Eisenmenger syndrome (ES) shares many aspects of the clinical and hemodynamic alterations and pulmonary microvascular changes with other forms of pulmonary arterial hypertension (PAH). However, patients with ES seem to have a better prognosis compared especially with those with idiopathic PAH. A common cause of death in patients with PAH, other than ES, is right ventricular (RV) failure as a consequence of the inability of the RV to cope with increased afterload. In ES, in contrast, it has been suggested that the RV is better adapted to increased afterload, having been exposed to volume and pressure overload since birth. Furthermore, regression of the physiological RV hypertrophy present at birth does not occur in some patients, particularly those with post-tricuspid shunts. Despite these potentially beneficial adaptive mechanisms, heart failure is not an uncommon cause of death in patients with ES; furthermore, patients with ES have a significantly decreased life expectancy compared with healthy controls.

**Background**—Patients with Eisenmenger syndrome (ES) have better survival, despite similar pulmonary vascular pathology, compared with other patients with pulmonary arterial hypertension. Cardiovascular magnetic resonance (CMR) is useful for risk stratification in idiopathic pulmonary arterial hypertension, whereas it has not been evaluated in ES. We studied CMR together with other noninvasive measurements in ES to evaluate its potential role as a noninvasive risk stratification test.

**Methods and Results**—Between 2003 and 2005, 48 patients with ES, all with a post-tricuspid shunt, were enrolled in a prospective, longitudinal, single-center study. All patients underwent a standardized baseline assessment with CMR, blood test, echocardiography, and 6-minute walk test and were followed up for mortality until the end of December 2013. Twelve patients (25%) died during follow-up, mostly from heart failure (50%). Impaired ventricular function (right or left ventricular ejection fraction) was associated with increased risk of mortality (lowest quartile: right ventricular ejection fraction, <40%; hazard ratio, 4.4 [95% confidence interval, 1.4–13.5]; \( P = 0.01 \) and left ventricular ejection fraction, <50%; hazard ratio, 6.6 [95% confidence interval, 2.1–20.8]; \( P = 0.001 \)). Biventricular impairment (lowest quartile left ventricular ejection fraction, <50% and right ventricular ejection fraction, <40%) conveyed an even higher risk of mortality (hazard ratio, 8.0 [95% confidence interval, 2.5–25.1]; \( P = 0.0004 \)). No other CMR or noninvasive measurement besides resting oxygen saturation (hazard ratio, 0.90 [0.83–0.97]/%; \( P = 0.007 \)) was associated with mortality.

**Conclusions**—Impaired right, left, or biventricular systolic function derived from baseline CMR and resting oxygen saturation are associated with mortality in adult patients with ES. CMR is a useful noninvasive tool, which may be incorporated in the risk stratification assessment of ES during lifelong follow-up. **(Circ Cardiovasc Imaging. 2015;8:e003596. DOI: 10.1161/CIRCIMAGING.115.003596.)**

Key Words: Eisenmenger syndrome ■ follow-up studies ■ magnetic resonance imaging ■ mortality
individual basis is needed for risk stratification, to assist with initiation of drug therapy, and subsequently for deciding about escalation of therapy and ultimately potentially listing for heart and lung transplantation. Cardiovascular magnetic resonance (CMR) has been implemented in the noninvasive evaluation of idiopathic PAH because of its superiority in assessing RV volumes and systolic function compared with echocardiography and its proven ability to predict mortality in prospective studies in both adults and children with various forms of PAH. In contrast, the value of CMR-derived assessment of cardiovascular function in ES remains unknown. We aimed to evaluate CMR in ES and its potential role in the noninvasive clinical risk assessment of patients with ES.

Methods

Patients and Study Design
Consecutively, clinically stable adults with Eisenmenger physiology were invited to participate and underwent the same day baseline investigations between 2003 and 2005. The study was conducted according to the declaration of Helsinki. The UK local research ethics committee approved the study [03-162] [04-044]. All patients/guardians gave written informed consent before participation.

Eisenmenger physiology was defined as a known intracardiac or extracardiac nonrestrictive defect, with increased pulmonary vascular resistance and reversed or bidirectional shunt resulting in hypoxemia. Patients with learning difficulties with capacity to consent and patients whose parent or guardian gave consent on their behalf were included. About defect and shunt location, only patients with a post-tricuspid defect were included. The well-described different physiology, adaptation, and timing of development of ES between patients with underlying pretricuspid shunts and post-tricuspid shunts were the main reasons for selecting only the latter patients for the study. Patients with unstable, decompensated heart failure, active hemoptysis, recent surgery, or nonelective hospitalization were excluded until stable and then invited to participate at a later date after complete resolution of the acute event. Patients with relative contraindication to CMR at baseline including those with a permanent pacemaker or implantable cardioverter defibrillator were excluded. All patients were followed up for mortality until the end of 2013. Deaths were identified from the hospital database, automatically updated by the Office for National Statistics, which registers all UK deaths. The cause of death was recorded for all patients.

Cardiovascular Magnetic Resonance
CMR was performed using a 1.5-Tesla scanner (Sonata, Siemens, Erlangen, Germany) with a phased array body coil. After routine assessment of anatomy, a short-axis contiguous stack of steady state–free precession cine images (7-mm slices) from the atrioventricular ring to the apex was acquired for measurement of biventricular volumes and function. Volumes and ejection fraction for the RV and LV at end diastole and end systole, indexed to body surface area, were calculated by manually contouring the epicardial and endocardial borders from short-axis images. Contouring included trabeculations and papillary muscles as part of the myocardial mass and excluded them from the blood pool. All CMR measurements were made by 1 observer (C.S.B.) and reported at the time of the baseline study. For patients with a ventricular septal defect, delineation between the RV and LV chambers at the defect was done using a line in direct continuity with the septum. RV and LV wall stress indices were calculated according to the formula: systolic blood pressure x end-systolic volume index/mass index.

Late gadolinium enhancement imaging (segmented fast low-angle shot inversion recovery sequence) was obtained 5 to 20 minutes after 0.1 mmol/kg IV gadolinium–DTPA administration in 30 of the 48 patients. Reasons for not performing LGE on all patients included patient factors (anxiety, inability to breath-hold, and renal insufficiency) and logistical factors (scheduling), as previously reported. Long-axis acquisitions were also obtained and repeated short-axis planes with altered direction of phase encoding to differentiate LGE from artifact.

Other Noninvasive Investigations
Venous blood was taken after 20 minutes of supine rest for B-natriuretic peptides (monoclonal antibody assay, Shionoria, Schering, West Sussex, England) together with other routine bloods. All patients completed a 6-minute walk test, and total walk distance was recorded in meters. Protocolized transthoracic echocardiography was performed as previously described, including tricuspid annular plane systolic excursion (measured using M-mode recording of the RV free wall long-axis motion from apical 4-chamber view) and myocardial tissue Doppler velocities (obtained from the RV and LV free wall and septum by placing a tissue Doppler sample volume at basal part of respective segment in an apical 4-chamber view).

Statistics
Continuous data are summarized as mean (SD), whereas categorical data are given as n (%). The association between variables and event-free all-cause survival was tested using a Cox proportional hazards model, with results presented as hazard ratios (HRs) and 95% confidence intervals. B-natriuretic peptides and creatinine were log transformed because of skewed distribution. Because of the relatively small number of outcome events, we focused on univariable and bivariable analyses. Both RV ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) were tested alongside other associated univariable parameters in a series of pairwise comparisons. Kaplan–Meier survival curves were used to illustrate survival prospects according to lower quartile of RVEF and LVEF, as well as lower quartile for both. Analysis was performed using SPSS version 22. A 2-sided P value of <0.05 was considered as statistically significant.

Results
Baseline Patient Characteristics
Forty-nine patients underwent a CMR as part of a protocolized study. One patient with isolated pretricuspid lesion was excluded from the analysis as per protocol, and 1 patient did not complete the whole CMR examination (available data were included in the analysis). There were 28 women (58%), the mean age at inclusion was 40±14 years, and 17% (n=8) of the patients had Down syndrome. Underlying cardiac anatomy was ventricular septal defect (n=31), atrioventricular septal defect (n=7), truncus arteriosus (n=7), and patent ductus arteriosus (n=3). Baseline CMR findings for the total population are summarized in Table 1. Of patients who underwent LGE CMR, 73% were LGE positive. Only 1 had LV LGE only. Of the 70% (21/30) with RV LGE, 53% (11/21) also had LV LGE. A strong correlation was observed between RVEF and LVEF (r=0.73; P<0.0001).

Mortality
Twelve patients (25%) died during follow-up. The cause of death was because of congestive heart failure (n=6), sudden death (n=2), hemoptysis (n=2), or other (n=2), respectively, Table 2. Significant univariable factors associated with mortality were resting transcutaneous oxygen saturation (HR, 0.90 [0.83–0.97]/%; P=0.007), as well as RVEF (HR, 0.96 [0.93–0.99]/%; P=0.02) and LVEF (HR, 0.94 [0.90–0.99]/%; P=0.01) measured by CMR (Table 3). These remained significant even when noncardiovascular causes (cancer or death) were excluded (saturation: HR, 0.87 [0.79–0.96]/%, P=0.004;
Table 1. Baseline Characteristics of the Eisenmenger Patients in the Study

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40±14</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.6±0.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22±4</td>
</tr>
<tr>
<td>Down syndrome, n (%)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>20 (42)</td>
</tr>
<tr>
<td>NYHA≥3, n (%)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>82±14</td>
</tr>
<tr>
<td>Previous arrhythmia, n (%)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Cardiovascular magnetic resonance</td>
<td></td>
</tr>
<tr>
<td>RVESV, mL/m²</td>
<td>81±32</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>50±16</td>
</tr>
<tr>
<td>RVMI, g/m²</td>
<td>59±31</td>
</tr>
<tr>
<td>RV wall stress index</td>
<td>94±56</td>
</tr>
<tr>
<td>LVESV, mL/m²</td>
<td>71±37</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>32±23</td>
</tr>
<tr>
<td>LVF, %</td>
<td>55±14</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>61±31</td>
</tr>
<tr>
<td>LV wall stress index</td>
<td>79±48</td>
</tr>
<tr>
<td>Max RAAl, cm²/m²</td>
<td>14±4</td>
</tr>
<tr>
<td>Max LAAl, cm²/m²</td>
<td>10±4</td>
</tr>
<tr>
<td>Fibrosis (LGE positive), n (%)*</td>
<td>22 (73)</td>
</tr>
<tr>
<td>RV fibrosis (LGE positive), n (%)*</td>
<td>21 (95)</td>
</tr>
<tr>
<td>LV fibrosis (LGE positive), n (%)*</td>
<td>12 (53)</td>
</tr>
<tr>
<td>RV and LV fibrosis (LGE positive), n (%)*</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
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<tr>
<td>TAPSE, cm</td>
<td>17±4</td>
</tr>
<tr>
<td>TDI RV systole (s'), cm/s</td>
<td>8±2</td>
</tr>
<tr>
<td>TDI LV diastole (s'), cm/s</td>
<td>6±3</td>
</tr>
<tr>
<td>TDI LV systole (s'), cm/s</td>
<td>8±2</td>
</tr>
<tr>
<td>TDI LV diastole (s'), cm/s</td>
<td>7±3</td>
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<tr>
<td>ECG</td>
<td></td>
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<tr>
<td>O 2 RS, ms</td>
<td>99±18</td>
</tr>
<tr>
<td>6-min walk test</td>
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</tr>
<tr>
<td>Oxygen saturation at rest, %</td>
<td>81±7</td>
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<tr>
<td>6-minute walk distance, m</td>
<td>367±108</td>
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<tr>
<td>Venous blood</td>
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<tr>
<td>Hb, g/dL</td>
<td>19.7±2.9</td>
</tr>
<tr>
<td>BNP, pmol/L</td>
<td>22±30</td>
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<tr>
<td>Ferritin, μg/L</td>
<td>51±65</td>
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<tr>
<td>Transferrin saturation, %</td>
<td>29±20</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>88±25</td>
</tr>
</tbody>
</table>

*Results based on a subset of 30 of the 48 patients.

RVEF: HR, 0.95 [0.91–0.99]/%, P=0.01; and LVEF: HR, 0.91 [0.86–0.97]/%, P=0.002 and even after further excluding death caused by hemoptysis and including only patients whose death was sudden or caused by heart failure (saturation: HR, 0.88 [0.81–0.96]/%, P=0.004; RVEF: HR, 0.96 [0.92–0.99]/%, P=0.02; and LVEF: HR, 0.93 [0.88–0.98]/%, P=0.006). The Kaplan–Meier survival curve stratified by the lower quartile for both RVEF (40%) and LVEF (50%; RVEF Log-rank, P=0.0055; LVEF Log-rank, P=0.0002) showed a significantly increased risk of death in ES patients with an RVEF of <40% or LVEF of <50% (Figures 1 and 2). Furthermore, our study shows that biventricular impairment (patients in the lowest quartile of both LVEF [<50%] and RVEF [<40%]) was associated with an even worse prognosis compared with impairment of only 1 ventricle (P=0.0001; Figure 3).

The ejection fraction of both the RV and the LV was tested pairwise against resting oxygen saturation, the only other univariable association with mortality, in a bivariable Cox regression analysis. Both lower quartile RVEF (HR, 4.4 [95% confidence interval, 1.4–13.5]; P=0.01) and lower quartile LVEF (HR, 6.6 [95% confidence interval, 2.1–20.8]; P=0.001) remained independently associated with mortality in patients with ES.

Discussion

This is the first study, to our knowledge, to report that CMR-derived indices of ventricular dysfunction are associated with mortality in patients with ES and post-tricuspid shunts. Systolic ventricular impairment, whether right or left, was associated with mortality in these patients. Furthermore, biventricular involvement was associated with even higher mortality.

RVEF and LVEF Are Associated With Mortality in ES

Despite relatively better survival prospects among adults with ES compared with other patients with PAH, life expectancy for those who make it to adulthood is shortened by 20 years if they have simple underlying cardiac defects and by 40 years when cardiac anatomy is more complex.19 Identifying new markers associated with mortality is thus both warranted and needed. CMR measures were recently shown to correlate with mortality both in children and in adults with idiopathic PAH.11–13 Furthermore, RVEF derived from CMR was shown to be a stronger predictor of mortality than invasively measured pulmonary vascular resistance in idiopathic PAH.12,20,21 In contrast, there were no CMR data to date relating to outcome for patients with ES. We have shown that CMR-derived RVEF correlates with mortality in patients with ES, a finding previously shown in idiopathic PAH. In addition, we found that LVEF was also associated with mortality, which is in contrast to reported findings in the remaining PAH patient populations. Moreover, we found that if both ventricles are impaired, the risk of death was the highest.

Our patient sample was physiologically homogeneous relative to previous reports, as patients with pretricuspid shunt ES were excluded because of the influence of the presence and location of the shunt on RV adaptation and hence natural history.16 CMR is recognized as the gold standard for quantification of right (and left) ventricular volumes and function.12 It is
also highly reproducible. It can be applied to accurately quantify ejection fraction without calculations based on geometric assumptions, which is specifically relevant for assessing patients with ES. Hence, it was possible to measure CMR-derived indices of ejection fraction in all patients, and no patient required exclusion because of complex underlying anatomy. Although multiple factors are also likely to be relevant for prognostication in ES, we show here that CMR-derived RVEF and LVEF are associated with mortality. CMR may, therefore, be a useful adjunct to resting transcutaneous oxygen saturation, echocardiography, and B-natriuretic peptides in the initial and ongoing follow-up evaluation of patients with ES.

CMR-derived ejection fraction in our ES study correlated with mortality, whereas previously reported clinically prognostic echocardiography and B-natriuretic peptide measures did not reach statistical significance in this study. The differences in findings may be explained by the smaller size in this study, and the fact that previous studies also included ES patients with pretricuspid shunts who are physiologically different from the ES patients with post-tricuspid shunts.

### Ventricular Dysfunction and Interdependence in ES

The presence of ventricular interdependence in the setting of congenital heart disease in general, and specifically in patients with ES, is well appreciated. In contrast to studies in idiopathic PAH, our study showed that increased mortality risk in patients with ES related not only to right but also to left ventricular systolic dysfunction. In ES, commonly, the posttricuspid shunt causes shared volume and pressure load to both ventricles that are comparable in size, whereas in other forms of pulmonary hypertension, the pressure load is directed primarily toward the RV. Detrimental effects may, therefore, directly affect both ventricles in ES. This ventricular interdependence, together with the fact that in ES, the RV is primed to high pressure since birth may account for the superior survival, in ES compared with patients with other forms of PAH. One could postulate that the RV is again relieved from high pressure with the onset of shunt reversal from right to left. When ventricular systolic dysfunction in ES ultimately ensues, it may be because of myocardial coronary insufficiency or maladaptation and may then progress rapidly. Evidence of ventricular fibrosis from LGE study was more common in the RV but was also found in the LV. We submit that the onset of RV and LV dysfunction in ES is usually a late sign, associated with a guarded prognosis, which our data support.

### Potential Causes of Ventricular Dysfunction in ES

In idiopathic PAH, patients respond initially to increased pulmonary pressure with adaptive RV hypertrophy. RV failure occurs when a hypertrophic response is exhausted, and the RV instead begins to dilate; a mechanism some have called RV maladaptation. Histology in idiopathic PAH has demonstrated reduced capillary density, RV cardiomyocyte growth arrest, and increased and marked RV fibrosis in the failing RV. Few data exist on myocardial histology in the RV or LV in ES. The relatively small number of patients with ES studied with LGE CMR in our study and the quality of LGE acquisition during the era of the study may have underpowered it to detect...
possible associations of LGE with mortality. Although, to date, there are no data to demonstrate a positive link between LGE fibrosis and outcome in ES, this area warrants further exploration. Impairment of systolic ventricular function occurs in ES late after a long initial adaptive ventricular response to volume with or without pressure overload and to cyanosis. To ascertain whether excessive hypertrophy or dilation was the underlying culprit for mortality similar to patients with idiopathic PAH, we calculated RV and LV wall stress indices. We could not show that wall stress specifically was associated with biventricular maladaptation in ES in this study. However, we found that resting cyanosis was associated with mortality in keeping with a previous study showing that resting oxygen saturation <85% was associated with a 3-fold increase in mortality. Cyanosis may adversely affect ventricular function, and its influence on the myocardium and other organ systems is both major and lifelong in ES. Although cyanosis and ventricular dysfunction were independently associated with mortality in our study, it is feasible that they are also interrelated.

Potential Clinical Implications for Risk Stratification in ES
Many easily reproducible invasive and noninvasive clinical markers are used in the evaluation of patients with PAH to predict mortality. European guidelines for PAH include a table adapted from the study by McLaughlin and McGoon with parameters that can assist in the clinical evaluation of disease severity, stability, and prognosis. Such parameters cannot be directly adopted in patients with ES who differ significantly from those with idiopathic PAH, both in terms of pathophysiology and outcome. An example of this is pericardial effusion in ES that, to date, does not seem to have an effect on mortality, yet it is important in

Figure 1. Kaplan–Meier survival curves with the survival distributions of patients with right ventricular ejection fraction (RVEF) <40% (lower quartile cutoff).

Figure 2. Kaplan–Meier survival curves with the survival distributions of patients with left ventricular ejection fraction (LVEF) <50% (lower quartile cutoff).
PAH.\textsuperscript{24,32} It is likely that clinical risk stratification algorithms will not be confined to 1 parameter in this condition, similar to other PAH causes. Our study suggests that CMR is useful as part of the armamentarium for clinical risk stratification of ES.

Limitations

We confined our study to ES patients with post-tricuspid shunts only to mitigate against heterogeneous underlying cardiac anatomy, early physiology, and longer-term cardiovascular adaptation. The precise degree and the mechanism to which the LV or RV shares pressure and volume overload at different times may of course have varied. Not all patients are suitable for CMR or can cooperate with current CMR algorithms; indeed, 1 study patient failed to complete our CMR protocol.

Many of our patients with ES were started on advanced therapy for PAH after their baseline assessment and, at variable times, may well have been a cofounder. However, because of the time-dependent nature of advanced therapy initiation, thereafter, therapy changes and the fact that we only had access to a single, baseline CMR investigation, statistical adjustment for the effect of advanced therapies in this study is not possible. Further studies with repeated CMR assessment will be required to clarify this point.

Future and larger studies may validate our results and assess the potential for prognostic value of newer CMR biomarkers, such as high resolution focal and diffuse myocardial fibrosis (more up to date 2-dimensional LGE optimized for more frail patients,\textsuperscript{39} 3D LGE,\textsuperscript{40} and T1 mapping techniques), and the potential to modify them with timely advanced PAH therapy.

Conclusions

Impaired right, left, and especially biventricular systolic function derived from baseline CMR and resting oxygen saturations correlate with mortality in adult patients with ES because of post-tricuspid shunts. CMR is a useful noninvasive tool, which may be incorporated in the risk stratification assessment of ES during lifelong follow-up.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Impaired right, left, or biventricular systolic function derived from cardiovascular magnetic resonance and lower baseline oxygen saturations are associated with increased risk of mortality in patients with Eisenmenger syndrome. The presence of biventricular impairment is associated with an even higher risk of mortality than isolated left or right ventricular impairment. Cardiovascular magnetic resonance is a highly reproducible method for quantification of left or right ventricular ejection fraction, which can be applied even to potentially complex underlying anatomy as in Eisenmenger syndrome. Cardiovascular magnetic resonance complements other imaging modalities including by providing additional information on the pulmonary vascular bed and the presence of in situ thrombosis without adding ionizing radiation exposure. Thus, cardiovascular magnetic resonance may be incorporated in the assessment protocol and prognostication algorithms for patients with Eisenmenger syndrome.
Impaired Right, Left, or Biventricular Function and Resting Oxygen Saturation Are Associated With Mortality in Eisenmenger Syndrome: A Clinical and Cardiovascular Magnetic Resonance Study

Annette S. Jensen, Craig S. Broberg, Riikka Rydman, Gerhard-Paul Diller, Wei Li, Konstantinos Dimopoulos, Stephen J. Wort, Dudley J. Pennell, Michael A. Gatzoulis and Sonya V. Babu-Narayan

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