Title
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Journal
Journal of the American Heart Association, 9(6)

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Publication Date
2020-03-17

DOI
10.1161/JAHA.119.014554

Peer reviewed

Journal of the American Heart Association

ORIGINAL RESEARCH

Determinants of Sudden Cardiac Death in Adult Patients With Eisenmenger Syndrome

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BACKGROUND: Patients with Eisenmenger syndrome are known to have a high incidence of sudden cardiac death (SCD), yet the underlying causes are not well understood. We sought to define the predictors of SCD in this population.

METHODS AND RESULTS: A retrospective analysis of all patients with Eisenmenger syndrome from 2 large tertiary referral centers was performed. ECGs, prolonged ambulatory recordings, echocardiograms, and clinical histories were reviewed; and the cause of death was identified. A total of 246 patients (85 [34.6%] men) with a mean age of 37.3 (±14.2) years were followed up for a median of 7 years. Over the study period, 136 patients died, with 40 experiencing SCD and 74 experiencing cardiac death (sudden and nonsudden). Age, atrial fibrillation, prolonged QRS duration, complete heart block, right atrial enlargement, right bundle branch block, increased right atrial pressure, impaired biventricular function, and the presence of a pacemaker were associated with increased risk of SCD, whereas advanced pulmonary hypertension therapies were protective. Atrial fibrillation (11.45-fold increased risk; $P<0.001$) and QRS duration ≥120 ms (2.06-fold increased risk; $P=0.034$) remained significant predictors of SCD in the multivariate analysis, whereas advanced pulmonary hypertension therapies were strongly protective against SCD ($P<0.001$).

CONCLUSIONS: Atrial arrhythmias, impaired ventricular function, and conduction system disease were associated with increased risk of SCD in this cohort of patients with Eisenmenger syndrome, providing an opportunity for early risk stratification and potential intervention. Clinical heart failure symptoms (New York Heart Association class ≥II) were predictive of increased mortality but not of SCD, suggesting a potential arrhythmic cause behind SCD.

Key Words: atrial fibrillation ■ cardiac arrhythmia ■ congenital heart disease ■ congestive heart failure ■ Eisenmenger syndrome ■ sudden cardiac death

Important advances in early diagnosis and management of congenital heart disease (CHD) over the past half century, including surgical techniques and postoperative care, have led to increased survival of children with CHD, with most of them now surviving to adulthood.[1,2] However, either untreated or residual large left-to-right cardiac shunts can lead to irreversible pulmonary arteriolar changes and pulmonary arterial hypertension, leading to reversal of the shunt and cyanosis, the hallmark of Eisenmenger syndrome.[3,4] Clinical heart failure symptoms, increased risk of arrhythmias, syncope, sudden death, as well as complex hematologic, thrombotic, hemorrhagic, pulmonary, and infectious complications are all recognized sequelae of Eisenmenger syndrome.[5,6] Timely repair of cardiac shunts has reduced the prevalence of Eisenmenger syndrome by 50% over the past 50 years.[1] Previous studies have identified predictors of mortality in this population, highlighting the influence of oxygen saturations, arrhythmia, and type of defect (whether pretricuspid or posttricuspid) as significant independent risk factors

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For Sources of Funding and Disclosures, see page 16.

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CLINICAL PERSPECTIVE

What Is New?

- Atrial fibrillation, prolonged QRS duration ≥120 ms, complete heart block, right bundle branch block, impaired biventricular function, and high-burden right ventricular pacing are predictors of sudden cardiac death in the population with Eisenmenger syndrome.
- Advanced pulmonary hypertension therapies are strongly protective against sudden death, cardiac death, and all-cause mortality.

What Are the Clinical Implications?

- Early identification of the population at risk would warrant closer follow-up and potentially intervention to treat arrhythmias and improve biventricular function.
- The intervention may consist of antiarrhythmic therapy, ablation, or early implementation of advanced pulmonary hypertension therapies.

Nonstandard Abbreviations and Acronyms

CHD	congenital heart disease
VSD	ventricular septal defect
PDA	patent ductus arteriosus
AVCD	atrioventricular canal defect
CHB	complete heart block
RA	right atrium (atrial)
RV	right ventricle (ventricular);
LV	left ventricle (ventricular)
QTc	QT interval corrected by the Bazett formula

for all-cause mortality.[7,8] Yet, little is known about the risk factors for sudden cardiac death (SCD) and prevention strategies in this population. In this context, we sought to determine the predictors of SCD in a cohort of patients with Eisenmenger syndrome followed up longitudinally at 2 large tertiary referral centers in the United States.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patient Population

Patient records from the Mayo Clinic Adult Congenital Heart Disease Clinic and the Ahmanson/UCLA Adult Congenital Heart Disease Center were queried from 1987 to 2015. All patients with a diagnosis of Eisenmenger syndrome were included in the analysis and followed up until June 2018, death, or cardiac transplantation. Eisenmenger syndrome was defined as the presence of irreversible pulmonary arterial hypertension in the setting of a large nonrestrictive intracardiac or extracardiac shunt, leading to shunt reversal and cyanosis. The study protocol was approved by the institutional review board at each institution. Individual consent was waived by the institutional review board because of the retrospective and deidentified nature of the data.

Data Review

The date of first contact with the treating institution was considered the date of the first cardiology or congenital heart consultation. Anatomical defects leading to Eisenmenger syndrome were obtained from documented clinical histories and confirmed by echocardiography. Simple defects were defined as ventricular septal defects (VSD), patent ductus arteriosus (PDA), or atrial septal defects (ASD), whereas complex CHD was defined as the presence of double outlet ventricles, single ventricles, transposition of the great arteries, conotruncal defects, or atrioventricular canal defects.

Baseline ECG findings were documented. Furthermore, serial ECGs, telemetry recordings, prolonged ambulatory ECGs, electrophysiology procedures, and pacemaker interrogations were reviewed in detail to define the arrhythmic history.

Findings on the last echocardiogram (or the last echocardiogram before cardiac transplantation) were recorded for the most recent physiologic parameters. These included a detailed anatomic characterization of the congenital defect, residual shunts, qualitative and quantitative assessments of the left ventricular and right ventricular size and function (when applicable), extent of tricuspid regurgitation, the estimated right ventricular systolic pressure, and, when available, the right ventricular index of myocardial performance or Tei index (calculated as the sum of the isovolumetric contraction and isovolumetric relaxation times divided by ejection time). When applicable (patients with a systemic left ventricle), the left ventricular ejection fraction (LVEF) was determined by either visual estimate or using the biplane Simpson method. Atrial size and pressure and the presence of a pericardial effusion were also documented. The right atrial (RA) pressure was estimated on the basis of the size of the inferior vena cava, magnitude of inspiratory collapse, and hepatic vein velocity curves. The echocardiographic estimate of RA pressure was previously shown to correlate with direct catheterization measurements of RA pressure.[9]

Cardiac catheterization data were reviewed for the presence of coronary artery disease, and the presence

of "coronary artery disease more than mild" was documented, if present. This was defined in this study to include both coronary atherosclerotic disease and significant compression of a coronary artery by the enlarged pulmonary.

Electronic medical records and, when necessary, paper medical records were reviewed, and clinical events and outcomes were recorded. For patients who underwent previous surgical interventions, details on the procedures performed were reviewed. The cause-specific mortality was the cause or disease leading directly to death, according to the World Health Organization definition. This was independently reviewed from many sources, including clinical notes, telemetry recordings, ECGs, resuscitation notes, autopsy reports (when available), and death certificates. SCD was defined as unexpected death occurring within 1 hour of the onset of symptoms or an unexpected unwitnessed death in a patient known to have been well at one time within the previous 24 hours. SCD may be caused by a fatal arrhythmia or a sudden pump failure with sudden decrease in cardiac output (which, in turn, could be caused by cardiac or noncardiac reasons, such as acute thromboembolic events or massive hemorrhage). If a noncardiac reason was clearly documented in a patient (ie, massive hemorrhage), the cause of death was adjudicated as noncardiac in this study.

Potential risk factors for SCD considered in this analysis included the presenting rhythm and baseline ECG findings, atrial and ventricular arrhythmias on longitudinal follow-up, presence of conduction system disease, prior syncope, need for a pacemaker (including type of device, epicardial versus transvenous, and type and amount of pacing), atrial and ventricular size and function on echocardiography, the presence of clinical heart failure symptoms (New York Heart Association [NYHA] class >II), presence of coronary artery disease, cerebrovascular disease, documented thromboembolism, hemoptysis, recurrent phlebotomies, infections, and pulmonary complications. The use of antiarrhythmic drugs, systemic anticoagulation, and advanced pulmonary hypertension therapies was also documented.

Statistical Analysis

Demographic and clinical information was obtained retrospectively for the 246 patients. Continuous variables were summarized with mean and SD, and categorical variables were summarized with number and percentage of patients. Outcomes of interest were estimated using the Kaplan-Meier method. These end points included SCD, cardiac death, noncardiac death, and all-cause mortality. Univariate Cox proportional hazard models were used to assess the associations of patient demographics and clinical measures with each of the end points. Significantly associated variables of interest (2-sided $P<0.05$) were then used in multivariate Cox proportional hazard models for each end point. In addition, the proportional hazard assumption was assessed using Schoenfeld residuals and assessing the relationship with time. The only variable in the primary group of variables that violated that assumption in the models was the use of advanced pulmonary hypertension medications. That variable was used as a stratifying factor in those models. Statistical analyses were performed using R Statistical Software, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Population

A cohort of 246 patients with documented Eisenmenger syndrome, 146 from Mayo Clinic and 100 from UCLA, were included in this analysis. Among these patients, 85 (34.6%) were men and 161 (65.4%) were women, with a mean age of 37.3 (±14.2) years and a median age of 37 years; they were followed up for 8.4±6.9 years, with a median follow-up of 7.1 years. General characteristics of this population are outlined in Table 1.

The most common anatomical defect was ventricular septal defect, present in 104 (42%) patients, followed by ASD in 60 (24.4%) patients (48 secundum ASD, 11 sinus venosus ASD, and 1 coronary sinus ASD), and PDA in 30 (12%) patients. Combined simple lesions were present in 14 (5.7%) cases. Atrioventricular canal defects were present in 42 (17%) patients. Complex CHD was present in 118 (48%) patients, and 32 (13%) patients had single-ventricle physiological characteristics.

Prior palliative cardiac surgeries (ie, atrial or ventricular septal closure or PDA ligation that subsequently reopened, Watterson or Potts shunts, or Mustard operations) had been performed in 38 (15.4%) patients; however, they still developed Eisenmenger syndrome over time. From the 246 patients, 42 (17%) had documented Down syndrome, with 19 (46%) men, and a mean age of 32±12.3 years (median age, 33.5 years). The most common congenital cardiac defect in this group was atrioventricular canal defect, present in 25 (60%) patients.

Clinical heart failure symptoms (NYHA class ≥II) were documented in 104 (42.3%) patients. Screening for coronary artery disease with coronary angiography was performed at the discretion of the treating physician, on the basis of clinical suspicion. Coronary artery stenosis more than mild was documented in only a minority of patients (9 [3.7%]), and this number includes one case of extrinsic compression of

Table 1. General Characteristics of the Population With Eisenmenger Syndrome

Characteristics	Value (N=246)
Male sex	85 (34.6)
Age at first contact, y	
No.	246 (100)
Mean (SD)	37.297 (14.221)
Median	36.749
Quartile 1, quartile 3	27.208, 46.060
Range	0.000–88.271
Anatomical defect	
No.	246 (100)
VSD	104 (42)
PDA	30 (12)
Secundum ASD	48 (19.5)
Sinus venosus ASD	11 (4.5)
Coronary sinus ASD	1 (0.4)
Atrioventricular canal	42 (17)
Complex congenital heart disease	118 (48)
Single ventricle	32 (13)
Down syndrome	
No.	42 (17)
Age, y, mean (SD)	32 (12.25)
VSD	14 (33.3)
PDA	5 (12)
ASD	2 (4.76)
Atrioventricular canal	25 (60)
Combined simple lesions	4 (9.5)
Complex congenital heart disease	26 (62)
Single ventricle	1 (2.4)
Coronary artery disease (>mild)	9 (3.7)
Clinical heart failure (NYHA class ≥II)	104 (42.3)
CVA	38 (15.4)
Thromboembolism	28 (11.4)
Syncope	20 (8.1)
Hemoptysis	36 (14.6)
Phlebotomies	31 (12.6)
Malignancy	10 (4.1)
Listed for transplant	19 (7.72)
Received transplant (combined heart/double lung)	7 (2.85)
LVEF	
N (with a left ventricle, for whom LVEF can be assessed)	218
LVEF, mean (SD), %	52 (11.7)
Median LVEF, %	55
Quartile 1, quartile 3, %	45, 60
Range, %	10–75
No. of patients with LVEF ≤40%	47 (21.6)
RA pressure overload (>10 mm Hg)	92 (49.7)
RV enlargement (moderate or severe)	134 (62.65)
RV systolic dysfunction (moderate or severe)	114 (55.3)
Tricuspid regurgitation (moderate or severe)	78 (31.7)
RVSP >60 mm Hg	142 (94)
RVSP >80 mm Hg	126 (83.4)
RVSP >100 mm Hg	88 (58.3)
Pericardial effusion (>mild)	12 (4.9)
Atrial fibrillation on first ECG	8 (3.5)
Atrial flutter/AT/IART on first ECG	1 (0.4)
Atrial fibrillation/flutter on any modality during follow-up	41 (16.7)
NSVT	22 (8.9)
Sustained VT	9 (3.7)
Antiarrhythmic drugs	75 (30.5)
Anticoagulation	55 (22.4)
Advanced pulmonary hypertension drugs	105 (42.7)
Ablation (all atrial-level or SVT ablations)	9 (3.7)
Pacemaker	13 (5.3)
ICD	4 (1.6)

Data are given as number (percentage), unless otherwise indicated. LVEF, RA pressure, RV size and function, degree of tricuspid regurgitation, estimated RVSP, and presence of pericardial effusion were determined on echocardiography in all patients for whom such an assessment was possible (ie, LVEF for patients with a left ventricle, RV size and function for patients with a right ventricle). RVSP was assessed for patients in whom a tricuspid regurgitation jet was present. ASD indicates atrial septal defect; CVA, cerebrovascular accident; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NSVT, nonsustained VT; NYHA, New York Heart Association; RA, right atrial; RV, right ventricular; RVSP, RV systolic pressure; SVT, supraventricular tachycardia; VSD, ventricular septal defect; VT, ventricular tachycardia; PDA, patent ductus arteriosus; AT, atrial tachycardia; and IART, intra-atrial reentrant tachycardia.

a coronary artery by the enlarged pulmonary artery, requiring stenting. A history of syncope was documented in 20 (8.1%) patients. Clinical thromboembolism was diagnosed in 28 (11.4%) patients, whereas a cerebrovascular accident was documented in 38 (15.4%) patients. Hemoptysis was documented during follow-up in 36 (14.6%) cases, and phlebotomies were performed in 31 (12.6%) of cases. A malignancy was discovered in 10 (4.1%) patients during follow-up. From the 19 (8%) patients with Eisenmenger syndrome listed for transplant, 7 (3%) received a combined heart/double-lung transplant by the end of the study.

Echocardiography

Of the 218 patients with a systemic left ventricle for whom an LVEF could be determined on the basis of the echocardiogram, the mean LVEF was 52% (±11.7%). Right ventricular enlargement (at least moderate or severe) was documented in 134 (62.6%) patients, and right ventricular dysfunction (at least moderate or severe) was present in 114 (55.3%) patients.

The RA pressure estimated by echocardiography was increased in 92 (49.7%) patients. The estimated right ventricular systolic pressure was >60 mm Hg in 94% of cases, >80 mm Hg in 83.4% of cases, and >100 mm Hg in 58.3% of cases. At least moderate or severe tricuspid regurgitation was detected in 43.3% of patients. A pericardial effusion (more than mild) was detected in 12 (4.9%) patients.

Electrocardiography

Atrial fibrillation was present on the initial ECG in 8 (3.5%) patients, 1 patient had atrial flutter, 2 patients had atrioventricular nodal reentrant tachycardia, 5 patients had an atrial tachycardia, and 6 patients had an ectopic atrial rhythm. For the remaining patients with sinus rhythm on their initial ECG, sinus tachycardia (heart rate >100 beats per minute) was present in 28 (12.2%) patients, and sinus bradycardia (heart rate <60 beats per minute) was present in 21 (9.2%) patients.

When feasible to estimate by ECG, right and left atrial enlargement were present in 96 (42.7%) and 59 (26.5%) patients, respectively. Conduction system disease with first-degree atrioventricular block was present in 33 (14.4%) patients, and third-degree atrioventricular block was present in 3 (1.3%) patients. The mean native QRS duration was 109.3 ms (±21.7 ms). QRS prolongation >100 ms was noted in 132 (58%) patients, and QRS duration ≥120 ms was noted in 67 (29.3%) patients. Three patients had a paced QRS on the initial ECG, and these were not included in the native QRS width analysis. Right bundle branch block was present in 91 (40.6%) cases, and left bundle branch block was present in 30 (13.5%) cases. The mean corrected QT interval using the Bazett formula was 449 ms (±36.42 ms).

Arrhythmia Burden and Management During Follow-Up

Reviewing serial ECGs, telemetry tracings, ambulatory ECGs, and procedural notes, atrial fibrillation was eventually demonstrated in 41 (16.7%) patients. In addition, 51 (20.7%) patients demonstrated an atrial or supraventricular tachycardia during follow-up. On the other hand, only 22 (8.9%) patients had documented nonsustained ventricular tachycardia and 9 (3.7%) had sustained ventricular tachycardia.

One or more antiarrhythmic drugs (ie, Vaughan Williams class I–IV and digoxin) were used in 75 (30.5%) patients. Of these, class III antiarrhythmic drug (amiodarone, sotalol, or dofetilide) was used in most cases (34 patients [45%]), followed by class II (β blockers in 15 patients [20%]), class IV (calcium channel blockers in 7 patients [9.3%]), and class I (sodium channel blockers in 3 patients [0.4%]). Of the latter, mexiletine, procainamide, and flecainide were each used in one patient. Digoxin was used singly or combined with other antiarrhythmic drugs in 27 (36%) patients.

Within this Eisenmenger cohort, 14 ablation procedures were performed for drug-refractory arrhythmias in 9 (3.7%) patients. All these ablations were done for atrial-level or supraventricular tachycardias, with most for focal atrial tachycardia or atrial flutter (intra-atrial reentrant tachycardia) and 2 for supraventricular tachycardias.

Cardiac Implantable Electronic Devices

A pacemaker was present in 13 (5.3%) patients, and a defibrillator was present in 4 (1.6%) patients (Table 2). Among the 13 pacing devices, there were 7 epicardial and 6 transvenous systems. One patient who initially presented with a transvenous device from another institution had this device removed and replaced with an epicardial system at Mayo Clinic. This was in the setting of complete atrioventricular canal, complete heart block, and recurrent cardioembolic strokes related to pacemaker wires. Of note, the patient had not been a candidate for systemic anticoagulation because of the risk of exsanguinating pulmonary hemorrhage. Three other patients had unrepaired intracardiac shunts, high-degree atrioventricular block, and transvenous pacemakers, without anticoagulation. Of these patients, 1 experienced 2 strokes, prompting the initiation of anticoagulation (the transvenous device was not replaced in this case), whereas the other 2 remained stroke free and were not anticoagulated. Another patient with unrepaired intracardiac shunt had a transvenous device and was treated with anticoagulation (in the absence of another documented indication for anticoagulation, such as atrial fibrillation or venous thromboembolism). He experienced a fatal spontaneous hemorrhagic stroke.

The indications for pacing in this population included complete heart block in 7 patients and sinus node dysfunction or sinoatrial exit block in 5 patients. Furthermore, chronotropic incompetence and combined sinus node and atrioventricular node dysfunction were documented in 3 patients. High burden of ventricular pacing was present in 7 patients (further details, arrhythmia history, indication and type of pacemaker, percentage of ventricular pacing, and patient outcomes are summarized in Table 2).

Anticoagulation and Advanced Pulmonary Hypertension Therapies

In this cohort with Eisenmenger syndrome, 55 (22.4%) patients were treated with anticoagulation (mostly with warfarin [Coumadin] for atrial fibrillation and flutter), and 105 (43%) patients were treated with advanced

Table 2. Pacemaker Patients, Clinical Characteristics, and Outcomes

Patient	Anatomic Defect	Arrhythmia	Type of Device	Indication for Pacing	Pacing %	Outcome
Mayo 1	Large inlet VSD and moderate-sized secundum ASD	Recalcitrant atrial fibrillation s/p multiple cardioversions, failed AAD	Epicardial	Chronotropic incompetence	N/A	SCD Died shortly after surgery, sudden hypotension
Mayo 2	Double-outlet RV with L-TGA and VSD, s/p Mustard	Multiple refractory atrial flutters s/p ablation, on AAD	Epicardial	Sinoatrial exit block and sinus node dysfunction	DDD AS-VS 74%, AP-VS 26%	Alive
Mayo 3	Left atrioventricular valve atresia, single ventricle (systemic RV)	Atrial fibrillation	Epicardial	Complete heart block	VVIR VP-100%	SCD Was feeling well prior, suspected malignant ventricular arrhythmia
Mayo 4	L-TGA and VSD	None	Transvenous	Complete heart block	Unknown, probably 100% VP	Died of heart failure
Mayo 5	Complete atrioventricular canal	Atrial fibrillation, on AAD	Epicardial	Sick sinus syndrome	A Fib 80% AP-VS 20%	Alive
Mayo 6	Complete atrioventricular canal	None	Transvenous, exchanged for epicardial after stroke	Complete heart block	VP-100%	Died of heart failure Experienced a stroke in the setting of documented thrombus on transvenous pacing wires Not anticoagulated because of risk of exsanguinating pulmonary hemorrhage
Mayo 7	Large membranous VSD	Refractory atrial tachyarrhythmias s/p cardioversions, on AAD	Epicardial	Sick sinus syndrome, atrioventricular node dysfunction	AP-VP 100%	SCD, presumed arrhythmic
Mayo 8	Double-inlet left ventricle	SVT and atrial tachycardia, on AAD	Epicardial	Complete heart block	Mostly VP, with occasional tracking of atrial tachycardia	SCD, presumed arrhythmic Had been feeling well prior, sudden collapse while dancing
UCLA 1	VSD	Ventricular ectopy requiring AAD	Transvenous	Second-degree atrioventricular block	Dual-chamber pacemaker Limited data Not paced on available ECGs	Alive
UCLA 2	D-TGA s/p Mustard with closure of the VSD, there was an intra-atrial baffle leak	No documented atrial fibrillation AVNRT on one ECG	Transvenous	Sinus node dysfunction, complete heart block	VVI Limited data Intermitted V-pacing on ECG	SCD
UCLA 3	D-TGA s/p Mustard without repair of the VSD	Sustained VT, on AAD	Transvenous	Complete heart block	CRT-D 1 ICD shock VP 99%	Noncardiac death Spontaneous hemorrhagic stroke
UCLA 4	L-TGA, double-inlet left ventricle	None	Transvenous	Complete heart block	DDD Limited data, unclear VP %	Alive Two strokes before anticoagulation, then warfarin (Coumadin) started
UCLA 5	VSD	Atrial fibrillation, SVT, on AAD	Epicardial	Sinus node dysfunction	AAI-DDD AP 99.4% VP 4.3%	Alive

AAD indicates antiarrhythmic drugs; A Fib, atrial fibrillation; AP, atrial pacing; ASD, atrial septal defect; AVNRT, atrioventricular nodal reentrant tachycardia; ICD, implantable cardioverter-defibrillator; RV, right ventricular; SCD, sudden cardiac death; s/p, status post; SVT, supraventricular tachycardia; TGA, transposition of the great arteries; VP, ventricular pacing; VSD, ventricular septal defect; VT, ventricular tachycardia; N/A, not applicable; L-TGA, Levo-transposition of the great arteries; D-TGA, Dextro-transposition of the great arteries; AS, atrial sensing; AP, atrial pacing; VS, ventricular sensing; VP, ventricular pacing; CRT-D, Cardiac resynchronization therapy and Defibrillator; UCLA, University of California Los Angeles; DDD, dual chamber pacing, dual sensing and dual response to sensing; VVI, ventricular pacing, ventricular sensing and inhibition to sensing; VVIR, the same as VVI but with rate response modulation; and AAI, atrial pacing, atrial sensing, and inhibition to sensing.

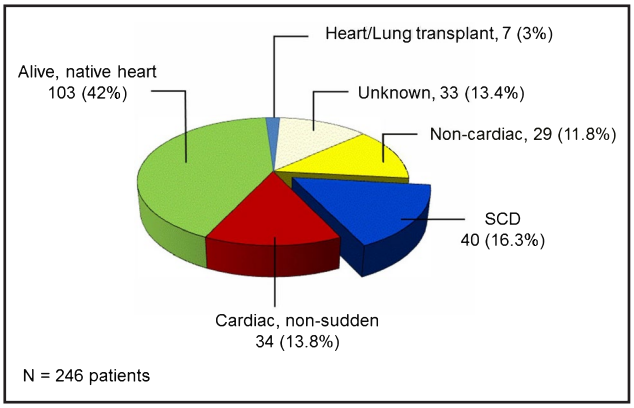

Figure 1. Clinical outcomes in patients with Eisenmenger syndrome. Of the 246 patients, 40 (16.3%) died of sudden cardiac death and 34 (13.8%) died of cardiac but nonsudden causes. Total cardiac mortality was calculated as the sum of sudden and nonsudden cardiac death (N=74 [30%]). SCD indicates sudden cardiac death.

pulmonary hypertension therapies, including phosphodiasterase-5 inhibitors, prostacyclin analogues, and endothelin-1 receptor antagonists.

Patient Outcomes

Among this cohort with Eisenmenger syndrome, 136 patients died, 7 underwent combined heart/lung transplantation, and 103 survived to the end of the study. The cause of death was SCD in 40 patients and cardiac nonsudden death (ie, heart failure) in 34 patients, for a total cardiac death of 74 patients (cardiac sudden and nonsudden) (Figure 1). In contrast, 29 patients had a clearly discernable noncardiac cause of death (eg, pneumonia, massive hemoptysis, massive hemorrhagic stroke or ischemic stroke, and other documented infectious or systemic complications), whereas 33 patients had an unknown or undocumented cause of death (ie, unavailable records, died at home or on hospice, or were lost to follow-up).

In addition to the 40 patients who died of SCD, there was another patient who had a poorly documented peripartum cardiac arrest during induction of labor ≈12 to 13 years before the diagnosis of Eisenmenger syndrome; she had a cesarean section and went on to live a normal life for many years. Outside testing at the time had revealed a dilated

Table 3. Clinical Parameters and Total Mortality (N=136)

Clinical Variable	No. of Patients of 246	Total No.	No. of Events	Hazard Ratio (95% CI)	*P* Value
Men	85	246	136	1.51 (1.07–2.14)	0.02*
Age, y (mean±SD)	37.3±14.2	246	136	1.03 (1.02–1.05)	<0.001*
VSD	104	246	136	1.11 (0.79–1.56)	0.535
PDA	30	246	136	1.16 (0.68–1.99)	0.585
Secundum ASD	48	246	136	2.11 (1.42–3.16)	<0.001*
Sinus venosus ASD	11	246	136	1.24 (0.58–2.66)	0.58
Coronary sinus ASD	1	246	136	9.58 (1.29–70.96)	0.027
Atrioventricular canal	42	246	136	0.76 (0.46–1.25)	0.272
VSD and ASD	9	246	136	4.34 (1.72–10.95)	0.002*
VSD and PDA	8	246	136	0.81 (0.26–2.56)	0.723
Single ventricle	32	246	136	0.62 (0.35–1.08)	0.09
Down syndrome	42	246	136	0.91 (0.57–1.45)	0.684
Clinical heart failure (NYHA class ≥II)	104	246	136	1.95 (1.39–2.74)	<0.001*
Atrial fibrillation on first ECG	8	229	128	2.44 (1.14–5.25)	0.022*
NSVT	22	246	136	0.37 (0.17–0.8)	0.012*
Ablation	9	246	136	0.57 (0.23–1.39)	0.215
Pacemaker	13	246	136	1.28 (0.62–2.61)	0.505
ICD	4	246	136	0.58 (0.14–2.33)	0.438
Antiarrhythmics	75	246	136	0.87 (0.6–1.27)	0.478
Anticoagulation	55	246	136	1.06 (0.71–1.6)	0.767
Advanced pulmonary hypertension drugs	105	246	136	0.22 (0.15–0.33)	<0.001*
CVA	38	246	136	0.7 (0.43–1.14)	0.152
Syncope	20	246	136	1.16 (0.63–2.15)	0.638

ASD indicates atrial septal defect; CVA, cerebrovascular accident; ICD, implantable cardioverter-defibrillator; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; VSD, ventricular septal defect; and PDA, Patent ductus arteriosus.

*$P<0.05$.

heart and a small ASD, and there was a suspicion of peripartum cardiomyopathy. However, she eventually became a patient at the Mayo Clinic, was found to have an ASD and anomalous pulmonary vein return, and established Eisenmenger syndrome 13 years after the index event. Because this event took place presumably before she had established Eisenmenger physiological characteristics, and because the circumstances are unclear (further documentation and telemetry tracings unavailable), she was not included in the statistical analysis of patients with SCD for this study. However, this event raised an important concern and she did not have further children.

Clinical Parameters and Predictors of Mortality

Total Mortality

Age (P<0.001), male sex (P=0.02), clinical heart failure symptoms with NYHA functional class of at least II (P<0.001), and atrial fibrillation on presentation to the tertiary care institution (P=0.022) were significantly associated with increased total mortality in the univariate analysis (Table 3). On the other hand, advanced pulmonary hypertension therapies were protective (P<0.001). Furthermore, there was an association between the presence of a secundum ASD and increased risk of death (hazard ratio [HR], 2.11; 95% CI, 1.42–3.16; P<0.001). Coronary sinus ASD seemed to predict worse outcomes as well (P=0.027); however, this anatomical defect was present in only one patient in this cohort. Finally, combined ASD and ventricular septal defects were associated with a higher mortality (HR, 4.34; 95% CI, 1.72–10.95; P=0.002).

SCD and Cause-Specific Mortality

Age (P=0.011) and atrial fibrillation (P<0.001) remained significant predictors of SCD, and advanced pulmonary hypertension therapies were strongly protective against sudden death (P<0.001) (Table 4). Furthermore, the presence of a pacemaker conferred a unique SCD-specific risk in this population (HR, 2.75; 95% CI, 1.07–7.06; P=0.036). On the other hand, functional class, defined as the presence of clinical heart failure symptoms (NYHA class at least II or greater), although

Table 4. Clinical Parameters and SCD (N=40)

Clinical Variable	Total No.	No. of Events	Hazard Ratio (95% CI)	*P* Value
Men	246	40	1.78 (0.95–3.34)	0.073
Age	246	40	1.03 (1.01–1.06)	0.011*
VSD	246	40	0.89 (0.47–1.68)	0.72
PDA	246	40	1.02 (0.36–2.86)	0.974
Secundum ASD	246	40	1.96 (0.93–4.15)	0.078
Sinus venosus ASD	246	40	1.82 (0.56–5.92)	0.32
Coronary sinus ASD	246	40	36.42 (4.38–302.62)	<0.001*
Atrioventricular canal	246	40	0.71 (0.28–1.81)	0.47
VSD and ASD	246	40	2.87 (0.38–21.96)	0.309
VSD and PDA	246	40	0.87 (0.12–6.35)	0.892
Single ventricle	246	40	0.98 (0.41–2.34)	0.96
Down syndrome	246	40	1.24 (0.57–2.71)	0.582
Clinical heart failure (NYHA class ≥II)	246	40	1.58 (0.85–2.95)	0.147
Atrial fibrillation on first ECG	229	38	6.35 (2.45–16.41)	<0.001*
NSVT	246	40	0.58 (0.18–1.88)	0.364
Ablation	246	40	0.76 (0.18–3.15)	0.702
Pacemaker	246	40	1.66 (0.69–3.99)	0.261
ICD	246	40	0.92 (0.13–6.71)	0.932
Antiarrhythmics	246	40	1.14 (0.6–2.2)	0.684
Anticoagulation	246	40	1.53 (0.78–3.02)	0.218
Advanced pulmonary hypertension drugs	246	40	0.21 (0.1–0.44)	<0.001*
CVA	246	40	0.74 (0.31–1.78)	0.504
Syncope	246	40	1.85 (0.72–4.72)	0.201

ASD indicates atrial septal defect; CVA, cerebrovascular accident; ICD, implantable cardioverter-defibrillator; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death; PDA, patent ductus arteriosus; and VSD, ventricular septal defect.

*P<0.05.

a significant predictor of cardiac mortality ($P<0.001$) and all-cause mortality ($P<0.001$), was not associated with sudden death.

There was no particular association between the type of anatomical defect leading to Eisenmenger syndrome and the risk of sudden death. Although a secundum ASD seemed to confer an increased risk of cardiac death and total mortality ($P<0.001$), there was no association between ASD and sudden death.

Furthermore, there was no significant association between the rare presence of coronary artery stenosis (including one case of extrinsic compression of the left main coronary artery requiring stenting), prior syncope, thromboembolism, cerebrovascular accident, phlebotomy or hemoptysis and SCD, cardiac mortality, or all-cause mortality, but there was a positive correlation between malignancy and noncardiac death (10.08-fold increased risk; $P=0.005$). Last, there was no association between Down syndrome and SCD in this cohort (Table 4).

Advanced pulmonary hypertension therapies and protection against sudden death

Advanced pulmonary hypertension therapies were found to be protective, reducing the risk of SCD by 5-fold (HR for SCD in the univariate analysis, 0.21; 95% CI, 0.1–0.44; $P<0.001$). Because these therapies were introduced in mainstream clinical practice after the publication of the landmark BREATHE-5 (The Bosentan Randomized Trial of Endothelin, Antagonist Therapy-5) trial in 2006, we investigated whether exposure to these therapies remained a significant predictor even after adjustment for the time factor. In a multivariate analysis taking into account the use of advanced pulmonary hypertension therapies and timing of presentation (before or after 2006), there was sufficient evidence to suggest significant protection against SCD with these medications (HR, 0.22; 95% CI, 0.10–0.46; $P<0.001$).

Echocardiography predictors of mortality and sudden death

Reduced LVEF (≤40%) was associated with increased risk of SCD (HR, 3.38; 95% CI, 1.71–6.66; $P<0.001$) and cardiac mortality (HR, 2.62; 95% CI, 1.57–4.37; $P<0.001$) (Table 5). Although the mean LVEF for the cohort was 52% (±11.7%), there were 47 patients with an LVEF ≤40%. For these patients, the overall mortality was 83%; 15 (32%) of patients succumbed to SCD (versus 16% for the entire cohort), and 24 (51%) succumbed to cardiovascular death (versus 30% for the entire cohort).

Although right ventricular dilation and systolic dysfunction were significantly associated with cardiac mortality, the association with SCD did not reach statistical significance (Table 5). On the other hand, right ventricular index of myocardial performance was a predictor of both SCD and cardiac mortality; however, this parameter was only reported on echocardiograms in 111 (45%) patients. There was no association between the estimated right ventricular systolic pressure on echocardiography and SCD.

An increased RA pressure (>10 mm Hg) was associated with a significant increase in SCD (HR, 2.49; 95% CI, 1.13–5.48; $P=0.024$), as well as cardiac mortality (3.34-fold increased risk; $P<0.001$). On the other hand, the presence of a pericardial effusion was associated

Table 5. Echocardiography and Outcomes

Echocardiographic Variable	Sudden Death		Cardiac Death		Noncardiac Death	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
LVEF (continuous variable)	0.96 (0.94, 0.99)	0.003†	0.97 (0.95, 0.99)	0.001†	1.02 (0.98, 1.05)	0.367
LVEF ≤40%	3.38 (1.71, 6.66)	<0.001†	2.62 (1.57, 4.37)	<0.001†	0.44 (0.15, 1.28)	0.131
RV enlargement*	1.28 (0.63, 2.62)	0.493	2.03 (1.14, 3.61)	0.015†	2.11 (0.78, 5.7)	0.141
RV dysfunction*	1.67 (0.84, 3.33)	0.144	2.78 (1.6, 4.83)	<0.001†	2 (0.8, 4.99)	0.139
RIMP	6.13 (1.92, 19.61)	0.002†	6.7 (2.85, 15.78)	<0.001†	1.11 (0.19, 6.49)	0.91
TR*	1.35 (0.58, 3.1)	0.486	1.55 (0.84, 2.86)	0.16	1.25 (0.51, 3.09)	0.626
RA >10 mm Hg	2.49 (1.13, 5.48)	0.024†	3.34 (1.85, 6.04)	<0.001†	0.82 (0.34, 2)	0.669
RVSP >60 mm Hg	0.89 (0.12, 6.76)	0.911	0.57 (0.17, 1.87)	0.352	1.65 (0.22, 12.41)	0.628
RVSP >80 mm Hg	1.11 (0.38, 3.27)	0.85	1.17 (0.52, 2.64)	0.702	4.47 (0.59, 33.65)	0.146
RVSP >100 mm Hg	1.04 (0.46, 2.38)	0.916	1.28 (0.69, 2.34)	0.432	1.77 (0.67, 4.66)	0.25
Pericardial effusion	2.19 (0.78, 6.16)	0.138	2.38 (1.14, 4.97)	0.021†	N/A	N/A

Mean LVEF=52% (±11.7%). LVEF indicates left ventricular ejection fraction; RA, right atrial; RIMP, RV index of myocardial performance; RV, right ventricular; RVSP, RV systolic pressure; TR, tricuspid regurgitation; and N/A, not applicable.

*Moderate or severe enlargement/dysfunction/regurgitation.

†$P<0.05$.

Table 6. Findings on the Initial ECG and Subsequent Risk of Death

Electrocardiographic Variable	Sudden Death		Cardiac Death		Noncardiac Death	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
A Fib	6.35 (2.45, 16.41)	<0.001*	3.66 (1.58, 8.49)	0.002*	0.99 (0.13, 7.43)	0.994
CHB	27.49 (2.97, 254.36)	0.004*	29.13 (7.81, 108.6)	<0.001*	N/A	N/A
QRS duration	1.03 (1.01, 1.04)	<0.001*	1.02 (1.01, 1.04)	<0.001*	1 (0.98, 1.02)	0.951
QRS ≥120 ms	2.34 (1.24, 4.43)	0.009*	2.19 (1.38, 3.49)	<0.001*	1.12 (0.47, 2.66)	0.79
RAE	2.11 (1.1, 4.05)	0.025*	1.51 (0.95, 2.41)	0.082	1.04 (0.47, 2.32)	0.926
RBBB	2.4 (1.23, 4.67)	0.01*	1.25 (0.78, 2.01)	0.346	1.33 (0.59, 3.02)	0.488
LBBB	1.66 (0.69, 3.99)	0.261	1.79 (0.96, 3.36)	0.068	0.67 (0.15, 2.87)	0.585
RVH	0.8 (0.42, 1.53)	0.496	0.91 (0.56, 1.48)	0.706	1.77 (0.7, 4.49)	0.232
LVH	0.22 (0.03, 1.58)	0.132	0.51 (0.19, 1.4)	0.191	1.31 (0.3, 5.68)	0.718
ST&T Δ	0.98 (0.45, 2.15)	0.964	1.06 (0.59, 1.92)	0.838	1.77 (0.7, 4.49)	0.232
QTc	1.01 (1, 1.02)	0.109	1.01 (1, 1.01)	0.064	1 (0.99, 1.01)	0.996

A Fib indicates atrial fibrillation; CHB, complete heart block; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; QTc, QT interval corrected by the Bazett formula; RAE, right atrial enlargement; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; ST&T Δ, ST interval and T-wave changes; and N/A, not applicable.

*P<0.05.

with increased cardiac mortality (2.38-fold increased risk; P=0.021).

Electrocardiography predictors of mortality

Atrial fibrillation (HR, 6.35; 95% CI, 2.45–16.41; P<0.001), complete heart block (HR, 27.49; 95% CI, 2.97–254.36; P=0.004), prolonged QRS duration (HR, 1.03; 95% CI, 1.01–1.04; P<0.001), especially when QRS duration ≥120 ms (HR, 2.34; 95% CI, 1.24–4.43; P=0.009), RA enlargement (HR, 2.11; 95% CI, 1.1–4.05; P=0.025), and right bundle branch block (HR, 2.4; 95% CI, 1.23–4.67; P=0.01) on ECG detected at the time of presentation to the treating institution were all significant predictors of SCD (Table 6).

Relationship between QRS interval prolongation and right ventricular function

Kruskal-Wallis rank sum test was conducted to examine the differences in QRS duration among right ventricular function categories (normal or mildly reduced, moderately reduced, or significantly reduced). The results suggest that the mean ranks of QRS duration are significantly different (χ^2=14.024; P=0.003) among the right ventricular function categories.

Arrhythmia monitoring and treatment on follow-up

There was no systematic screening for arrhythmia in all patients with Eisenmenger syndrome, and testing occurred on the basis of clinical suspicion and symptoms, at the discretion of the treating physician. There was no significant association between further atrial or ventricular arrhythmias detected during follow-up and the risk of SCD. There was also no association between antiarrhythmic medication use or ablation (which was performed in 9 patients for atrial-level or supraventricular arrhythmias, none for ventricular arrhythmias) and mortality. Paradoxically, the incidental detection of nonsustained ventricular tachycardia on noninvasive testing was associated with a decreased risk of death in this study (HR, 0.37; 95% CI, 0.17–0.8; P=0.012). These patients were more likely to be placed on antiarrhythmic medications (77%, mostly class III antiarrhythmic drug and β blockers), and 82% were also on advanced pulmonary hypertension therapies, which were protective. Only 2 of these patients had an implantable cardioverter-defibrillator.

Ventricular pacing and SCD

The presence of a pacemaker was associated with a uniquely increased risk, which was specific to sudden death (HR, 2.75; 95% CI, 1.07–7.06; P=0.036). Of the 13 patients who received a pacemaker, 5 had SCD, 2 died of progressive heart failure, and 1 died of a massive spontaneous cerebral hemorrhage (in the setting of anticoagulation).

Observationally, patients with a high burden of ventricular pacing were more likely to die, whereas patients who had atrial-only pacing (in the setting of sinus node dysfunction or sinoatrial exit block) were more likely to survive to the end of this study (Table 2). Furthermore, sudden death occurred in patients with both epicardial and transvenous devices and, according to the cardiology notes, it was likely caused by a malignant ventricular arrhythmia and unlikely to be

Table 7. Summary of Clinical, ECG, and Echocardiographic Predictors of SCD (Univariate Analysis)

Clinical Variable	Total No.	No. of Events	Hazard Ratio (95% CI)	*P* Value
Age	246	40	1.03 (1.01, 1.06)	0.011†
Heart failure (NYHA class ≥II)	246	40	1.58 (0.85, 2.95)	0.147
LVEF ≤40%	218	34	3.38 (1.71, 6.66)	<0.001†
RV enlargement*	214	33	1.28 (0.63, 2.62)	0.493
RV dysfunction*	206	34	1.67 (0.84, 3.33)	0.144
RAP >10 mm Hg	185	27	2.49 (1.13, 5.48)	0.024†
Atrial fibrillation	229	38	6.35 (2.45, 16.41)	<0.001†
CHB	229	38	27.49 (2.97, 254.36)	0.004†
QRS duration	229	38	1.03 (1.01, 1.04)	<0.001†
QRS ≥120 ms	229	38	2.34 (1.24, 4.43	0.009†
RAE	225	38	2.11 (1.1, 4.05)	0.025†
RBBB	224	37	2.4 (1.23, 4.67)	0.01†
Pacemaker	246	40	2.75 (1.07, 7.06)	0.036†
Advanced pulmonary hypertension drugs	246	40	0.21 (0.1, 0.44)	<0.001†

CHB indicates complete heart block on ECG; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAE, right atrial enlargement on ECG; RAP, estimated right atrial pressure on echocardiography; RBBB, right bundle branch block on ECG; RV, right ventricular; and SCD, sudden cardiac death.

*Moderate or severe enlargement/dysfunction/regurgitation.

†$P<0.05$.

linked to lead-related complications, such as paradoxical emboli or hemorrhage.

Multivariate analysis

In the univariate analysis, age, systemic ventricular function, RA enlargement, right bundle branch block, complete heart block, presence of a pacemaker, QRS duration, and atrial fibrillation on presentation were found to be significant predictors of SCD, whereas advanced pulmonary hypertension therapies were found to be strongly protective against sudden death (Table 7). On the other hand, although the presence of clinical heart failure symptoms (NYHA class ≥II) was predictive of both cardiac mortality and total mortality, this was not a significant predictor of SCD.

Because of the low number of patients and events (40 SCD events), not all significant univariate predictors of sudden death (summarized in Table 7) could be included in the multivariate analysis. On the basis of the relative clinical significance of these parameters and the findings of the univariate analysis, we further focused our multivariate analysis on age, atrial fibrillation, QRS duration, clinical heart failure symptoms, LVEF, and advanced pulmonary hypertension therapies. The use of advanced pulmonary hypertension therapies was found to violate the proportional hazards assumption (hazard was not constant over time), and therefore this was used as a stratifying variable in those multivariate models.

In the multivariate analysis, atrial fibrillation, prolonged QRS duration, and advanced pulmonary hypertension therapies remained significant independent predictors of SCD, even when accounting for the presence of reduced left ventricular systolic function (Figure 2). On the other hand, although LVEF ≤40% was a significant predictor of SCD when corrected for patient age, sex, and the presence of clinical heart failure symptoms (NYHA class ≥II), it was no longer significant when corrected for the presence of atrial fibrillation, prolonged QRS duration, or advanced pulmonary hypertension therapies, further emphasizing the importance of these 3 factors (Figure 2).

Furthermore, functional class (NYHA class ≥II) remained a significant differentiator in the multivariate analysis between the risk of cardiac death (ie, advanced heart failure), for which it was a significant predictor of mortality ($P<0.001$), and the risk of SCD, for which NYHA class was not significant. Survival curves free of SCD are shown for the main predictors, atrial fibrillation, QRS duration ≥120 ms, and advanced pulmonary hypertension medications (Figure 3).

DISCUSSION

Survival of patients with CHD, including those with Eisenmenger syndrome, has significantly improved, yet prior studies describing the cause of death in Eisenmenger syndrome noted that more than half of patients die suddenly or from complications related to heart failure.[8] This large retrospective cohort analysis identifies several important factors that are associated with sudden death in adults with Eisenmenger syndrome. Atrial fibrillation and a prolonged QRS duration (≥120 ms) were significant independent predictors of

Models w/ QRS duration ≥ 120ms

A Endpoint: Sudden Cardiac Death

	HR (95% CI)	P value
Advanced Pulmonary Hypertension Meds	0.14 (0.06, 0.33)	<0.001
Atrial fibrillation	11.45 (3.81, 34.4)	<0.001
QRS duration >= 120ms	2.06 (1.06, 4)	0.034

B Endpoint: Sudden cardiac death

	HR (95% CI)	P value
Male sex	1.8 (0.94, 3.48)	0.078
Age at first contact	1.04 (1.01, 1.06)	0.006
Heart Failure Symptoms (NYHA ≥II)	1.13 (0.58, 2.2)	0.714
QRS duration >= 120ms	2.51 (1.31, 4.8)	0.006

Models w/ LVEF <= 40

C Endpoint: Sudden cardiac death

	HR (95% CI)	P value
Advanced Pulmonary Hypertension Meds	0.17 (0.07, 0.4)	<0.001
Atrial fibrillation	6.96 (1.99, 24.33)	0.002
QRS duration	1.02 (1, 1.04)	0.015
LVEF <= 40%	1.46 (0.68, 3.14)	0.335

D Endpoint: Sudden cardiac death

	HR (95% CI)	P value
Male sex	1.44 (0.7, 2.94)	0.318
Age at first contact	1.03 (1, 1.05)	0.077
Heart Failure Symptoms (NYHA ≥II)	1.27 (0.61, 2.64)	0.528
LVEF <= 40%	2.94 (1.43, 6.05)	0.003

Figure 2. Multivariate models of sudden cardiac death, including the presence of atrial fibrillation, prolonged QRS duration, left ventricular function, and advanced pulmonary hypertension therapies. HR indicates hazard ratio; LVEF, left ventricular ejection fraction; Med, medication; and NYHA, New York Heart Association.

SCD in the multivariable analysis; left ventricular dysfunction and right ventricular apical pacing raise important concerns for the same outcome. In addition to mitigating against overall mortality and cardiac mortality, the use of pulmonary vasodilator therapy was found to be independently and strongly protective against SCD.

Interestingly, the presence of clinical heart failure symptoms (NYHA class ≥II) conferred an increased risk of cardiac death and total mortality, but not a particularly increased risk of SCD, suggesting that there might be an independent cause for SCD, potentially arrhythmic, outside of progressive heart failure. Lower LVEF was associated with increased mortality, and this was true for both SCD and overall cardiac mortality. Although a moderately or severely reduced ejection fraction (≤40%) was a significant predictor of SCD and cardiac death in the univariate analysis and when adjusted for patient age, sex, and functional class, it was no longer a significant predictor of SCD once adjusted for the presence of atrial fibrillation, prolonged QRS duration, and the use of advanced pulmonary hypertension therapies, further underscoring the importance of these 3 parameters.

Right ventricular enlargement and right ventricular systolic dysfunction were associated with increased

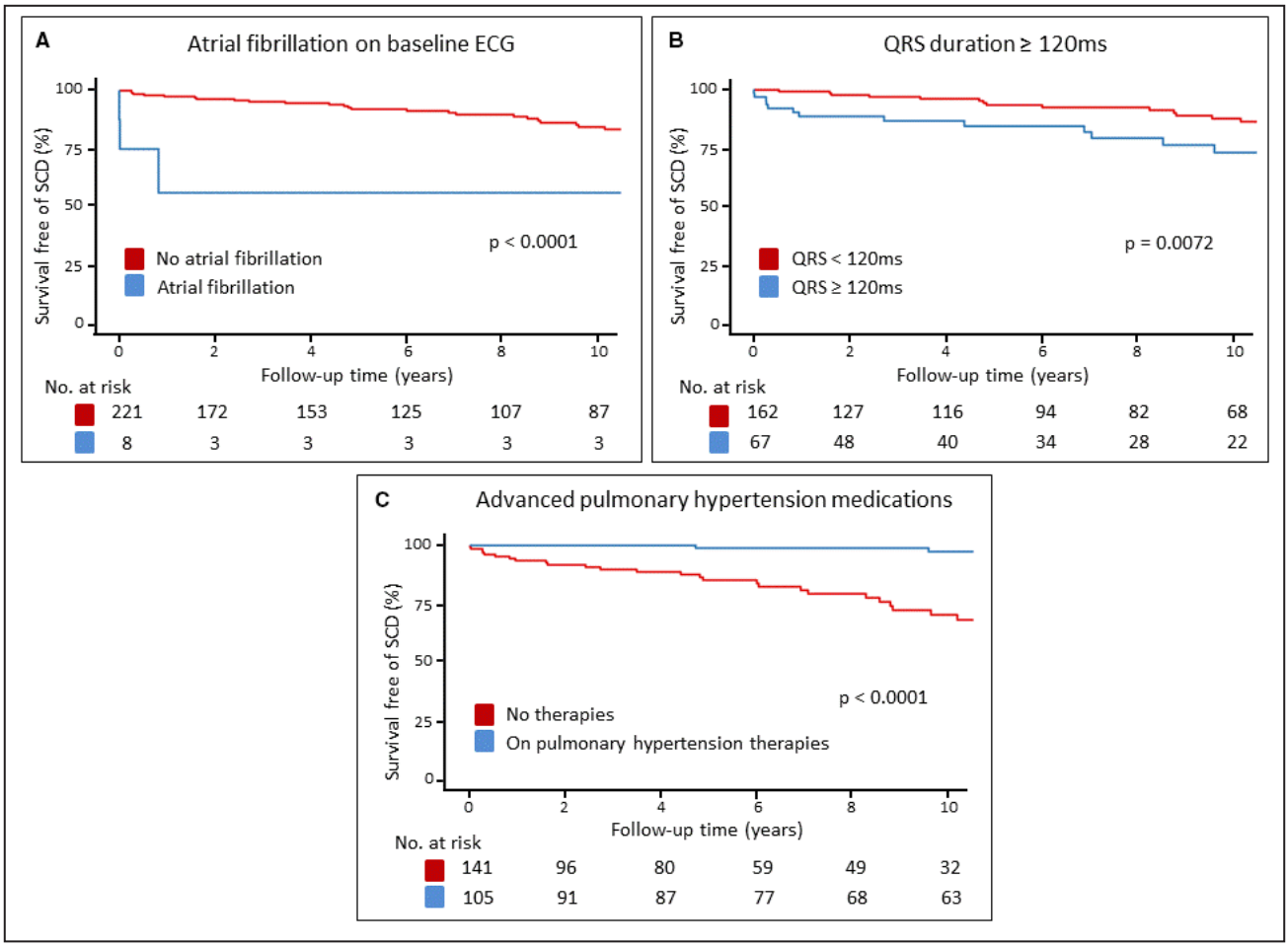

Figure 3. Survival free of sudden cardiac death on the basis of the presence of atrial fibrillation, QRS interval ≥120 ms, and the use of advanced pulmonary hypertension medications.

cardiac mortality, yet the association with SCD did not reach statistical significance. An abnormal myocardial performance index or right ventricular index of myocardial performance was significantly associated with SCD; however, these data were available only in 45% of patients. On the other hand, increased RA pressure estimated on echocardiography (ie, RA pressure >10 mm Hg) was associated with increased risk of SCD, cardiac death, and total mortality. RA pressure overload is a known poor prognostic marker in primary pulmonary arterial hypertension,[10,11] and can reflect right ventricular overload, which, in turn, can lead to subendocardial fibrosis, prolonged refractory periods, and ventricular arrhythmias. The deleterious effects of volume loading on right ventricular refractoriness and proarrhythmia are well demonstrated in animal models, and increasing right ventricular volume challenges were associated with marked increases in ventricular effective refractory periods and higher probability of ventricular extrasystoles, likely underpinning a type of stretch-induced arrhythmia-mediation.[12]

Pericardial effusion correlated with increased cardiac mortality (2.38-fold increased risk; *P*=0.021), but not increased risk of SCD. The development of a pericardial effusion in the setting of severe pulmonary arterial hypertension is a known indicator of adverse outcomes, and it is thought to be caused by impaired myocardial venous and lymphatic drainage secondary to impaired right ventricular diastolic function and right heart failure.[10]

Several ECG findings correlated with SCD in the univariate analysis, but the small number of patients and events precluded inclusion in the multivariate model. RA enlargement on ECG (similar to RA pressure overload on echocardiography), the presence of a right bundle branch block, and prolonged QRS duration were significant predictors of SCD. Furthermore, the presence of complete heart block and the need for a pacemaker, especially when associated with a high burden of right ventricular pacing, were significant univariate predictors of SCD (Table 7).

Previous studies have demonstrated an association between worsening right ventricular function and

the electromechanical delay seen in patients with right bundle branch block. Furthermore, it has been demonstrated that ECG parameters of right ventricular conduction delay correlate with echocardiographic parameters of right ventricular systolic function.[13] In this cohort of patients with Eisenmenger syndrome, we demonstrated a significant correlation between the presence of right bundle branch block and SCD (2.4-fold increased risk; P=0.01). Mechanistically, right ventricular pressure or volume overload places strain on the right bundle and the associated Purkinje network, which travel subendocardially on the right ventricular septum; therefore, the presence of a right bundle branch block can herald right ventricular strain and subsequently contribute to further worsening of the right ventricular systolic function by altered hemodynamics, dyssynchrony, delayed opening of the pulmonary valve, and inefficient right ventricular emptying.[13]

Prolongation of the QRS interval was significantly associated with mortality, both sudden death and cardiac mortality. Furthermore, a QRS interval ≥120 ms predicted a 2.34-fold increased risk of SCD (P=0.009). In this setting, QRS prolongation is likely a marker of intraventricular conduction delay caused by increased right ventricular strain, and we demonstrated a significant correlation between QRS duration and worsening right ventricular systolic function (χ^2=14.024; P=0.003) in this population of patients with Eisenmenger syndrome. More important, prolongation of the QRS interval has been previously shown to be a predictor of malignant ventricular arrhythmias and of SCD in the population with CHD.[14,15] For example, in patients with repaired tetralogy of Fallot and subsequent right ventricular volume overload, the risk of symptomatic arrhythmia was higher in the presence of marked right ventricular enlargement and marked QRS prolongation. In fact, SCD in these patients is mainly attributed to malignant ventricular arrhythmias.[15] Furthermore, in patients treated with Mustard palliation for transposition of the great arteries, there was an inverse correlation between right ventricular systolic function and QRS duration, and patients with a QRS interval ≥140 ms were at highest risk of sustained ventricular tachycardia and SCD.[14] In addition, it has been shown that QRS fragmentation, beyond QRS duration, correlates with SCD in the adult population with CHD[16]; therefore, closer attention to patients with prolonged QRS and to the QRS morphological characteristics themselves (with or without QRS fragmentation) is warranted as a risk-stratification and prevention strategy against malignant ventricular arrhythmias and SCD.

Atrial fibrillation was found to be strongly predictive of SCD in the multivariate analysis (11.45-fold increased risk; P<0.001), and it was also a predictor of cardiac mortality (6.18-fold increased risk; P<0.001) and all-cause mortality (4.16-fold increased risk; P<0.001). Previous studies have looked at arrhythmias in patients with CHD and identified a high burden of supraventricular tachycardia and atrial fibrillation over a mean follow-up of 6 years[7,17,18]; and the presence of sinus rhythm was previously found to be associated with better survival.[7] The present study specifically outlines the particular risk of SCD associated with atrial fibrillation. Atrial fibrillation may be a marker of a sicker substrate, with worse atrial and ventricular overload and maladaptive remodeling. In turn, atrial fibrillation could lead to worsening atrial and ventricular function and lower stroke volumes because of the loss of the atrial pump. Furthermore, the resulting progressive ventricular decompensation could create the substrate necessary for arrhythmia.

Although ventricular arrhythmias are documented in only a minority of patients with Eisenmenger syndrome, they are thought to confer a high risk of SCD.[17] Paradoxically, the discovery of nonsustained ventricular tachycardia in this study was associated with a decreased risk of all-cause mortality (HR, 0.37; 95% CI, 0.17–0.8; P=0.012); we postulate that these events would have drawn close clinical scrutiny and potentially different management, perhaps using antiarrhythmic approaches and pulmonary vasodilator therapy. Because these patients were monitored, it is possible that arrhythmia was discovered earlier in the clinical course; therapeutic measures were potentially taken, rather than having SCD as their initial presentation.

The presence of a pacemaker, especially when associated with a high burden of right ventricular pacing for pacemaker-dependent patients, was found to be a significant predictor of SCD, highlighting again perhaps the effect of discordant ventricular contraction. Furthermore, the presence of transvenous leads with direct access to the systemic circulation has been previously found to confer a >2-fold increased risk of systemic thromboemboli, even after adjustment for other risk factors, such as older age or atrial fibrillation.[19] As the medical community has become more aware of the risks associated with lead thrombosis on transvenous leads, epicardial devices have been more recently preferentially used. More important, the deleterious effect of high-burden ventricular pacing in our study was noted for both epicardial and transvenous devices, suggesting that this is related to the ventricular pacing itself, rather than to embolic complications, and therefore likely through similar mechanisms to that seen in acquired heart disease.[20]

Advanced pulmonary hypertension therapies were found to offer a strong survival advantage in this population with Eisenmenger syndrome (P<0.001),

and, in contrast to idiopathic pulmonary hypertension, it is hypothesized that exposure to increased pulmonary artery pressures early in life may lead to the retention of the right ventricular fetal phenotype, with better adaptation to pressure overload and optimized energy metabolism. However, over time, these mechanisms eventually become maladaptive (typically within the fourth decade of life). Therefore, timely treatment with advanced pulmonary hypertension therapies could help prevent this critical late step toward decompensation. Mechanistically, these medications may help reduce the risk of SCD by preventing maladaptive ventricular remodeling, subendocardial fibrosis, and the development of potential foci for reentrant ventricular arrhythmias, or by preventing right ventricular volume overload, increased refractoriness, and the development of stretch-induced triggered ventricular arrhythmias. These are intriguing findings with vast ramifications for the treatment of pulmonary hypertension in CHD as they would have a significant impact on care and cost. Ideally, before recommendations to change practice, a prospective study is necessary to assess the impact of these therapies on the ECG and imaging parameters predictive of sudden death. Assessing these parameters before and after the successful introduction and up titration of advanced pulmonary hypertension therapies could be an important step toward understanding the mechanism underlying these protective effects.

Finally, there was a signal of concern for increased total mortality in patients with a secundum ASD (2.11-fold increase in total mortality; $P<0.001$) and in patients with combined ASD and ventricular septal defect (4.34-fold increase in total mortality; $P=0.002$). However, there was no association between these or other anatomical defects and SCD. The finding that a secundum ASD would confer an increased risk of overall mortality warrants further study. These patients are likely not representative of the general ASD population, as the great majority of patients with an isolated ASD do well for a long time, but a minority of patients do develop Eisenmenger syndrome and may have an inherently different, higher-risk substrate. Anecdotally, some patients with ASD and normal pulmonary pressure continue to develop pulmonary hypertension over time despite ASD closure, suggesting that perhaps there might have been a component of undiagnosed idiopathic pulmonary hypertension. On the other hand, pretricuspid defects (and ASD would be the prototype of such defect) were previously shown to confer a higher overall mortality than posttricuspid defects in the specific cohort with Eisenmenger syndrome, because of worse adaptation of the right ventricle to volume overload as opposed to pressure overload.[7]

Study Limitations

Because this study was performed at 2 large tertiary care institutions, referral bias was inevitable; however, this reflects the contemporary practice of treating patients with complex CHD at designated centers of expertise. Furthermore, the immortal time bias is relevant herein, as patients may be more likely to present to the tertiary care center when they start to decompensate. As our patients presented for treatment over a time span of 28 years, for older cases, only paper records were available. Not all objective data were available for all patients, and not all patients had a baseline ECG or an echocardiogram documented at the tertiary care institution.

All patients treated at the participating institutions were included in this study. However, our understanding of the pathophysiological characteristics of disease and of the optimal interventions has evolved over time. For example, the association between transvenous pacemaker leads and paradoxical embolism in patients with shunts was first published in 2006, and the BREATHE-5 trial demonstrating the safety and efficacy of pulmonary arterial hypertension therapies in patients with Eisenmenger syndrome was published in the same year. Thus, with evolving medical knowledge, contemporary patients are benefiting from more advanced therapies compared with their predecessors. Yet, their survival and causes of death were analyzed together as one cohort.

CONCLUSIONS

This study provides a first-time in-depth analysis of the causes of sudden death in a longitudinal large cohort with Eisenmenger syndrome. Older age, atrial fibrillation, prolonged QRS duration, complete heart block, RA enlargement and right bundle branch block on ECG, increased RA pressures on echocardiography, lower LVEF, and the presence of a pacemaker, especially when associated with high burden of ventricular pacing, were all found to be significant predictors of SCD. On the other hand, clinical heart failure symptoms were predictive of increased cardiac mortality and all-cause mortality, but not particularly associated with increased SCD, suggesting a potential arrhythmic mechanism behind SCD.

The baseline ECG can be used as a predictive tool to identify a higher-risk category of patients who may benefit from closer monitoring and aggressive arrhythmia surveillance and treatment.

High-risk patients may benefit from systematic monitoring for arrhythmias, and advanced pulmonary hypertension therapies should be potentially considered early in the symptomatic patient, given the strong association with increased survival, as well as protection from SCD. Multicenter studies, specifically to address whether cardiac resynchronization

therapy or physiological pacing, although technically challenging, might prevent the deleterious effects of high-burden subpulmonic ventricular pacing, are needed.

ARTICLE INFORMATION

Received November 9, 2019; accepted January 31, 2020.

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Acknowledgments

We thank Carole Warnes, MD, for her critical review of the manuscript.

Sources of Funding

This work was supported by a grant from the Mayo Clinic Cardiovascular Department.

Disclosures

None.

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