.1</td>
<td>0.003</td>
<td>0.93</td>
</tr>
<tr>
<td>RV stroke volume (mL)</td>
<td>-4.2 ± 5.5</td>
<td>0.001</td>
<td>0.98</td>
</tr>
<tr>
<td>RV mass (g)</td>
<td>13.7 ± 14.1</td>
<td>0.0002</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Note that measure of end-diastolic volume, stroke volume and mass are not indexed for body surface index. SD, standard deviation; LV, left ventricular; RV, right ventricular.
Table S4. Intra-observer variability data from the EURO-MR study from 10 patients at the Glasgow center selected at random. Scans were reanalysed blinded to the initial results.

<table>
<thead>
<tr>
<th></th>
<th>Mean difference ± SD</th>
<th>Paired t-test (1st analysis vs. 2nd analysis)</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction (%)</td>
<td>-1.2 ± 2.7</td>
<td>0.21</td>
<td>0.98</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>-0.2 ± 1.8</td>
<td>0.77</td>
<td>0.99</td>
</tr>
<tr>
<td>LV stroke volume (mL)</td>
<td>-1.3 ± 2.6</td>
<td>0.14</td>
<td>0.99</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>-5.4 ± 4.9</td>
<td>0.007</td>
<td>0.99</td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>-0.8 ± 3.0</td>
<td>0.40</td>
<td>0.98</td>
</tr>
<tr>
<td>RV end-diastolic volume (mL)</td>
<td>-0.1 ± 6.3</td>
<td>0.96</td>
<td>0.99</td>
</tr>
<tr>
<td>RV stroke volume (mL)</td>
<td>-1.2 ± 2.9</td>
<td>0.21</td>
<td>0.98</td>
</tr>
<tr>
<td>RV mass (g)</td>
<td>6.7 ± 10.2</td>
<td>0.07</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Note that measure of end-diastolic volume, stroke volume and mass are not indexed for body surface index. SD, standard deviation; LV, left ventricular; RV, right ventricular.