Echocardiographic Predictors of Outcome in Eisenmenger Syndrome

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Background—Eisenmenger syndrome differs significantly from other types of pulmonary arterial hypertension in its physiology and prognosis. We sought to assess the relationship between the echocardiographic characteristics of patients with Eisenmenger syndrome and mortality.

Methods and Results—Clinical and echocardiographic variables were assessed in 181 consecutive patients with Eisenmenger syndrome, excluding those with complex congenital heart disease. Patients’ mean age was 39.1 ±12.8 years, 59 (32.6%) were male, 122 (67.4%) were in functional class III or higher, and 74 (40.9%) were on advanced therapies. Mean oxygen saturation at rest was 85.1 ±7.8%, and median B-type natriuretic peptide was 55.4 ng/L. Over a median follow-up of 16.4 months, 19 patients died; the strongest predictors of mortality were tricuspid annular plane systolic excursion and peak systolic velocity, myocardial performance (expressed as total isovolumic time and ratio of systolic to diastolic duration), and elevated central venous pressure (expressed as right atrial [RA] area, RA pressure, and ratio of RA to left atrial area), even after we accounted for advanced therapies. A composite score based on the strongest echocardiographic predictors of outcome, including 1 point for each of the following: tricuspid annular plane systolic excursion <15 mm, ratio of right ventricular effective systolic to diastolic duration ≥1.5, RA area ≥25 cm², ratio of RA to left atrial area ≥1.5, was highly predictive of clinical outcome (area under the curve 0.90 ±0.01), with no improvement when B-type natriuretic peptide and resting saturations were added into the model.

Conclusions—Echocardiographic parameters of right ventricular function and RA area predict mortality in Eisenmenger patients. A new composite echocardiographic score, described herewith, may be incorporated into the noninvasive, periodic assessment of these patients. (Circulation. 2012;126:1461-1468.)

Key Words: echocardiography ■ Eisenmenger syndrome ■ heart defects, congenital ■ pulmonary hypertension ■ survival

Eisenmenger syndrome is defined as severe pulmonary arterial hypertension (PAH) in conjunction with congenital heart disease and reversal of shunt with ensuing cyanosis.1 Eisenmenger syndrome frequently occurs in patients with large, nonrestrictive intracardiac or extracardiac communications, including atrial septal defects, ventricular septal defects, atrioventricular septal defects, and patent ductus arteriosus (PDA). It has been suggested that up to 10% of patients with congenital heart disease may develop Eisenmenger syndrome,2 although this may reflect a different era of late diagnosis and suboptimal care.3,4 Advanced therapies targeting PAH have been shown to improve hemodynamics, symptoms, quality of life, and possibly survival in patients with Eisenmenger syndrome.5,6 The timing of initiation of such therapies in Eisenmenger patients remains controversial but is based primarily on subjective assessment of disease severity and progression of symptoms.

Clinical Perspective on p 1468

Echocardiography is widely used in the assessment of patients with various types of PAH because it provides accurate information on cardiac anatomy and physiology. In patients with idiopathic PAH, ventricular septal shift, right atrial enlargement, tricuspid annular plane systolic excitation (TAPSE), and the presence of pericardial effusion are predictors of unfavorable outcome and are routinely used for risk
Eisenmenger patients with a structurally biventricular heart and a morphological left ventricle (LV) supporting the systemic circulation were excluded to facilitate a meaningful echocardiographic analysis. Demographic and clinical data were collected at the time of echocardiography, whereas B-type natriuretic peptide (BNP) measurement and 6-minute walk test data were collected within 1 month of the echocardiogram (Figure 1). Echocardiography was prospectively analyzed in 25% and retrospectively analyzed in 75% of cases (echocardiographic data were interpreted in this case over a 3-month period from March to May 2011) by 2 different observers blinded to other results (including outcome) and to each other. Data from a single echocardiographic assessment were collected for all patients in the study. Follow-up was considered from the date of echocardiography and continued until patients either died or were censored at the end of the study. Survival status was assessed through the National Health Service computer system, linked to a national database of patient survival held by the UK Office for National Statistics. Approval by the local research ethics committee was obtained; all patients gave informed consent to the study.

Echocardiographic Measurements

Echocardiographic examination was performed with the use of a Vivid 7 (General Electric Healthcare, Milwaukee, WI) and an IE-33 ultrasound system (Philips Medical Systems, Andover, MA). Images were acquired with the use of an M4S and SS-1 variable frequency harmonic phased-array transducer. Doppler echocardiography was performed according to the recommendations of the American Society of Echocardiography.\(^\text{10,11}\) Two cardiologists with advanced expertise in echocardiography interpreted the 2-dimensional echocardiographic images. Three consecutive cycles were averaged for each parameter. Left atrial (LA) area, right atrial (RA) area, RV inlet, LV ejection fraction, and LV end-diastolic diameter were measured. TAPSE was measured with the use of M-mode of the tricuspid lateral annulus motion. Transmirtal and tricuspid pulsed-wave Doppler velocities were recorded from the apical 4-chamber view with the sample volume placed at the tips of the valve leaflets, respectively. Early (E) and late (A) velocities and E/A ratio were measured from the mitral and tricuspid inflow profile. The myocardial systolic (tricuspid valve s’), early diastolic (mitral valve [MV] e’ and tricuspid valve [TV] e’), and late diastolic (MV a’, TV a’) velocities were obtained at the lateral mitral and tricuspid annulus by placing a tissue Doppler sample volume at the basal part of the respective segment. No tissue Doppler or long-axis function parameters were collected for the ventricular septum because the majority of patients had ventricular septal defects. Durations of systole and diastole were measured from the clearest Doppler signal of tricuspid regurgitation from the apical (most common) or parasternal view. Effective systolic duration was measured from the onset to the end of tricuspid regurgitation. Effective diastolic duration was measured from the onset of tricuspid regurgitation to the onset of the subsequent tricuspid regurgitation signal. The ratio between effective systolic and diastolic duration was then calculated. We also calculated RV fractional area change from the 4-chamber view. Retrograde transtricuspid pressure drop (gradient) was calculated from the tricuspid regurgitation continuous wave velocity signal with the use of the modified Bernoulli equation 4V^2. The pulmonary flow acceleration time and the right ventricular outflow tract velocity-time integral were also recorded. The pulmonary effective ejection time was measured from the onset to the cessation of pulsed-wave Doppler signal of transpulmonary velocities and indexed to the heart rate (Ejection Time/\sqrt{RR}). We calculated Tei index as (Systolic Time−Ejection Time)/Ejection Time, derived from the pulsed-wave Doppler. The total isovolumic time (t-IVT), which represents the sum of both isovolumic relaxation time and isovolumic contraction time, was estimated with the following formula: t-IVT=RR interval−(Ejection Time−Filling Time).\(^\text{12}\) This was then multiplied by heart rate and expressed as seconds per minute. The tissue Doppler imaging of RV myocardial acceleration during isovolumic contraction was measured at the lateral angle of the tricuspid annulus and indexed to the heart rate (RV isovolumic acceleration). The RA pressure was estimated on the basis of inferior vena cava diameter and collapsibility.\(^\text{13}\)

Statistical Analysis

Analyses were performed with the use of R version 2.13.2 (R Foundation for Statistical Computing). Data were summarized as number (percentage) for categorical variables and mean±SD or median (25th to 75th percentile) for continuous variables, as appropriate. The relation between echocardiographic parameters and death was assessed with the use of univariable and multivariable Cox proportional hazard regression analysis, with the date of echocardiography used as start date. Patients in whom advanced therapies were initiated or escalated during the follow-up period were not censored to avoid introducing bias (informative censoring). Multiple imputations were used to account for missing data (package Amelia). The 10 imputed databases were used to assess a risk prediction model, which included significant echocardiographic predictors alone or in conjunction with BNP and resting oxygen saturations with the use of Cox analysis. Bootstrapping was implemented on the imputed databases (package Boot; n=10 000 replicates), and the confidence intervals of the hazard ratio for the echocardiographic score were calculated with the adjusted bootstrap percentile method. Receiver operating curve analysis for censored data (package Survival ROC) was implemented and averaged across all imputed databases. For all analyses, a 2-tailed \(P\) value <0.05 was used as the criterion for statistical significance.

Results

Overall, 181 patients with Eisenmenger syndrome were included: 75 with a ventricular septal defect (5 had an additional PDA), 57 with complete atrioventricular septal defect, 29 with atrial septal defect, 16 with PDA alone, 3 with truncus arteriosus, and 1 with an aortopulmonary window.
Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All (n=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>59 (32.6%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>39.1 ± 12.8</td>
</tr>
<tr>
<td>Down syndrome, n (%)</td>
<td>74 (40.9%)</td>
</tr>
<tr>
<td>Cardiac defect, n (%)</td>
<td></td>
</tr>
<tr>
<td>Pre tricuspid</td>
<td>29 (16.0%)</td>
</tr>
<tr>
<td>Post tricuspid</td>
<td>152 (84.0%)</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>85.1 ± 7.8%</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
</tr>
<tr>
<td>NYHA VII</td>
<td>59 (32.6%)</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>122 (67.4%)</td>
</tr>
<tr>
<td>Heart rate at rest, bpm</td>
<td>76.3 ± 14.5</td>
</tr>
<tr>
<td>6-min walk test, m</td>
<td>300.9 ± 97.9</td>
</tr>
<tr>
<td>BNP concentration, ng/L</td>
<td>55.4 [31.1 to 134.9]</td>
</tr>
<tr>
<td>Advanced therapy, n (%)</td>
<td>74 (40.9%)</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>34 (18.8%)</td>
</tr>
<tr>
<td>Bosentan</td>
<td>32 (17.7%)</td>
</tr>
<tr>
<td>Bosentan+Sildenafil</td>
<td>8 (4.4%)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>16.4 [7.2 to 45.5]</td>
</tr>
</tbody>
</table>

The mean age of the patients at baseline was 39.1 ± 12.8 years; 59 (32.6%) were male, and 74 (40.9%) had Down syndrome (Table 1). Overall, 74 patients (40.9%) were on bosentan and/or sildenafil therapy at the time of the echocardiographic examination. Most patients were symptomatic (67.4% in New York Heart Association class ≥III). Cyanosis at rest was present in 70.2% of patients; 39.3% had a BNP > 50 ng/L.

Echocardiographic Characteristics of the Patients

Echocardiographic results of the patients are presented in Table 2. Overall, 66.9% of patients had a dilated RV, with an inlet diameter > 40 mm. RV impairment, defined as a TAPSE < 15 mm, was present in 65.2% of patients, but only 23.2% had a TAPSE < 15 mm, suggesting that in most cases longitudinal ventricular function was only mildly impaired. Similarly, although RV myocardial velocity (TV s') < 12 cm/s was present in 68.5%, it was < 8 cm/s in only 18.2% of patients. t-IVT (13.4 ± 8.3 s/min) was prolonged, and ratio of RV effective systole to diastolic duration (1.38 ± 0.6) was elevated compared with normal values, reflecting impaired RV ejection. The pulmonary acceleration time was short (70.8 ± 14.3 ms), in agreement with elevated pulmonary vascular resistance.

Influence of Type of Defect on Echocardiographic Parameters

RV and RA size were larger in patients with pretricuspid shunts (atrial septal defect) than in those with posttricuspid defects (P < 0.001 and P = 0.001, respectively). There was no difference in longitudinal RV systolic function between the 2 groups; however, RV fractional area change (P < 0.001) and myocardial acceleration during isovolumic contraction (P = 0.01) were lower in patients with pretricuspid shunts. In patients with posttricuspid defects, RV function was best in those with an atrioventricular septal defect compared with those with a ventricular septal defect and PDA, with a higher TAPSE (20.2 ± 4.9 versus 16.6 ± 3.4 and 17.2 ± 4.2 mm; P < 0.001, P = 0.04, respectively) and TV s' (10.3 ± 1.7 versus 9.4 ± 2.2 and 9.7 ± 2.5 cm/s; P = 0.03, P = 0.26, respectively). Pulmonary acceleration time appeared longest in patients with PDA (80.9 ± 19.6 ms) compared with patients with ventricular septal defect (68.8 ± 12.5 ms; P = 0.003) or atrioventricular septal defect (70.7 ± 11.5 ms; P = 0.01).

Echocardiography in Eisenmenger Syndrome

Over a median follow-up period of 16.4 (7.2–45.5) months, 19 patients died: 7 of heart failure and multiorgan failure, 5 of sudden cardiac death, and 2 of hemoptysis; in 5, the cause of death was unknown. A lower TAPSE and larger RA area as well as RA/LA ratio were strong predictors of all-cause mortality (Figure 2a). Patients with a TAPSE < 15 mm had a mortality rate > 30% at 3 years (Figure 3). Other significant predictors included RV myocardial systolic velocity (TV s'), TV e'/a' ratio, MV e', ratio of RV effective systole to diastolic duration, t-IVT, and RA pressure. The relation between mortality and RA area, as well as the ratio of RA/LA
area, was maintained even after exclusion of patients with pretricuspid shunts (hazard ratio, 3.28 per 10-cm² increase; 95% confidence interval, 1.63–6.58; \( P < 0.001 \); and hazard ratio, 2.58; 95% confidence interval, 3.70–46.73; \( P < 0.0001 \), respectively). Resting oxygen saturation and BNP concentration were also predictive of outcome on univariate analysis.

On multivariate Cox regression analysis, including TAPSE with each of the other significant predictors of death, the predictors of outcome were RA area, ratio of RA/LA area, ratio of RV effective systolic to diastolic duration, TV e/a’ , and MV e’ (Figure 2B). The prognostic power of these echocardiographic parameters was not influenced by advanced therapies. In fact, little change in the prognostic power of each parameter was found when they were included in the Cox model with established advanced therapy at the time of echocardiography (binary variable) (Figure 4). When the RA area and the ratio of RA/LA were included in a multivariable model, both were predictive of outcome (\( P = 0.003 \) and \( P = 0.002 \), respectively). However, this was not the case for RA pressure.

With the use of multiple imputations, 10 imputed databases were generated. A composite score, based on the strongest echocardiographic predictors of outcome, was generated; and 1 point was attributed to each of the following: TAPSE <15 mm, ratio of RV effective systolic to diastolic duration...
This score was strongly related to mortality (odds ratio, 3.69; 95% confidence interval, 2.31–5.91 by bootstrap analysis). On receiver operating curve analysis, the average area under the curve for the composite score in the imputed databases was 0.90 ± 0.01 compared with 0.67 ± 0.00 for TAPSE alone (Figure 5). The predictive power of the echocardiographic score did not improve either by the inclusion of diastolic parameters (TV e’/a’ and MV e’) or by the inclusion of BNP concentration (>50 ng/L) and resting saturation (<80%).

Discussion

Our study demonstrates that echocardiographic parameters can be applied to predict clinical outcome in Eisenmenger patients. Parameters reflecting RV function and elevated central venous pressures predicted all-cause mortality, assessed either alone or even more so in a composite score. We believe that this score may be used in the risk stratification of Eisenmenger patients and could influence the decision to escalate therapy.

Our data confirm significant differences in the pathophysiology of Eisenmenger syndrome compared with other types of PAH but also indicate important similarities. Patients with Eisenmenger syndrome have a significantly better prognosis compared with idiopathic PAH and connective tissue disease–associated PAH. Many patients survived for decades after the initial diagnosis of congenital heart disease, even before the advent of advanced targeted PAH therapy. The difference in outcome is thought to be related to better adaptation of the RV to systemic or high pulmonary artery pressure.

Central venous pressures predicted all-cause mortality, assessed either alone or in a composite score. The score with diastolic parameters (TV e’/a’ and MV e’), the score with BNP concentration and resting saturation, and TAPSE alone were compared using receiver operating curves.
pressures, which in turn maintains its function longer. In support of this view, the longitudinal function of the RV was maintained or mildly impaired in the majority of patients in our study. However, even small reductions in TAPSE were associated with adverse outcome in our cohort. Furthermore, even though RV dilation was prevalent, it was less severe than that described in idiopathic PAH and was not related to clinical outcome in our patients. Other markers of RV dysfunction provided prognostic information complementary to that of TAPSE. The duration of tricuspid regurgitation, a marker of impaired adaptation to pressure overload and of RV failure, was strongly related to outcome. Other known parameters shown to carry prognostic value in idiopathic PAH, such as LV eccentricity index, presence of pericardial effusion, and the RV myocardial performance index, were not predictive of outcome in our patients. However, t-IVT, which reflects the degree of ventricular dyssynchrony, was predictive of death (P = 0.047) but did not appear to provide prognostic information beyond that of TAPSE. Pericardial effusion was common in our Eisenmenger cohort (present in one quarter of patients) but did not have prognostic value, even after exclusion of patients with Down syndrome, perhaps suggesting a different underlying pathogenic mechanism compared with other types of PAH.

Although Eisenmenger patients may have a slower disease progression compared with idiopathic PAH, their long-term prognosis is far from normal. Multiorgan involvement and ultimately failure due to chronic cyanosis and congestion appear to play an important role in pathophysiology. RA dilation is a reflection of long-standing pressure overload and ensuing heart failure. Eisenmenger patients with pretricuspid shunts, who are thought to have a worse prognosis compared with those with posttricuspid shunts, are expected to have larger atria because of the long-standing shunt at the atrial level. However, the relation between RA size and survival was not confounded by the inclusion of pretricuspid shunts in our study because this relation remained strong even after the exclusion of patients with pretricuspid defects. RA dilation, beyond being a marker of right-sided overload and possibly stiffness of a hypertrophied RV, is also a predisposing factor for arrhythmia. Sudden death is common in this condition and is thought to be largely arrhythmic in cause. In patients with severe PAH, both ventricular and supraventricular arrhythmia can lead to rapid and major hemodynamic compromise and can thus lead to death.

Endothelin receptor antagonists such as bosentan (assessed in a randomized controlled trial in this setting), phosphodiesterase inhibitors, and prostanooids are now commonly considered for Eisenmenger patients. European guidelines recommend initiation of such therapy in class III or greater Eisenmenger patients, but suggestions have been made for inclusion of class II patients. In this study, World Health Organization functional class was not related to the risk of death. The evaluation of functional class is highly subjective and is likely to underestimate the functional status and disease severity. Moreover, recent data undermine the importance of symptoms in predicting mortality. This raises the question of whether echocardiography can be used to refine risk stratification in Eisenmenger syndrome, with the purpose of identifying a high-risk subgroup that could benefit from earlier therapy. This becomes particularly relevant in the light of recent evidence of the survival benefits of advanced therapies in this population. In our study, the association of echocardiographic parameters (a low TAPSE, high RA area, ratio of RA/LA area, and increased ratio of right ventricular effective systolic to diastolic duration) identified patients with a >3-fold increased risk of death, with a very high area under the curve on receiver operating curve analysis.

Although not the focus of this study, BNP concentration was confirmed as a strong predictor of all-cause mortality. BNP concentration appeared, however, to provide only little additional prognostic information to that of the echocardiographic score. BNP concentration should nevertheless be part of the periodic assessment of patients with PAH, and efforts should be made to prospectively develop and validate a score that includes echocardiographic and clinical data in a large Eisenmenger cohort over a longer follow-up period. Such a score would be invaluable in the management of these complex patients, assisting both robust prognostic assessment and optimization of advanced therapy.

Study Limitations
This is a single-center study, representative of the spectrum of patients followed in tertiary specialist centers. Patients with complex cardiac anatomy (≈20% of the Eisenmenger population under our care) were excluded from the study given the difficulty in applying echocardiographic measures employed here in patients with single ventricle or systemic RV in a uniform manner. The follow-up period in this study varied significantly in this contemporary cohort of patients, with a relatively short median follow-up of 16.4 months. Consequently, event rates were relatively low. Multiple imputations had to be used to account for missing data, which are inevitably present in an echocardiographic study such as this. To avoid informative censoring leading to bias, patients in whom advanced therapies were introduced during follow-up were not censored. It is, however, possible that their functional status might improve, potentially modifying their survival as predicted by the baseline echocardiographic score. Future larger studies may provide additional information and validate these echocardiographic measures in patients with Eisenmenger syndrome as well as the potential change in response to therapy in these patients.

Clinical Implications
Cardiac physiology and chronic adaptation to long-standing advanced pulmonary vascular resistance with underlying congenital heart disease and cyanosis (Eisenmenger syndrome) is strongly predictive of mortality in this adult population. Easily acquired and widely available echocardiographic indices, such as TAPSE, ratio of RV effective systolic to diastolic duration, RA area, and ratio of RA to LA area, are predictive of mortality, both independently and even more so in a composite score, and should therefore be incorporated routinely in the periodic assessment of Eisenmenger patients. A more aggressive management approach could be encouraged for patients identified as high risk on the
basis of these criteria, including advanced therapy, particularly because recent evidence has suggested that the latter improves functional capacity and possibly survival.

Conclusion
Echocardiographic parameters of RV function and RA area predict mortality in Eisenmenger patients. A new composite echocardiographic score, described hereafter, may be incorporated into the noninvasive, periodic assessment of these patients.

Disclosures
Drs Gatzoulis, Diller, Wort, and Dimopoulos and the Royal Brompton Hospital Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension have received unrestricted education grants and have acted as consultants for Actelion UK, Pfizer UK, Bayer UK, and GSK UK.

References
CLINICAL PERSPECTIVE

Although echocardiography provides accurate information on cardiac anatomy and physiology, as well as prognosis data in patients with idiopathic pulmonary arterial hypertension, only few data exist on the prognostic power of echocardiographic parameters in adults with Eisenmenger syndrome, which was the subject of this study. Our data from a single center on a large contemporary cohort of adults with Eisenmenger syndrome showed that echocardiographic indices of right ventricular function (tricuspid annular plane systolic excursion, ratio of right ventricular effective systolic to diastolic duration) and right atrial area are predictive of mortality, assessed either alone or even more so in a composite score. Because the assessment of functional class remains difficult, especially in patients with congenital heart disease, we believe that this score may be used in the risk stratification of Eisenmenger patients and could influence the decision to initiate or escalate therapy.

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