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 MD PhD[1,2±], Craig S Broberg MD [1,3±],
Riikka Rydman MD PhD[1,4], Gerhard-Paul Diller MD PhD MSc[1,5], Wei Li MD PhD[1],
Konstantinos Dimopoulos MD PhD MSc[1], Stephen J Wort MD PhD[1], Dudley J Pennell FRCP FMedSc[1],
**Michael A Gatzoulis MD MRCPH PhD[1], Sonya V Babu-Narayan MB BS BSc MRCP PhD[1]*

1 NIHR Cardiovascular Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust, National Heart and Lung Institute, Imperial College London, UK
2 Department of Cardiology, Rigshospitalet, Copenhagen, Denmark.
3 Adult Congenital Heart Program, Knight Cardiovascular Institute, Oregon Health &Science University Portland, Oregon, USA
4 Section of Clinical Physiology, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
5 Division of Adult Congenital and Valvular Heart Disease, Department of Cardiovascular Medicine, University Hospital Muenster, Muenster, Germany.
± The first and second author contributed equally

Corresponding author:
*Professor Michael A. Gatzoulis MD MRCPH PhD FACC FESC
Adult Congenital Heart Centre and Centre for Pulmonary Hypertension
NIHR Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, and the National Heart & Lung Institute, Imperial College, London, UK,
Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK.
Tel.: +44 20 73518602, Fax: +44 20 73518629, E-mail: m.gatzoulis@rbht.nhs.uk

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Abstract

Background: Patients with ES have better survival, despite similar pulmonary vascular pathology, compared to other patients with pulmonary arterial hypertension (PAH). Cardiovascular magnetic resonance (CMR) is useful for risk stratification in idiopathic PAH (IPAH), whereas it has not been evaluated in ES. We studied CMR together with other non-invasive measurements in Eisenmenger syndrome (ES) in order to evaluate its potential role as a non-invasive risk stratification test. **Methods and Results:** Between 2003 and 2005, 48 ES patients, all with a post-tricuspid shunt, were enrolled in a prospective, longitudinal, single centre study. All patients underwent a standardized baseline assessment with CMR, blood test, echocardiography and 6 minute walk test (6MWT), and were followed 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; RVEF, LVEF) was associated with increased risk of mortality (lowest quartile; RVEF<40%; HR=4.4 [95% CI 1.4-13.5], *p*=0.01, lowest quartile; LVEF<50%; HR=6.6 [95% CI 2.1-20.8], *p*=0.001). Biventricular impairment (lowest quartile LVEF<50% and RVEF <40%) conveyed an even higher risk of mortality (HR=8.0 [95% CI 2.5-25.1], *p*=0.0004). No other CMR or non-invasive measurement besides resting oxygen saturation (HR=0.90 [0.83-0.97]/%, p=0.007) was associated with mortality. **Conclusions:** Impaired right, left or bi-ventricular systolic function derived from baseline CMR and resting oxygen saturation are associated with mortality in adult patients with ES. CMR is a useful non-invasive tool, which may be incorporated in the risk stratification assessment of ES during lifelong follow-up**.**

Keywords: Eisenmenger syndrome, Cardiovascular Magnetic Resonance, ventricular impairment, ejection fraction, mortality.

Introduction

Eisenmenger syndrome (ES) shares many aspects of the clinical and hemodynamic alterations as well as pulmonary microvascular changes with other forms of pulmonary arterial hypertension (PAH) [1, 2]. However, ES patients seem to have a better prognosis compared especially with those with idiopathic PAH [3, 4]. A common cause of death in patients with PAH, other than ES, is RV failure as a consequence of the inability of the RV to cope with increased afterload [2, 5] 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 [6, 7]. Furthermore, regression of the physiological right ventricular 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 ES patients; furthermore, ES patients have a have significantly decreased life expectancy compared to healthy controls [8-10]. Improved ability to estimate prognosis on an 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 non-invasive evaluation of idiopathic PAH due to its superiority in assessing RV volumes and systolic function compared to echocardiography and its proven ability to predict mortality in prospective studies in both adults and children with various forms of PAH [11-13]. 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 non-invasive clinical risk assessment of ES patients.

Methods

Patients and study design

Consecutive, clinically stable adults with Eisenmenger physiology were invited to participate and underwent 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 prior to participation.

Eisenmenger physiology was defined as a known intra-cardiac or extra-cardiac non-restrictive defect, with increased pulmonary vascular resistance and reversed or bi-directional shunt resulting in hypoxemia [14-15]. Patients with learning difficulties with capacity to consent and patients, whose parent or guardian gave consent on their behalf, were included. Regarding defect and shunt location, only patients with a post-tricuspid defect were included. The well described different physiology, adaptation and timing of development of Eisenmenger syndrome between patients with underlying pre and post tricuspid shunts [16]was the main reason for selecting only the latter patients for the study. Patients with unstable, decompensated heart failure, active hemoptysis, recent surgery and/or non-elective 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 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. Cause of death was recorded for all patients.

Cardiovascular Magnetic Resonance (CMR)

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 (7mm 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 epi- 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 one observer (CSB) and reported at the time of the baseline study. For patients with a ventricular septal defect (VSD), 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 index was calculated according to the formula: Systolic Blood Pressure (BP) x End-Systolic Volume index (ESVi)/ Mass index (Mi) [17].

Late Gadolinium Enhancement (LGE) imaging (segmented fast low-angle shot inversion recovery sequence) was obtained 5-20 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 [18]. Long axis acquisitions were also obtained as well as repeated short axis planes with altered direction of phase encoding to differentiate LGE from artifact.

Other non-invasive investigations

Venous blood was taken after 20 minutes supine rest for B- natriuretic peptides (BNP; monoclonal antibody assay, Shionoria, Schering, West Sussex, England) together with other routine bloods. All patients completed a 6-minute walk test (6MWT), and total walk distance

was recorded in metres. Protocolized transthoracic echocardiography was performed as previously described [15] including tricuspid annular plane systolic excursion (TAPSE) (measured using M-mode recording of the RV free wall long axis motion from apical four-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 four-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 and 95% confidence intervals. BNP and creatinine were log transformed due to skewed distribution. Due to the relatively small number of outcome events, we focused on uni- and bivariable analyses. Both, right ventricular (RVEF) and left ventricular ejection fraction (LVEF) were tested alongside other associated univariable parameters in a series of pair wise 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 two-sided p-value of <0.05 was considered as statistical significant.

Results

Baseline patient characteristics

Forty nine patients underwent a CMR as part of a protocolised study [15]. One patient with isolated pre-tricuspid lesion was excluded from the analysis as per protocol and one 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's 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 summarised in **Table 1.** Of patients that underwent LGE CMR, 73% were LGE positive. Only one 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. Cause of death was due to congestive heart failure (n=6), sudden death (n=2), haemoptysis (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 right (HR=0.96 [0.93-0.99]/%, p=0.02) and left ventricular ejection fraction (HR=0.94 [0.90-0.99]/%, p=0.01) measured by CMR, **Table 3**. These remained significant even when non-cardiovascular causes (carcinoma and acute abdomen) were excluded (saturation:HR=0.87 [0.79-0.96]/%, p=0.004, RVEF:HR=0.95 [0.91-0.99]/%, p=0.01, LVEF: (HR=0.91 [0.86-0.97]/%, p=0.002) and even after further excluding death due to hemoptysis and including only patients whose death was sudden or due to heart failure (saturation: HR=0.88 [0.81-0.96]/%, p=0.004), RVEF: HR=0.96 [0.92-0.99]/%, p=0.02), 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 a RVEF below 40% or LVEF below 50%, **Figure 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 to impairment of only one 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% CI 1.4-13.5], *p*=0.01) and lower quartile LVEF (HR=6.6 [95% CI 2.1-20.8], *p*=0.001) remained independently associated with mortality in ES patients.

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.

RV and LV ejection fraction are associated with mortality in Eisenmenger syndrome

Despite relatively better survival prospects amongst adults with ES, compared to 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 (PVR) 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 ES patients, 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 highest.

Our patient sample was physiologically homogeneous relative to previous reports, as pre-tricuspid shunt ES patients were excluded due to the influence of the presence and location of the shunt on right ventricular 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 geometrical assumptions, which is specifically relevant for assessing ES patients. Hence, it was possible to measure CMR derived indices of ejection fraction in all patients and no patient required exclusion due to complex underlying anatomy. Whilst, multiple factors are also likely to be relevant for prognostication in ES, we show here that CMR-derived right and left ventricular ejection fraction is associated with mortality. CMR may therefore, be a useful adjunct to resting transcutaneous oxygen saturation, echocardiography and BNP in the initial and ongoing follow-up evaluation of ES patients.

CMR derived ejection fraction in our ES study correlated with mortality, whereas previously reported clinically prognostic echocardiography and BNP measures did not reach statistical significance in the current study [22-24]. The differences in findings may be explained by the smaller size in the current study, and the fact that previous studies also included ES patients with pre-tricuspid shunts who are physiologically different from the ES patients with post-tricuspid shunts [16].

Ventricular dysfunction and interdependence in Eisenmenger syndrome

The presence of ventricular interdependence in the setting of congenital heart disease in general, and specifically in patients with ES, is well appreciated [15,25]. In contrast to studies in idiopathic PAH, our study showed that increased mortality risk in ES patients related not only to right but also to left ventricular systolic dysfunction. In ES, commonly the post-tricuspid shunt causes shared volume and pressure load to both ventricles [26] which are comparable in size, whereas in other forms of pulmonary hypertension the pressure load is directed primarily towards 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 [6, 7] may account for the superior survival, in ES compared to patients with other forms of pulmonary arterial hypertension. 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 due to myocardial coronary insufficiency and/or maladaptation and may then progress rapidly [5, 27]. 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 supports.

Potential causes of ventricular dysfunction in Eisenmenger syndrome

In idiopathic PAH, patients respond initially to increased pulmonary pressure with adaptive RV hypertrophy. Right ventricular 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 [5, 27]. Few data exist regarding myocardial histology in the RV or LV in ES [28, 29]. The relatively small number of ES patients 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 [19], this area warrants further exploration. Impairment of systolic ventricular function occurs in ES late, following 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 idiopathic PAH patients [30, 31] we calculated RV and LV wall stress index. 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 below 85% was associated with a three-fold increase in mortality [32]. Cyanosis may adversely affect ventricular function [33, 34] and its influence on the myocardium and other organ systems [32, 35-38] is both major and lifelong in ES. Whilst cyanosis and ventricular dysfunction were independently associated with mortality in our study it is feasible that they are also inter-related.

Potential clinical implications for risk stratification in ES

A number of easily reproducible invasive and non-invasive clinical markers are used in the evaluation of PAH patients to predict mortality. European guidelines for PAH include a table adapted from McLaughlin and McGoon with parameters that can assist in the clinical evaluation of disease severity, stability and prognosis [2]. Such parameters cannot be directly adopted in ES patients, who differ significantly from idiopathic PAH, both in terms of pathophysiology and outcome. An example of this is pericardial effusion in ES which to date does not appear to have an impact on mortality, yet is important in PAH [24, 32]. It is likely that clinical risk stratification algorithms will not be confined to one parameter in this condition, similar to other PAH aetiologies. 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 mechanism to which the left or right ventricle share 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 one study patient failed to complete our CMR protocol.

A number of our ES patients were started on advanced therapy for PAH after their baseline assessment and, at variable times, which may well have been a cofounder. However, due to 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 2D LGE optimised for more frail patients [39], 3D LGE [40] and T1 mapping techniques), and the potential to modify them with timely, advanced PAH therapy.

Conclusion

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

References

1. Griffin N, Allen D, Wort J, Rubens M, Padley S. Eisenmenger syndrome and idiopathic pulmonary arterial hypertension: Do parenchymal lung changes reflect aetiology? *Clinical Radiology*. 2007;62:587-595
2. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G, Guidelines ESCCfP. Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the European Society Of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society Of Heart And Lung Transplantation (ISHLT). *Eur Heart J*. 2009;30:2493-2537
3. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation*. 2006;114:1417-1431
4. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 1996;15:100-105
5. Rain S, Handoko ML, Vonk Noordegraaf A, Bogaard HJ, van der Velden J, de Man FS. Pressure-overload-induced right heart failure. *Pflugers Archiv : European journal of physiology*. 2014;466:1055-1063
6. Bradlow WM B-NS, Mohiaddin RH. Pulmonary hypertension in congenital heart disease. *Springer: Cardiac CT and MR for Adult Congenital Heart Disease*. 2014:553-572
7. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: The unique hearts of patients with Eisenmenger syndrome. *Am J Cardiol*. 2002;89:34-38
8. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J*. 1998;19:1845-1855
9. Cantor WJ, Harrison DA, Moussadji JS, Connelly MS, Webb GD, Liu P, McLaughlin PR, Siu SC. Determinants of survival and length of survival in adults with Eisenmenger syndrome. *Am J Cardiol*. 1999;84:677-681

10. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K, Gatzoulis MA. Survival Prospects and Circumstances of Death in Contemporary Adult Congenital Heart Disease Patients Under Follow-Up at a Large Tertiary Centre. *Circulation*. 2015. [Epub ahead of print]
11. Blalock S, Chan F, Rosenthal D, Ogawa M, Maxey D, Feinstein J. Magnetic resonance imaging of the right ventricle in pediatric pulmonary arterial hypertension. *Pulmonary circulation*. 2013;3:350-355
12. Peacock AJ, Vonk Noordegraaf A. Cardiac magnetic resonance imaging in pulmonary arterial hypertension. *European respiratory review : an official journal of the European Respiratory Society*. 2013;22:526-534
13. van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD, Postmus PE, Vonk-Noordegraaf A. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J*. 2007;28:1250-1257
14. Broberg CS, Jayaweera AR, Diller GP, Prasad SK, Thein SL, Bax BE, Burman J, Gatzoulis MA. Seeking optimal relation between oxygen saturation and hemoglobin concentration in adults with cyanosis from congenital heart disease. *Am J Cardiol*. 2011;107:595-599
15. Broberg CS, Ujita M, Prasad S, Li W, Rubens M, Bax BE, Davidson SJ, Bouzas B, Gibbs JS, Burman J, Gatzoulis MA. Pulmonary arterial thrombosis in Eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. *J Am Coll Cardiol*. 2007;50:634-642
16. Moceri P, Kempny A, Liodakis E, Alonso Gonzales R, Germanakis I, Diller GP, Swan L, Marino PS, Wort SJ, Babu-Narayan SV, Ferrari E, Gatzoulis MA, Li W, Dimopoulos K. Physiological differences between various types of Eisenmenger syndrome and relation to outcome. *Int J Cardiol*. 2015;179:455-460
17. Giardini A, Lovato L, Donti A, Formigari R, Oppido G, Gargiulo G, Picchio FM, Fattori R. Relation between right ventricular structural alterations and markers of adverse clinical outcome in adults with systemic right ventricle and either congenital complete (after Senning operation) or congenitally corrected transposition of the great arteries. *Am J Cardiol*. 2006;98:1277-1282

18. Broberg CS, Prasad SK, Carr C, Babu-Narayan SV, Dimopoulos K, Gatzoulis MA. Myocardial fibrosis in Eisenmenger syndrome: A descriptive cohort study exploring associations of late gadolinium enhancement with clinical status and survival. *J Cardiovasc Magn Reson*. 2014;16:32
19. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A, Harries C, Goktekin O, Gibbs JS, Gatzoulis MA. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: A combined retrospective and case-control study. *Eur Heart J*. 2006;27:1737-1742
20. Agarwal R, Gomberg-Maitland M. Prognostication in pulmonary arterial hypertension. *Heart failure clinics*. 2012;8:373-383
21. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk-Noordegraaf A. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol*. 2011;58:2511-2519
22. Diller GP, Alonso-Gonzalez R, Kempny A, Dimopoulos K, Inuzuka R, Giannakoulas G, Castle L, Lammers AE, Hooper J, Uebing A, Swan L, Gatzoulis M, Wort SJ. B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: Predictive value and response to disease targeting therapy. *Heart*. 2012;98:736-742
23. Van De Bruaene A, De Meester P, Voigt JU, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R, Vachiery JL, Paelinck B, Morissens M, Budts W. Right ventricular function in patients with Eisenmenger syndrome. *Am J Cardiol*. 2012;109:1206-1211
24. Moceri P, Dimopoulos K, Liodakis E, Germanakis I, Kempny A, Diller GP, Swan L, Wort SJ, Marino PS, Gatzoulis MA, Li W. Echocardiographic predictors of outcome in Eisenmenger syndrome. *Circulation*. 2012;126:1461-1468
25. Davlouros PA, Kilner PJ, Hornung TS, Li W, Francis JM, Moon JC, Smith GC, Tat T, Pennell DJ, Gatzoulis MA. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: Detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. *J Am Coll Cardiol*. 2002;40:2044-2052

26. Hopkins WE, Waggoner AD. Right and left ventricular area and function determined by two-dimensional echocardiography in adults with the Eisenmenger syndrome from a variety of congenital anomalies. *Am J Cardiol*. 1993;72:90-94
27. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, Naeije R, Newman J, Oudiz RJ, Provencher S, Torbicki A, Voelkel NF, Hassoun PM. Right heart adaptation to pulmonary arterial hypertension: Physiology and pathobiology. *J Am Coll Cardiol*. 2013;62:D22-33
28. Maron BJ, Clark CE, Henry WL, Fukuda T, Edwards JE, Mathews EC, Jr., Redwood DR, Epstein SE. Prevalence and characteristics of disproportionate ventricular septal thickening in patients with acquired or congenital heart diseases: Echocardiographic and morphologic findings. *Circulation*. 1977;55:489-496
29. Hirose Y, Ishida Y, Hayashida K, Satoh T, Shimotsu Y, Nishimura T. Viable but denervated right ventricular myocardium: A case of Eisenmenger reaction. *Cardiology*. 1997;88:609-612
30. Kopec G, Moertl D, Miszalski-Jamka T, Waligora M, Tyrka A, Sarnecka A, Podolec P. Left ventricular mass is preserved in patients with idiopathic pulmonary arterial hypertension and Eisenmenger's syndrome. *Heart, lung & circulation*. 2014;23:454-461
31. Moledina S, Pandya B, Bartsota M, Mortensen KH, McMillan M, Quyam S, Taylor AM, Haworth SG, Schulze-Neick I, Muthurangu V. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. *Circ Cardiovasc Imaging*. 2013;6:407-414
32. Kempny A, Dimopoulos K, Alonso-Gonzalez R, Alvarez-Barredo M, Tutarel O, Uebing A, Piatek P, Marino P, Swan L, Diller GP, Wort SJ, Gatzoulis MA. Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. *Int J Cardiol*. 2013;168:4784-4789
33. Chowdhury UK, Sathia S, Ray R, Singh R, Pradeep KK, Venugopal P. Histopathology of the right ventricular outflow tract and its relationship to clinical outcomes and arrhythmias in patients with tetralogy of Fallot. *J Thorac Cardiovasc Surg*. 2006;132:270-277

34. Broberg CS, Chugh SS, Conklin C, Sahn DJ, Jerosch-Herold M. Quantification of diffuse myocardial fibrosis and its association with myocardial dysfunction in congenital heart disease. *Circ Cardiovasc Imaging*. 2010;3:727-734
35. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV, Salukhe TV, Piepoli MF, Poole-Wilson PA, Best N, Francis DP, Gatzoulis MA. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. *Circulation*. 2008;117:2320-2328
36. Perloff JK. Systemic complications of cyanosis in adults with congenital heart disease. Hematologic derangements, renal function, and urate metabolism. *Cardiology clinics*. 1993;11:689-699
37. Vongpatanasin W, Brickner ME, Hillis LD, Lange RA. The Eisenmenger syndrome in adults. *Annals of internal medicine*. 1998;128:745-755
38. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. *Circulation*. 2007;115:1039-1050
39. Piehler KM, Wong TC, Puntil KS, Zareba KM, Lin K, Harris DM, Deible CR, Lacomis JM, Czeyda-Pommersheim F, Cook SC, Kellman P, Schelbert EB. Free-breathing, motion-corrected late gadolinium enhancement is robust and extends risk stratification to vulnerable patients. *Circ Cardiovasc Imaging*. 2013;6:423-432
40. Keegan J, Gatehouse PD, Haldar S, Wage R, Babu-Narayan SV, Firmin DN. Dynamic inversion time for improved 3d late gadolinium enhancement imaging in patients with atrial fibrillation. *Magn Reson Med*. 2015;73:646-654

Figure legends

Figure 1

Kaplan-Meier survival curves with the survival distributions of patients with RVEF <40% (lower quartile cut-off)

Figure 2

Kaplan-Meier survival curves with the survival distributions of patients with LVEF <50% (lower quartile cut-off)

Figure 3

Kaplan-Meier survival curves with the survival distributions of patients with LV or RV impairment (defined as lower quartile EF) versus both RV and LV impairment.

Tables

Table 1 Baseline characteristics of the Eisenmenger patients in the study

	All patients (n=48)
Age, years	40±14
BSA, m^2	1.6±0.2
BMI, kg/m^2	22±4
Down's syndrome, n (%)	8 (17)
Male gender, n (%)	20 (42)
NYHA ≥3, n (%)	17 (35)
Heart rate, beats/min	82±14
Previous arrhythmia, n (%)	11 (23)
Cardiovascular magnetic resonance	
RVEDVi, mL/m^2	81±32
RVESVi, mL/m^2	41±24
RVEF, %	50±16
RVMi, g/m^2	59±31
RV wall stress index	94±56
LVEDVi, mL/m^2	71±37
LVESVi, mL/m^2	32±23
LVEF, %	55±14
LVMi, g/m^2	61±31
LV wall stress index	79±48
Max RAAi, cm^2/m^2	14±4
Max LAAi, cm^2/m^2	10±4
Fibrosis (LGE positive), n (%)*	22 (73)
RV Fibrosis (LGE positive), n (%)*	21 (95)
LV Fibrosis (LGE positive), n (%)*	12 (55)
RV and LV fibrosis (LGE positive), n (%)*	11 (50)

Echocardiogram	
TAPSE, cm	17±4
TDI RV systole (s'), cm/s	8±2
TDI RV diastole (e'), cm/sec	6±3
TDI LV systole (s'), cm/s	8±2
TDI LV diastole (e'), cm/sec	7±3
Electrocardiogram	
QRS, ms	99±18
6 minute walk test	
Oxygen saturation at rest, %	81±7
6-minute walk distance, m	367±108
Venous blood	
Hb, g/dL	19.7±2.9
BNP, pmol/L	22±30
Ferritin, µg/L	51±65
Transferrin saturation, %	29±20
Creatinine, µmol/L	88±25

BSA; Body Surface Area, BMI; Body Mass Index, NYHA; New York Heart Association functional class, CMR; cardiovascular magnetic resonance, RVEDVi; right ventricular end-diastolic volume index, RVESVi; right ventricular end-systolic volume index, RVEF; right ventricular ejection fraction, RVMi; right ventricular mass index, RV; right ventricle, RV wall stress index (systolic blood pressure (BP) x RVESVi/RVMi), LVEDVi; left ventricular end-diastolic volume index, LVESVi; left ventricular end-systolic volume index, LVEF; left ventricular ejection fraction, LVMi; left ventricular mass index, LV; left ventricle, LV wall stress index (systolic blood pressure (BP) x LVESVi/LVMi), MaxRAAi; maximal right atrial areal index, Max LAAi; maximal left atrial areal index, LGE; late gadolinium enhancement, TAPSE; tricuspid annular plane systolic excursion, TDI; tissue doppler imaging, RV systole (s'); myocardial systolic velocity from basal RV free wall, RV diastole (e'); myocardial early diastolic velocity from RV free wall, LV systole (s'); myocardial systolic velocity from basal LV free wall, LV diastole (e'); myocardial early diastolic velocity from basal LV free wall, Hb; haemoglobin, BNP; brain natriuretic peptide

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

Table 2 Cause of death in the Eisenmenger patient population

Total number of deaths, n (%)	**12 (25)**
Cardiac causes, n (%)	**10 (83)**
- Heart failure, n (%)	6*(60)
- Sudden cardiac death, n (%)	2 (20)
- Haemoptysis, n (%)	2 (20)
Non-cardiac causes, n (%)	**2 (17)**
- Bladder Cancer, n (%)	1 (50)
- Acute abdomen, n (%)	1 (50)

*1 patient died during transplantation

Table 3 Univariate predictors of adverse clinical outcome in Eisenmenger patients

Variable	Hazard ratio (95% CI)	P
Age at scan, yrs	1.04 (1.00-1.08)	0.08
Male gender, n (%)	1.54 (0.47-5.08)	0.49
Down's syndrome, present	0.95 (0.21-4.29)	0.95
NYHA≥3	2.66 (0.85-8.36)	0.09
Heart rate, beats/min	1.03 (0.99-1.08)	0.16
Previous arrhythmia, presence	0.62 (0.08-4.75)	0.65
RVEDVi, mL/m^2	1.00 (0.98-1.02)	0.63
RVESVi, mL/m^2	1.00 (0.98-1.02)	0.89
RVEF, %	0.97 (0.93-0.99)	**0.02**
RVMi, g/m^2	1.01 (0.98-1.04)	0.51
RV wall stress index	1.00 (0.98-1.01)	0.61
LVEDVi, mL/m^2	1.01 (0.99-1.03)	0.44
LVESVi, mL/m^2	1.02 (1.00-1.05)	0.10
LVEF, %	0.94 (0.90-0.99)	**0.01**
LVMi, g/m^2	1.02 (1.00-1.05)	0.06
LV wall stress index	1.00 (0.98-1.02)	0.96
MaxRAAi, cm^2/m^2	1.00 (1.00-1.00)	0.39
MaxLAAi, cm^2/m^2	1.00 (1.00-1.00)	0.19
Fibrosis (LGE positive)*	0.88 (0.13-5.82)	0.90
RV Fibrosis (LGE positive) *	0.47 (0.08-2.74)	0.47
LV Fibrosis (LGE positive)*	2.50 (0.45-14.04)	0.30
RV and LV fibrosis (LGE positive)*	1.41 (0.25-7.90)	0.70
TDI RV systole (s'), cm/sec	1.05 (0.70-1.58)	0.82
QRS, ms	1.01 (0.97-1.05)	0.61
Oxygen saturation rest, %	0.90 (0.83-0.97)	**0.007**
6-min walk distance, m	1.00 (0.99-1.00)	0.27
Log(BNP), pmol/L	2.87 (0.69-11.95)	0.15
Log(Creatinine), µmol/L	21.67 (0.20-2404.04)	0.20

NYHA; New York Heart Association functional class, RVEDVi; right ventricular end-diastolic volume index, RVESVi; right ventricular end-systolic volume index, RVEF; right ventricular ejection fraction, RVMi; right ventricular mass index, RV; right ventricle, RV wall stress index (systolic blood pressure (BP) x RVESVi/RVMi), LVEDVi; left ventricular end-diastolic volume index, LVESVi; left ventricular end-systolic volume index, LVEF; left ventricular ejection fraction, LVMi; left ventricular mass index, LV; left ventricle, LV wall stress index (systolic blood pressure (BP) x LVESVi/LVMi), MaxRAAi; maximal right atrial area index, MaxLAAi; maximal left atrial areal index, TAPSE; tricuspid annular plane systolic excursion, TDI; tissue doppler imaging, BNP; brain natriuretic peptide.

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