Cardiac Magnetic Resonance Parameters Predict Transplantation-Free Survival in Patients With Fontan Circulation

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Background—Several clinical risk factors for death and heart transplantation have been identified in patients with Fontan circulation. It is unknown whether cardiac magnetic resonance (CMR) measurements of ventricular size and function are independently associated with these outcomes and further improve risk stratification.

Methods and Results—Data on patients with Fontan circulation who had a CMR study from January 2002 to January 2011 were retrospectively reviewed. The end point was time to death or listing for heart transplantation after the CMR study. The median age of the 215 patients was 18.3 years (25th, 75th percentiles: 14, 26) with a median age at Fontan of 3.6 years (2.3, 7.1). During a median post-CMR follow-up period of 4.1 years (2.6, 6.2), 24 patients (11%) reached the end point: 20 deaths, 3 transplantations, and 1 transplantation listing. In a multivariable Cox regression model with clinical parameters only, protein-losing enteropathy was associated with transplantation-free survival. A multivariable model, including clinical and CMR parameters, showed that in addition to protein-losing enteropathy, ventricular indexed end-diastolic volume >125 mL/body surface area raised to the 1.3 power was associated with transplantation-free survival. A likelihood-ratio test comparing the 2 models showed that the addition of indexed end-diastolic volume resulted in a significantly improved end point prediction ($P<0.001$)—*C*-index increased from 0.63 to 0.79.

Conclusions—CMR-derived ventricular indexed end-diastolic volume is an independent predictor of transplantation-free survival in patients late after the Fontan operation and adds incremental value over clinical symptoms alone for risk stratification. **(*Circ Cardiovasc Imaging*. 2014;7:502-509.)**

Key Words: Fontan procedure ■ heart defects, congenital ■ magnetic resonance imaging

Patients with functional single ventricle (FSV) congenital heart disease comprise a complex and heterogeneous population that is usually palliated with the Fontan procedure. Despite important improvements in both mortality and morbidity among young patients,[1] adverse outcomes become increasingly frequent as patients approach adulthood.[2,3] Several risk factors, such as protein-losing enteropathy (PLE) and decreased exercise parameters, are associated with death and heart transplantation in this population.[4,5] Ventricular size and function are also thought to be clinically important; however, few studies support their association with important outcomes.[2,3,6] Indeed, most publications on FSV size and function in this population have used surrogate outcomes.[1,7–10] Because of the technical limitations of echocardiography in these patients, cardiac magnetic resonance (CMR) remains the preferred modality for the assessment of ventricular size and function.[11] Accordingly, the goal of this study was to determine whether CMR measurements of ventricular size and function improve risk stratification for transplantation-free survival in patients late after the Fontan operation.

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Methods

Patients

A database search identified all patients who underwent a Fontan operation, had a postoperative CMR study at Boston Children's Hospital between January 2002 and January 2011, and had a minimum of 1 year of follow-up or reached the defined end point after CMR. Exclusion criteria were inability to measure ventricular size and function because of technically inadequate data and lack of clinical follow-up information. The Boston Children's Hospital Committee on Clinical Investigation approved this retrospective study and waived the requirement for informed consent.

Clinical Parameters

Demographic and clinical data, including underlying diagnoses and type of FSV based on ventricular dominance, were abstracted from the

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medical records. The type of surgical palliation was classified as lateral tunnel, right atrium-to-pulmonary artery anastomosis, right atrium-to-right ventricle connection, or extracardiac conduit. Additional parameters included age at Fontan, time from Fontan to CMR, length of post-CMR follow-up, history of Fontan revision, and number and type of surgical and catheterization interventions before CMR, including age at volume-unloading surgery (eg, bidirectional Glenn). Arrhythmia history was compiled by review of Holter monitors, electrocardiograms, electrophysiology catheterizations, and clinic notes. Episodes of atrial ectopy, atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular ectopy, nonsustained ventricular tachycardia (≥3 beats lasting <30 s), sustained ventricular tachycardia (lasting ≥30 s), and arrhythmia-related cardiac arrest were recorded, along with their temporal relation to the CMR study. Other relevant clinical variables included history of congestive heart failure (defined as New York Heart Association class II or greater), PLE, stroke, thrombus, seizures, liver disease, or pacemaker or defibrillator placement.

Clinical End Points

The primary end point was time to all-cause mortality, listing for cardiac transplantation, or receiving a heart transplantation. Dates of listing for cardiac transplantation, transplantation, or death were confirmed against the New England Organ Bank and the Social Security Death Index databases. For survival analyses, follow-up was measured from the date of CMR to either first occurrence of the end point or last known follow-up date with documented transplant-free survival.

CMR Techniques

CMR studies were performed with 1.5 Tesla scanners (GE Medical Systems, Milwaukee, WI, and Philips Healthcare, Best, the Netherlands). The details of the CMR protocols used in our laboratory for assessment of patients after the Fontan operation have been published.[12–14] Briefly, ventricular assessment was performed by an electrocardiographically gated, steady-state free precession cine CMR in vertical and horizontal ventricular long-axis planes and a stack of slices in a ventricular short-axis plane encompassing the atrioventricular junction through the cardiac apex. Assessment for the presence of late gadolinium enhancement (LGE) used a protocol with an inversion-recovery prepared, phase-sensitive, ECG-triggered, breath-hold segmented fast gradient echo pulse sequence in the ventricular long- and short-axis planes. Imaging was performed ≈15 minutes after injection of 0.2 mmol/kg gadopentetate dimeglumine (Magnevist; Bayer HealthCare, Tarrytown, NY).[14]

CMR Data Analysis

If a patient had multiple CMR studies, the most recent study was used for analysis. Ventricular volumes and function were measured by manual tracing of endocardial and epicardial borders on each short-axis steady-state free precession cine slice at end-diastole (maximal area) and end-systole (minimal area) as previously described.[12] Analysis was performed using commercially available software (QMass; Medis Medical Imaging Systems, Leiden, the Netherlands). Simpson method was applied to calculate end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), stroke volume (SV), ventricular mass, and mass/volume ratio. Ventricular morphology was classified as left ventricular, right ventricular, or biventricular (eg, unbalanced atrioventricular canal) according to previously published criteria.[1] Ventricular type was classified as biventricular if both ventricles had an EDV *Z* score >–4. Published normative data from Alfakih et al[15] were used for ventricular *Z* score calculations. Regardless of the dominant ventricular morphology type, when 2 ventricles contributed to the systemic circulation, ventricular volumes and mass were summated to allow for calculation of total functional EDV, ESV, EF, SV, mass, and mass/volume ratio. To better account for differences in body size, EDV, ESV, SV, and ventricular mass were indexed to body surface area (BSA) raised to the 1.3 power.[16] This method was selected based on studies showing that volumetric parameters are best adjusted to BSA raised to the 1.3 to 1.4 power.[16–18] These studies have demonstrated a nonlinear relationship between ventricular volumes and BSA, a relationship that is primarily influenced by a change in heart rate as a function of age. Although commonly used in clinical studies in adult patients, indexing ventricular volumes to BSA alone fails to account for the variance across a population that includes pediatric patients.[16–18] Analyses were repeated indexing to BSA alone to ensure the indexing strategy did not substantially change results. To facilitate comparison with other studies, results are also reported as indexed to BSA. For patients who had the myocardial delayed enhancement imaging technique performed, studies were reviewed for the presence of LGE as previously described.[14] Assessment of atrioventricular and semilunar valvar regurgitation by phase contrast imaging was performed using QFlow (Medis Medical Imaging Systems).[19]

Exercise Testing

Metabolic exercise testing data were included if the study occurred within 1 year of the CMR and if the patient reached maximal aerobic effort. Maximal aerobic effort was defined as a respiratory exchange ratio of ≥1.09 or achieving ≥75% of predicted heart rate for age and sex.[20] Studies with submaximal aerobic effort were excluded from the analysis to eliminate bias from noncardiac factors. The following parameters were recorded: work rate, relative oxygen consumption, oxygen consumption at ventilatory anaerobic threshold, oxygen pulse, heart rate, respiratory rate, blood pressure, ventilatory exchange ratio, and breathing reserve.

Statistical Analysis

Categorical data were summarized using frequencies and percentages and compared between those who reached the end point and those who did not using a Fisher exact test. Continuous variables were summarized as median (25th, 75th percentiles) or mean±SD, as appropriate, and were compared using a Mann–Whitney *U* test. A multivariable Cox proportional hazards survival model with forward stepwise selection was used to identify independent risk factors for the end point. The analysis included the entire study group. Bootstrap resampling with a sample size of 215 and 20 000 repetitions was used to estimate SEs for hazard ratios and *P* values. Candidate predictor variables were initially considered for inclusion if $P<0.2$ in univariable analysis; $P<0.05$ was required for retention in the final model. Likelihood-ratio statistics were used to compare models with clinical history variables only and those with clinical history and CMR variables. Harrell *C*-index was used to quantify how well each model discriminated between patients who experienced the end point and those who did not. If continuous variables were independently associated with the primary end point, cut points were calculated that allowed maximal discrimination by the *C*-index to improve interpretation of the data. Cumulative survival functions were constructed with Kaplan–Meier estimates for categorical variables included in the final Cox regression model, and event times were compared by the log-rank test.

All statistical tests were 2-sided, and results were considered statistically significant if $P<0.05$. Data analysis was performed using SPSS version 21.0 (SPSS Inc, Chicago, IL).

Statement of Responsibility

The authors had full access to the data and take responsibility for their integrity. All authors have read and agreed to the article as written.

Results

Patient Characteristics

During the study period, 261 patients who had undergone a Fontan operation had a total of 437 CMR examinations. Of these, 39 (15%) patients did not have quantitative assessment of ventricular size and function predominately because of metallic artifacts from stainless steel coils or other ferromagnetic implanted devices. An additional 7 patients were unable to complete the examination because of anxiety. The remaining

215 patients comprised the study cohort, and their most recent CMR examination was used for analysis. The demographic, clinical, and surgical outcomes of the excluded patients were similar to those of the study group, except that the included patients had a longer time because of their Fontan (14.6 [9.5, 19.3] versus 11.2 [7.7, 16.1] years; *P*=0.004) and more commonly had right ventricular morphology (56% versus 31%; *P*=0.006) and heterotaxy syndrome (22% versus 9%; *P*=0.02).

Table 1. Demographic and Clinical Characteristics

	All Patients (n=215)	Transplantation-Free Survival (n=191)	Death or Transplantation (n=24)	*P* Value
Sex (men)	136 (63%)	119 (62%)	17 (71%)	0.50
Age at Fontan, y	3.6 (2.3, 7.1)	3.5 (2.3, 6.6)	4.2 (2.3, 13.0)	0.31
Age at CMR, y	18.3 (14, 26)	18.3 (14, 26)	18.1 (8, 33)	0.98
Time from Fontan to CMR, y	14.6 (10, 19)	14.7 (10, 19)	13.4 (5, 21)	0.65
Follow-up time after CMR, y	4.1 (2.6, 6.2)	4.3 (2.7, 6.4)	2.5 (1.1, 4.5)	<0.001
Body surface area at CMR, m^2	1.6 (1.4, 1.9)	1.6 (1.4, 1.9)	1.7 (1.0, 2.0)	0.93
Cardiac diagnosis				0.27
Tricuspid atresia	52 (24%)	45 (24%)	7 (29%)	
Double-inlet left ventricle	36 (17%)	35 (18%)	1 (4%)	
HLHS	34 (16%)	26 (14%)	8 (34%)	
Unbalanced AV canal	21 (10%)	18 (9%)	3 (13%)	
Double-outlet right ventricle	20 (9%)	19 (10%)	1 (4%)	
Complex 2 ventricle	17 (8%)	16 (8%)	1 (4%)	
Hypoplastic TV/RV	16 (7%)	15 (8%)	1 (4%)	
Pulmonary atresia/IVS	10 (5%)	9 (5%)	1 (4%)	
Mitral atresia	9 (4%)	8 (4%)	1 (4%)	
Heterotaxy	20 (9%)	17 (9%)	3 (13%)	0.47
Ventricular morphology				0.10
Left ventricle	96 (45%)	90 (47%)	6 (25%)	
Right ventricle	66 (30%)	55 (29%)	11 (46%)	
Biventricular	53 (25%)	46 (24%)	7 (29%)	
Surgical history				
Neonatal surgery	108 (50%)	99 (52%)	9 (38%)	0.20
Bidirectional Glenn	112 (52%)	97 (51%)	15 (63%)	0.39
Fontan revision (after CMR)	19 (9%)	15 (8%)	4 (17%)	0.24
Fontan type				0.001
Lateral tunnel	151 (70%)	140 (73%)	11 (46%)	
RA-pulmonary artery	44 (21%)	38 (20%)	6 (25%)	
Extracardiac	11 (5%)	8 (4%)	3 (12%)	
RA-RV	9 (4%)	5 (3%)	4 (17%)	
Morbidity				
Liver disease	34 (16%)	25 (13%)	9 (38%)	0.005
Congestive heart failure	60 (28%)	41 (22%)	19 (79%)	<0.001
Thrombus	32 (15%)	24 (13%)	8 (33%)	0.01
Seizures	22 (10%)	19 (10%)	3 (13%)	0.72
Stroke	41 (19%)	35 (18%)	6 (25%)	0.42
Protein-losing enteropathy	14 (7%)	6 (3%)	8 (33%)	<0.001
Atrial flutter/fibrillation	65 (30%)	53 (28%)	12 (50%)	0.03
Nonsustained VT	35 (16%)	28 (15%)	7 (29%)	0.08
Sustained VT	8 (4%)	5 (3%)	3 (13%)	0.05
Resuscitated cardiac arrest	2 (1%)	1 (1%)	1 (4%)	0.21
Defibrillator (after CMR)	4 (2%)	3 (2%)	1 (4%)	0.38

Values are expressed as n (%) or median (25th, 75th percentile). CMR indicates cardiac magnetic resonance; HLHS, hypoplastic left heart syndrome; IVS, intact ventricular septum; RA, right atrium; RV, right ventricle; TV, tricuspid valve; and VT, ventricular tachycardia.

Table 1 describes the demographic and clinical characteristics of the study cohort. Most notably, the patients had a median age of 18.3 (14, 26) years at the time of CMR and a median interval between Fontan surgery and CMR of 14.6 (10, 19) years. The lateral tunnel was the most common type of Fontan operation (70%).

Death and Transplantation

During a median follow-up period of 4.1 years (2.6, 6.2) after CMR, 24 of the 215 patients (11%) reached an end point: death (n=20), heart transplantation (n=3), and heart transplantation listing (n=1). Causes of death were heart failure (n=10), presumed arrhythmogenic cardiac arrest (n=5), complications immediately after surgical procedures (n=3), and complications after heart transplantation (n=2). For the entire cohort, cumulative freedom from the end point was 97% at 1 year and 87% at 5 years.

CMR Data

Table 2 compares the CMR parameters between patients with and without the end point. LGE data were available in 132 patients (61%), and of those, 43 (33%) had positive LGE within the ventricular myocardium. Positive LGE was not associated with the end point by univariate analysis (P=0.18) but was associated with a higher EDV_i (104 [88, 144] versus 91 [73, 108] mL/BSA$^{1.3}$; P=0.001), ESV_i (53 [40, 75] versus 39 [30, 48] mL/BSA$^{1.3}$; P<0.001), and $mass_i$ (63 [47, 87] versus 50 [40, 62] g/BSA$^{1.3}$; P<0.001) and a lower EF (51% [41, 55] versus 55% [50, 61]; P=0.001). Similarly, heart rate at CMR was not associated with the end point by univariate analysis (P=0.25).

Exercise Testing

Of the 215 study patients, 103 (48%) had a metabolic exercise test within 1 year of their CMR study in which they achieved maximal aerobic capacity. Their exercise test results are shown in Table 3. In this group, 10 patients (10%) reached the end point. The data of all patients and a comparison between those with and without the end point are shown in Table 3. Lower peak oxygen consumption, relative oxygen consumption at ventilatory anaerobic threshold, and peak work rate were associated with the end point. The small number of end point events precluded multivariable analysis.

Predictors of Death or Transplantation

Table 1 compares the patient characteristics and clinical variables between those with and without the end point. Ventricular morphology, Fontan type, history of liver disease, congestive heart failure, thrombus, PLE, atrial fibrillation or flutter, and sustained ventricular tachycardia were all associated with the end point by univariate analysis. Table 2 compares CMR parameters between those with and without the end point. Patients with the end point had higher EDV_i, ESV_i, indexed SV, and $mass_i$ by univariate analysis. Ventricular EF was not associated with the end point when analyzed as a continuous variable; however, an EF <40% was associated with the end point (P=0.002).

Table 4 shows several multivariable Cox proportional hazard models with bootstrapping resampling for predicting the end point. The first model (C-index, 0.75) was restricted to CMR parameters that were significantly associated with the end point in univariate analysis. The second model (C-index, 0.63) was restricted to clinical variables that were significantly associated with the end point by univariate analysis. A third model (C-index, 0.80) considered all significant clinical and CMR parameters and showed that PLE and higher EDV_i independently predicted death or transplantation. The addition of CMR-measured EDV_i to a model with clinical parameters increased the model C-index from 0.63 to 0.80, with a statistically significant improvement in the model (P<0.001). To

Table 2. Comparison of CMR Parameters Between Patients With and Without the End Point

	All Patients (n=215)	Transplantation-Free Survival (n=191)	Death or Transplantation (n=24)	*P* Value
Heart rate at CMR	79 (66, 91)	77 (65, 91)	83 (66, 96)	0.25
EDV_i, mL/BSA$^{1.3}$	94 (76, 115)	93 (75, 113)	131 (90, 166)	0.001
EDV_i, mL/BSA	107 (87, 130)	104 (86, 127)	128 (106, 182)	0.001
ESV_i, mL/BSA$^{1.3}$	42 (32, 57)	41 (31, 54)	55 (36, 94)	0.007
ESV_i, mL/BSA	48 (36, 64)	46 (36, 62)	64 (39, 104)	0.01
SV_i, mL/BSA$^{1.3}$	50 (42, 60)	50 (42, 57)	63 (47, 81)	0.008
SV_i, mL/BSA	57 (48, 67)	56 (48, 65)	65 (57, 85)	0.007
Ejection fraction, %	55 (47, 61)	55 (48, 60)	53 (38, 63)	0.26
Ejection fraction <40%	24 (11%)	16 (8%)	8 (33%)	0.002
$Mass_i$, g/BSA$^{1.3}$	55 (43, 68)	52 (43, 65)	75 (56, 103)	0.001
$Mass_i$, g/BSA	60 (48, 81)	58 (48, 77)	84 (60, 104)	0.002
Mass/volume ratio, g/mL	0.57 (0.48, 0.70)	0.57 (0.48, 0.70)	0.55 (0.46, 0.73)	0.62
≥Moderate AVVR	25 (12%)	21 (11%)	4 (17%)	0.50
≥Moderate SLVR	10 (5%)	8 (4%)	2 (8%)	0.31
Positive LGE*	43 (33%)	35 (30%)	8 (47%)	0.18

Values are expressed as median (25th, 75th percentile) or n (%). AVVR indicates atrioventricular valve regurgitation; BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; LGE, late gadolinium enhancement; SLVR, semilunar valve regurgitation; and SV, stroke volume.

*Subgroup analysis with 132 patients.

Table 3. Exercise Testing Data

Characteristic	All Patients (n=103)	Transplantation-Free Survival (n=93)	Death or Transplantation (n=10)	*P* Value
Peak Vo_2, mL/kg per minute	23 (17, 26)	23 (18, 28)	15 (14, 18)	0.001
% Predicted peak Vo_2	60 (49, 68)	62 (52, 70)	39 (36, 51)	<0.001
Vo_2 at VAT, mL/kg per minute	13 (10, 16)	13 (10, 17)	8 (7, 11)	<0.001
% Predicted Vo_2 at VAT	34 (30, 41)	35 (32, 42)	26 (19, 30)	<0.001
Peak work rate, W	112 (84, 148)	116 (89, 150)	76 (59, 105)	0.07
% Predicted work rate	53 (65, 74)	65 (54, 74)	42 (30, 66)	0.001
Peak O_2 pulse index, mL O_2/beat per BSA	9 (7, 11)	9 (7, 11)	10 (8, 10)	0.87
% Predicted peak O_2 pulse	74 (64, 86)	75 (65, 87)	67 (54, 85)	0.21

Values are expressed as median (25th, 75th percentile). % predicted indicates percentage of predicted for age and sex; BSA, body surface index; VAT, ventilatory anaerobic threshold; and Vo_2, oxygen consumption.

facilitate interpretation of the model and its practical use, an EDV_i cutoff value of >125 mL/BSA$^{1.3}$ was found to have the highest discrimination, with a *C*-index to 0.79. Comparison of the multivariable Cox proportional hazard model, including clinical and CMR parameters, with a dichotomized EDV_i also showed a significant improvement in the model (P<0.001).

Kaplan–Meier plots showing freedom from death or transplantation stratified by PLE status and EDV_i >125 mL/BSA$^{1.3}$ are shown in Figure 1. Kaplan–Meier plots of freedom from death or transplantation comparing patients with no risk factors and clinical history risk factors plus CMR-measured EDV_i are shown in Figure 2. The additive discriminating effect of EDV_i >125 mL/BSA$^{1.3}$ on freedom from the end point was significant (P<0.001).

Discussion

This study provides the largest analysis of CMR-derived ventricular size and function measurements and their association with adverse clinical outcomes late after the Fontan operation. In this cohort, PLE and ventricular dilation were independently predictive of death or heart transplantation. Importantly, we found that CMR-derived ventricular EDV_i significantly improved risk stratification for transplantation-free survival in a relatively large cohort of patients with Fontan circulation.

Previous Studies

Khairy et al[2] analyzed a similar-sized cohort (n=261) for determinants of long-term outcomes after the Fontan operation. In their multivariable model, PLE, hypoplastic left heart syndrome, elevated right atrial pressure, and need for diuretic therapy were predictors of death and transplantation. Our data support their findings of the importance of PLE. In contrast to our study, assessment of ventricular size and function by any modality was not part of their study.

The Pediatric Heart Network (PHN) has published several reports from the Fontan Cross-Sectional Study, where CMR data were available in 161 patients.[1] When compared with our study, patients in the PHN cohort had a smaller FSV EDV_i (85±25 versus 102±44 mL/BSA$^{1.3}$; P<0.001). This cohort was also younger at the time of their evaluation (11.9±3.4 versus 20.5±10.2 years; P<0.001), more likely to have a bidirectional Glenn operation (75% versus 52%; P<0.001), and less likely to have a right atrium-to-pulmonary artery Fontan (13% versus 21%; P=0.01). Longitudinal follow-up of the PHN cohort may shed light on changes in FSV size and function as the cohort reaches adulthood. Relevant to our study, analysis of the PHN data demonstrated good reproducibility of CMR-measured FSV size and function, which was superior to 2-dimensional (2D) echocardiographic measurements.[11]

Clinical Implications

The results of our study support the clinical value of measuring ventricular size by CMR in patients with an FSV. This study does not explain why ventricular dilation is such an important risk factor in this population. It is conceivable that ventricular dilation is the final common pathway of several pathophysiologic processes, including chronic volume overload from valvar regurgitation, aortopulmonary collateral burden,[13] systolic dysfunction, delayed or lack of volume-unloading surgery (eg, bidirectional Glenn), or sinus node dysfunction. Given the association between higher EDV_i and death or transplantation, evaluating therapies aimed at inhibiting dilatation of

Table 4. Independent Risk Factors for Death or Need for Transplantation*

Predictor	Hazard Ratio	95% CI	*P* Value	*C*-Index*
CMR variables only				0.75
EDV_i (per 10 mL/BSA$^{1.3}$)	1.10	1.04–1.17	0.002	
Clinical history variables only†‡				0.63
PLE	3.5	1.5–8.5	0.005	
Clinical history and CMR variables†				0.80
PLE	8.5	1.9–38.2	0.005	
EDV_i (per 10 mL/BSA$^{1.3}$ increase)	1.12	1.05–1.19	0.001	
Clinical history and CMR variables‡				0.79
PLE	7.8	1.1–57.1	0.04	
EDV_i >125 mL/BSA$^{1.3}$	7.7	2.8–21.1	<0.001	

BSA indicates body surface area; CI, confidence interval; EDV_i, indexed end-diastolic volume; and PLE, protein-losing enteropathy.

*Multivariable Cox proportional hazards survival model (n=215; total number of end points, 24).

†Comparison of the clinical history variable model vs clinical history and CMR variable model: P=0.005.

‡Comparison of the clinical history variable model vs clinical history and CMR variable model (with dichotomized EDV$_i$): P<0.001.

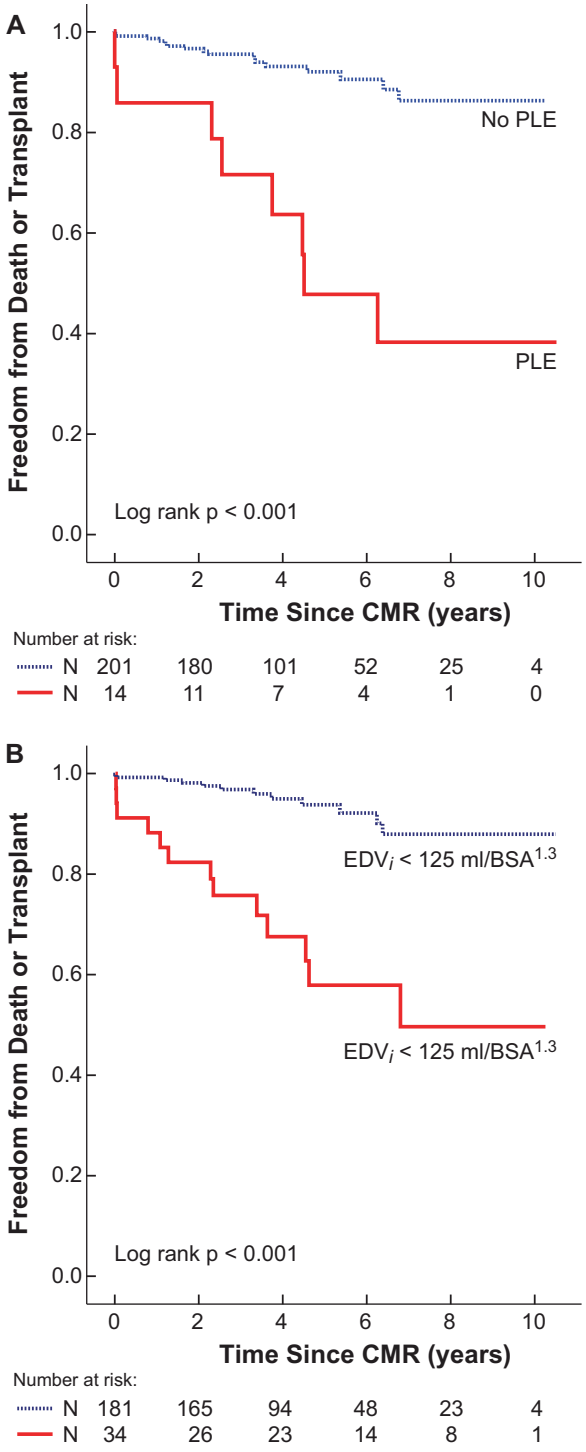

Figure 1. Freedom from death or transplantation by individual risk factors. Kaplan–Meier plot of cumulative freedom from the end point (death or transplantation) stratified by **A**, protein-losing enteropathy (PLE; *P*<0.001) and (**B**) indexed end-diastolic volume (EDV_i) >125 mL/$BSA^{1.3}$ (*P*<0.001). BSA indicates body surface area; and CMR, cardiac magnetic resonance.

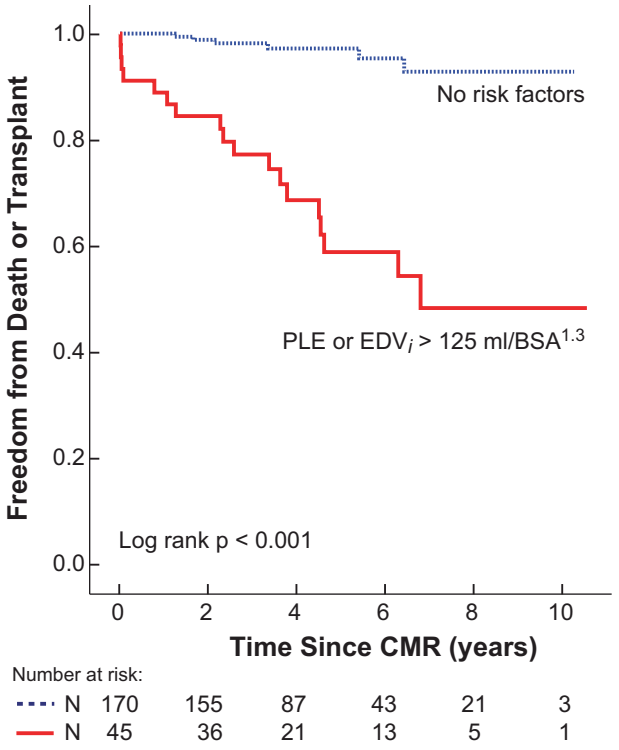

Figure 2. Freedom from death or transplantation by cumulative risk factors. Kaplan–Meier plot of cumulative freedom from the end point (death or transplantation) stratified by no risk factors and protein-losing enteropathy (PLE) or indexed end-diastolic volume (EDV_i) >125 mL/$BSA^{1.3}$ (*P*<0.001). BSA indicates body surface area; and CMR, cardiac magnetic resonance.

the FSV is warranted. Such interventions may include diuretic and afterload-reducing medications, transcatheter occlusion of aortopulmonary collaterals, or volume-unloading surgery.

Although FSV EDV_i was the strongest parameter associated with the end point, several other CMR parameters were significant by univariate analysis, including higher $mass_i$, ESV_i, and indexed SV and an EF <40%. These observations highlight the importance of CMR-derived ventricular size and function parameters with regard to the assessment of risk for death and heart transplantation. When compared with 2D echocardiography, CMR offers improved reproducibility and is typically regarded as the optimal modality for the assessment of ventricular size and function parameters.[11] Although positive LGE analyzed as a binary parameter (present versus absent) was not associated with the end point, further studies should evaluate the use of quantitative analysis of degree of LGE. Indeed, in a smaller cohort, we have previously shown that quantitative analysis of LGE in patients with Fontan circulation is associated with ventricular dilatation and dysfunction.[14] Future studies should investigate the clinical use of recently described CMR parameters, such as ventricular synchrony,[21] quantitative measurements of ventricular LGE burden,[14] and quantification of the myocardial extracellular volume fraction, an indicator of diffuse fibrosis.[22] Finally, indices of diastolic function may also shed light on FSV mechanics and may be important for risk stratification in this population.

Limitations

The single-center, CMR-centric study design limits the generalizability of this study across all patients with Fontan circulation. In particular, CMR evaluation in patients with pacemakers and defibrillators currently remains a strong relative contraindication.[23] These devices were present in 13% of the PHN

Fontan Cross-Sectional Study patients.[1] This selection bias may result in under-representation of arrhythmia-related events that could result in poor outcomes. Subgroup analyses of the PHN cohort showed that a pacemaker was associated with a poorer functional status and slight decrease in ventricular EF.[24] Symptomatic and sicker patients could also be over-represented in this study cohort because these patients often get heightened surveillance by CMR imaging. To facilitate comparison between patient characteristics and outcomes in our study and those of other recent studies, Table I in the Data Supplement compares the current cohort with those published by the PHN[1] and by Khairy et al.[2]

Measures of renal and liver function as calculated by the MELD-XI score have recently been shown to be associated with death and need for transplantation in this population.[25] In our study, however, contemporaneous serological data were not available for calculation of the MELD-XI score in most patients. Finally, from a methodological perspective, it would have been desirable to split the cohort into 2, building a predictive model in 1 group of patients and validating the model in the other group. Unfortunately, the relatively small number of end point events precludes this type of analysis. Therefore, a prospective multicenter study evaluating all of these clinical, imaging, and serological parameters in a larger cohort with more patients reaching the end point would likely improve our ability to stratify risk in patients late after the Fontan operation.

Conclusions

In patients late after the Fontan operation, ventricular dilation and presence of PLE are independent predictors of death and heart transplantation. This study is the first to demonstrate the predictive value of ventricular evaluation by CMR in a large cohort of patients. CMR-derived parameters of ventricular size add incremental value for risk stratification when compared with clinical variables alone. These data may aid in the design of trials aimed at evaluating therapies that target these risk factors.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Rathod et al analyzed clinical and cardiac magnetic resonance (CMR) parameters in 215 patients late after the Fontan operation to determine whether CMR-derived parameters of ventricular size and function were associated with death and cardiac transplantation. The study also aimed to determine whether CMR parameters improved risk stratification when compared with clinical variables alone. In this cohort, protein-losing enteropathy and higher functional single ventricular end-diastolic volume index measured by CMR were independently predictive of death or heart transplantation. In addition, they found that CMR-derived end-diastolic volume index significantly improved risk stratification for transplantation-free survival in patients with Fontan circulation. These findings indicate that CMR evaluation of ventricular size and function in this population is clinically helpful and highlights the negative effect of ventricular dilatation in the Fontan circulation. These data may aid in the design of trials aimed at evaluating therapies that target ventricular dilatation.