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ORIGINAL RESEARCH

IMAGING

Single Ventricular Torsional Mechanics After Fontan Palliation and Their Impact on Outcomes

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ABSTRACT

BACKGROUND Abnormal left ventricular (LV) rotational mechanics in biventricular hearts are associated with adverse outcomes; however, these are less well characterized for hearts with functionally single ventricles.

OBJECTIVES The purpose of this study was to characterize ventricular rotational mechanics in the Fontan circulation and their relationship to outcomes.

METHODS Single-center, retrospective analysis of magnetic resonance examinations for 329 Fontan patients (15 [IQR: 10-21] years) and 42 controls. The ventricular cine short-axis stack was analyzed to derive torsion metrics. Torsion calculated as the difference between apical and basal rotation normalized to ventricular length.

RESULTS Fontan patients had higher indexed ventricular end-diastolic volume (97 mL/body surface area$^{1.3}$ vs 72 mL/body surface area$^{1.3}$), lower ejection fraction (53% vs 60%), and lower proportion of basal clockwise rotation (62% vs 93%), apical counterclockwise rotation (77% vs 95%), and positive torsion (82% vs 100%); $P < 0.001$ for all. A composite outcome of death or heart transplant-listing occurred in 31 (9%) patients at a median follow-up of 3.9 years. Torsion metrics were associated with the outcome; although, on multivariate analysis only right ventricular (RV) morphology and indexed ventricular end-diastolic volume were independently associated. LVs with negative torsion, and RVs regardless of torsional pattern, had worse outcomes compared to LVs with positive torsion ($P = 0.020$).

CONCLUSIONS Single ventricles in a Fontan circulation exhibit abnormal torsional mechanics, which are more pronounced for RV morphology. Abnormal torsion is associated with death or need for heart transplantation. Fontan patients with LV morphology and preserved torsion exhibit the highest transplant-free survival and torsion may offer incremental prognostic data in this group of patients. (JACC Adv 2023;2:100360) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AVVR = atrioventricular valve regurgitation

BSA = body surface area

CMR = cardiac magnetic resonance imaging

EDV$_i$ = indexed end-diastolic volume

EF = ejection fraction

ESV$_i$ = indexed end-systolic volume

FT = feature tracking

GCS = global circumferential strain

LV = left ventricle

RV = right ventricle

SV = single ventricle

The Fontan operation is the final stage in a series of palliative procedures performed in children born with single ventricle (SV) physiology. There are an estimated 70,000 patients with a Fontan circulation worldwide, a number that is expected to double over the next 20 years.[1] While long-term outcomes have improved with advancements in surgical techniques and medical management, a significant risk of morbidity and mortality remains. The estimated 20-year survival is 61% to 85%, with a risk of late mortality of approximately 2.1% per year.[2] Ventricular dilation and dysfunction are established risk factors for poor outcomes in the Fontan population.[3,4] However, there is growing interest to find more nuanced markers for risk stratification and prognostication in patients with SV.

A normal left ventricle (LV) has a complex arrangement of myofibers that gradually change from a subendocardial right-handed helix to a subepicardial left-handed helix.[5] This enables an efficient contraction pattern known as torsion, which consists of clockwise basal rotation and simultaneous counterclockwise apical rotation, as viewed from the apex. Indeed, in a biventricular circulation, abnormalities in ventricular torsion have been associated with adverse outcomes.[6] Defects in ventricular torsion have also been described in SVs, and are associated with reduced ejection fraction (EF), electrocardiographic abnormalities, and increased circulating biomarkers, such as pro B-type natriuretic peptide levels.[7-12] Unlike large studies conducted for individuals with structurally normal hearts, the SV torsion literature has been limited by relatively small cohort sizes and lack of long-term outcomes, such as death. Furthermore, much of the literature is based on studies using echocardiography, which can be limited by poor acoustic windows.

The present study aims to characterize rotational contraction patterns in SVs using cardiac magnetic resonance imaging (CMR). Additionally, it explores if differences in torsion exist based on the ventricular morphology and whether torsional abnormalities are associated with death or need for heart transplantation for Fontan patients. The main hypotheses for the study are: 1) SVs would have reduced torsion (difference between basal and apical angular rotation divided by the length) compared to age-matched controls; 2) torsion abnormalities would be worse in single right ventricles (RVs) compared to single LVs; and 3) reduced torsion would be associated with death or need for heart transplantation.

METHODS

This was a single-center, retrospective cohort study. The Institutional Review Board (IRB-P00036587) approved the study and informed consent was waived.

STUDY POPULATION. All patients with a Fontan circulation and at least 1 available CMR after 7/1/05 were screened for eligibility. The patients' care teams ordered CMR as a part of their clinical care. A total of 156 patients with a significantly sized second ventricle contributing to the systemic circulation (defined as >20% of the combined end-diastolic volume) were excluded. Ventricular morphology was classified as either LV or RV. One CMR was analyzed per patient and when multiple CMRs were available, the oldest available study was used. A total of 46 patients with inadequate image quality for volumetric and feature tracking (FT) analysis were excluded. Additionally, patients who were listed for heart transplant prior to the CMR were excluded. Controls were identified as individuals who had a CMR that was interpreted as normal and who did not have known systemic or genetic disease with cardiovascular involvement. Controls were age-matched 1:8 with cases. Demographics, electrocardiogram, and clinical data were extracted from electronic medical records and when multiple data points were available, the ones closest to the CMR were included.

CMR PROTOCOL. The Fontan imaging protocol at our center has been previously described.[3,4] Briefly, studies were performed on a 1.5-T scanner (Achieva, Phillips Healthcare, Best) using surface coils chosen based on patient size. A ventricular short-axis balanced steady-state free precession cine stack with breath-holding and ECG-gating was used for volumetric and FT analysis. Typical slice thickness was 8 to 10 mm. Typical spatial resolution was 1.7 to 2 mm by 1.7 to 2 mm and temporal resolution was 30 to 40 ms with 30 reconstructed phases per cardiac cycle. Ventricular volumes and blood flow were measured using commercially available software (cvi42, Circle Cardiovascular Imaging Inc; and QMass, Medis Medical Imaging Systems). The following conventional measurements were recorded: indexed end diastolic volume (EDV$_i$), indexed end-systolic volume (ESV$_i$), indexed stroke volume, EF, indexed ventricular mass (mass$_i$), and ascending aortic flow as a measure of ventricular output. Mass and volume measurements were indexed to body surface area (BSA)[1,3].[13] When 2 ventricles contributed to the systemic circulation, their mass and volumes were combined. The degree of atrioventricular valve

regurgitation (AVVR) and aortic regurgitation was categorized as significant when reported as > mild or as a regurgitation fraction ≥20%. For controls, only the LV measurements were considered.

FEATURE TRACKING AND ROTATIONAL MECHANICS. FT analysis was performed on the short-axis cine stack of images using a commercially available software (cvi42, Circle Cardiovascular Imaging Incas previously described.[14] Briefly, the endocardial and epicardial borders were manually traced at end-diastole for all slices from the apex to the base of the ventricle and contours were manually adjusted to ensure adequate tracking. The apical slice was defined as the most apical slice with blood pool throughout the entire cardiac cycle. The basal slice was defined as the most basal slice with a full rim of myocardium throughout the entire cardiac cycle. A minimum of 5 slices was required for inclusion and no more than 10 slices were traced. For controls, the above analysis was performed on the LV. As viewed from the apex, counterclockwise displacement was recorded as positive and clockwise displacement was recorded as negative. The following parameters were collected: direction of rotation (clockwise or counterclockwise), degree of circumferential displacement of each slice, peak systolic twist (apical-basal displacement), peak systolic torsion (twist normalized to ventricular length) in degrees per a centimeter (deg/cm), and peak systolic and diastolic torsion rate in degrees per second (deg/s). Global circumferential strain (GCS) was recorded based on all the analyzed slices. For each patient, the degree of rotation of each slice was plotted against the slice number and the slope of a linear regression line through these points was recorded as torsional gradient, and the correlation coefficient was recorded as torsional concordance (**Central Illustration**).

OUTCOMES. A composite adverse outcome was defined as having any of the following: all-cause mortality, or listing for heart transplantation. For time-to-event analysis, follow-up was measured from the date of the CMR to the composite outcome (using the earliest outcome event in the case of multiple qualifying events), or last known documented follow-up in the medical record.

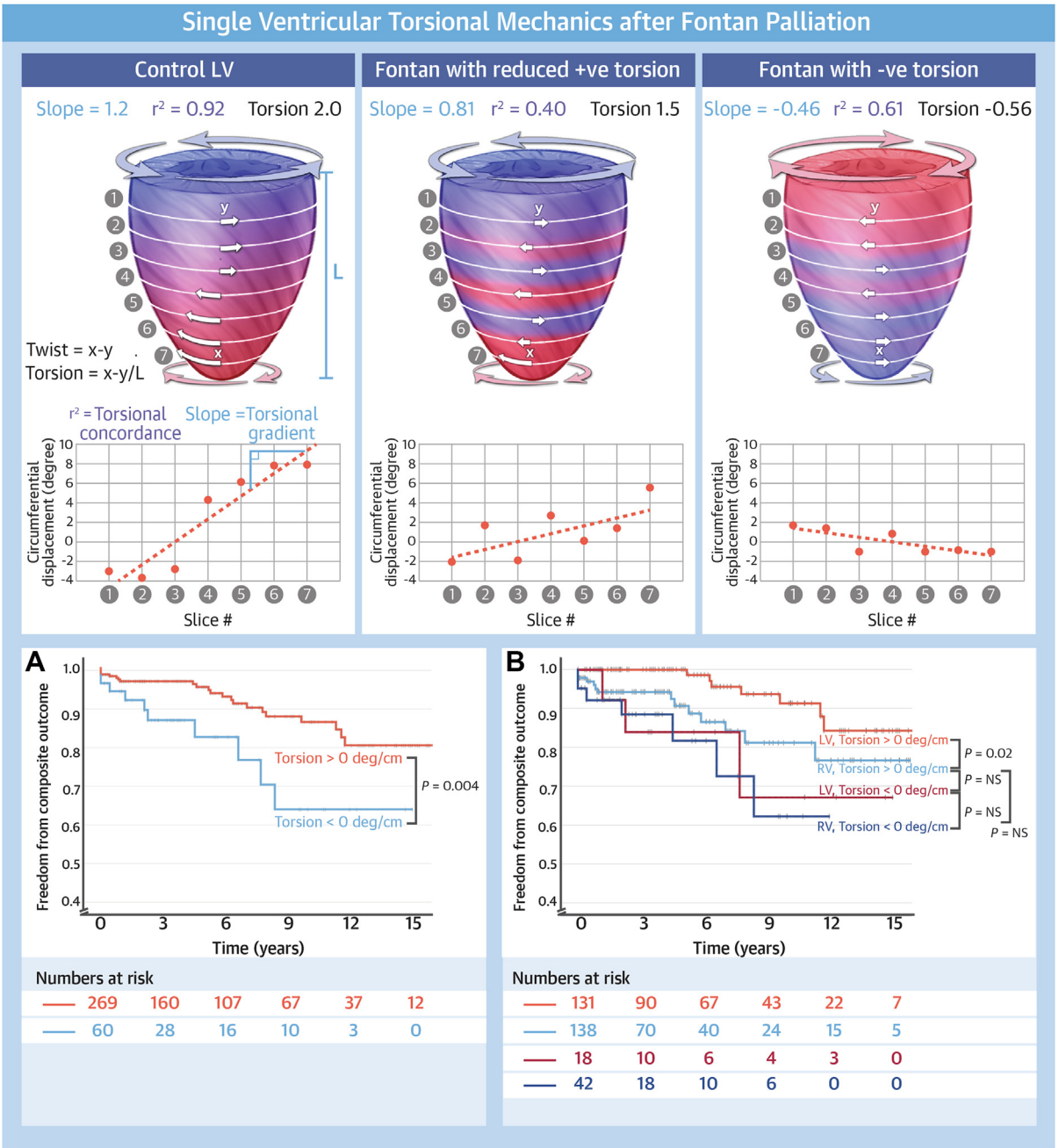
STATISTICAL ANALYSES. Data are presented as a median (IQR) except when noted and as a frequency (percentage) for categorical variables. Continuous variables were compared between groups using a Mann-Whitney *U* test, while proportions were compared using a Fisher exact test. Correlation between continuous variables was quantified using the Spearman Rho (ρ). LV and RV groups were further divided into quartiles. The presence of a trend in the prevalence of the composite outcome within these quartiles was assessed using the Mantel-Haenszel test. Univariate and multivariable Cox logistic regression analyses were performed to assess relationships between predictors and the time to composite outcome. At most, 4 variables were included in the multivariate Cox models and variables were chosen based on clinical relevance and significance on univariate analysis. Kaplan-Meier survival curves with log rank tests were constructed to compare freedom from the composite outcome between groups. A *P* value of ≤0.05 was considered statistically significant. Interobserver and intraobserver reliability was assessed for a subset of variables using a random set of 25 patients (13 LV, 12 RV) that would allow for a CI of <0.3 for a true intraclass correlation coefficient of 0.8. Measurements for intraobserver analysis were performed >3 months apart and those for interobserver analysis were performed by 2 separate observers. Analysis was accomplished using a two-way mixed effects model to estimate the intraclass correlation coefficient with 95% CIs. Bland-Altman plots were constructed to visually depict the agreement.[15] Statistical analyses were performed using SPSS version 27.0 (IBM corporation) and STATA/SE 13.1 (StataCorp LP).

RESULTS

PATIENT CHARACTERISTICS. The study cohort included 329 Fontan patients with a median age at CMR of 14.8 (IQR: 10.3-20.6) years and 42 controls with a median age of 15.7 (IQR: 11.0-19.7) years. **Table 1** presents underlying primary cardiac diagnoses for the patient cohort and their type of Fontan operations and indications for CMRs in the control cohort. The controls undergoing evaluation for cardiomyopathy had a normal CMR as well as normal clinical and genetic evaluations at follow-up. Ventricular morphology was RV in 180 patients (55%) and LV in 149 patients (45%). Compared to controls, Fontan patients had a lower BSA and a higher proportion of male sex (**Table 2**).

CMR ANALYSES. Conventional CMR parameters for the study cohort are presented in **Table 3**. Compared to controls, Fontan patients had larger ventricular volumes and mass, and lower EF, cardiac output, and GCS. When compared to the LV group, patients in the RV group had larger ventricular volumes, lower EF, and more AVVR. The average number of slices analyzed per patient was smaller in controls (6.0 ± 1.3) compared to cases (6.9 ± 1.0; $P < 0.001$)

CENTRAL ILLUSTRATION **Representative Rotational Patterns for a Control LV and 2 Single Ventricles With a Fontan Circulation and Kaplan-Meier Survival Plots Stratified by Direction of Torsion and Ventricular Morphology**



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Schematic representing rotational mechanics in left ventricle of a control patient, single ventricle in a Fontan patient with reduced magnitude but normal direction of torsion (>0 deg/cm) and, single ventricle in a Fontan patient with negative torsion. As viewed from the apex, counterclockwise rotation is displayed as positive and clockwise rotation as negative. *Twist* is defined as the difference between maximum global circumferential displacement for the basal and the apical most slices (x-y). *Torsion* is defined as twist divided by the length of the ventricle (x-y/L). Circumferential displacement in degrees on the vertical axis and slice number on the horizontal axis. *Torsional gradient* is defined as the slope of the linear regression line **(dashed line)** between points **(red dots)** represented by slice number on the horizontal axis and the maximum circumferential displacement of each slice on the vertical axis. *Torsional concordance* is the correlation coefficient of this linear regression line. **(A)** Compared to patients with negative torsion, those with positive torsion experienced a higher freedom from death or transplantation. **(B)** When further stratified by ventricular morphology, the left ventricular group with positive torsion experienced the highest freedom from the composite outcome. LV = left ventricle.

TABLE 1 Primary Cardiac Diagnosis, Type of Fontan Operation, and Indications for CMR in Controls

Primary anatomic diagnosis for Fontan patients (N = 329)
Hypoplastic left heart syndrome (40%)
Tricuspid atresia (20%)
Double-inlet left ventricle (16%)
Double-outlet right ventricle (10%)
Pulmonary atresia with intact ventricular septum (6%)
Unbalanced common atrioventricular canal defect (4%)
Other complex congenital heart disease (4%)
Type of Fontan operation
Lateral tunnel (72%)
Extracardiac conduit (17%)
Right atrium to pulmonary artery (9%)
Other (2%)
Indications for CMR in control group (N = 42)
Family history of cardiomyopathy (57%)
Concern for arrhythmogenic right ventricular dysplasia (7%)
Family history of a bicuspid aortic valve (7%)
Family history of sudden cardiac death (7%)
Questionable echocardiogram abnormality (21%)

CMR = cardiac magnetic resonance.

and smaller in the RV group (5.6 ± 1.2) compared to the LV group (6.4 ± 1.2; $P < 0.001$).

Rotational mechanics from CMR-FT analysis for Fontan patients and healthy controls are presented in Table 4. Compared with controls, Fontan patients had abnormalities in direction and magnitude of basal and apical rotation, twist, torsion, time to peak twist, and diastolic torsion rate or "untwisting" rate. Within the Fontan cohort, torsion abnormalities were more common in the RV group when compared to the LV group (Figure 1). The mean torsion for the control group was 1.43 ± 0.49 deg/cm). Among Fontan patients, 97 (29%) had torsion <0.45 deg/cm (mean -2 SD of control group). There was no correlation between age and torsion for the entire cohort (n = 371; correlation coefficient, $\rho = 0.08$, $P = 0.123$), within the Fontan group ($\rho = 0.10$, $P = 0.080$) or within the control group ($\rho = 0.0$, $P = 0.995$). Within the Fontan group, torsion was associated with EDV_i ($\rho = -0.33$, $P < 0.001$), ESV_i ($\rho = -0.41$, $P < 0.001$), EF ($\rho = 0.43$, $P < 0.001$), GCS ($\rho = -0.35$, $P < 0.001$), torsional gradient ($\rho = 0.88$, $P < 0.001$), and torsional concordance ($\rho = 0.69$, $P < 0.001$). A venn diagram depicts the overlap between ventricular dilation, AVVR, and torsion (Figure 2). Patients with more than mild AVVR (n = 46) had lower torsion (0.4 deg/cm [IQR: −0.3 to 0.9 deg/cm]) and twist (1.8 deg [IQR: −1.0 to 3.0 deg]) compared to those without significant AVVR (n = 255; torsion 0.9 deg/cm IQR [0.4-1.4 deg/cm]; twist 3.2 [IQR: 1.5-5.0 deg]; $P = 0.002$ for torsion and <0.001 for twist). Patients with dilated ventricles (defined as top tertile, EDV_i >112 ml/BSA$^{1.3}$; n = 109) had lower torsion (0.5 deg/cm [IQR: −0.3 to 1.0 deg/cm]) and twist (1.9 deg [IQR: −1.0 to 3.5 deg]) compared to those with less dilated ventricles (n = 220; torsion 0.9 deg/cm [IQR: 0.5-1.4 deg/cm] twist 3.5 [IQR: 1.9-5.3 deg] respectively; $P = 0.001$ for both.

Complete right bundle branch block pattern was present in 23 patients and complete left bundle branch block pattern was present in 1 patient. Of the 23 patients with complete right bundle branch block pattern, 21 were RV morphology and 2 were LV morphology. The patient with complete left bundle branch block pattern had LV morphology. Patients with bundle branch block had larger EDV_i (120.2 ml/BSA$^{1.3}$, [IQR: 99.6-166.4 ml/BSA$^{1.3}$] vs 94.6 ml/BSA$^{1.3}$ [IQR: 79.2-118.5 ml/BSA$^{1.3}$]; $P = 0.001$), lower EF (48.3% [IQR: 34.5%-54.3%] vs 53.6% [IQR: 47.5%-58.2%]); $P = 0.001$), worse GCS (−12.5% [IQR: −16.5% to −9.1%] vs −15.2% [IQR: −17.3% to −12.7%]); $P = 0.02$); lower torsion (0.4 deg/cm [IQR: −0.7 to 1.1 deg/cm] vs 0.8 deg/cm [IQR: 0.4-1.3 deg/cm]; $P = 0.007$); and lower twist (1.5 deg [IQR: −1.6 to 3.3 deg] vs 3.0 deg [IQR: 1.5-4.8 deg]; $P = -0.002$).

OUTCOME ANALYSES. With a median follow-up period of 3.9 (IQR: 1.1-8.3) years, 31 (9.4%) of the patients met the composite outcome with 22 deaths and 9 heart transplant listings, of which 3 patients

TABLE 2 Baseline Characteristics for Fontan Patients and Controls

	Groups				*P* Value			
	All Fontan Patients (N = 329)	RV (N = 180)	LV (N = 149)	Control LV (N = 42)	All Fontan vs Control LV	RV vs Control LV	LV vs Control LV	LV vs RV
Age at CMR, y	14.8 (10.3-20.6)	13.6 (10.0-17.8)	16.6 (12.1-24.3)	15.7 (11.0-19.7)	0.927	0.120	0.098	<0.001[a]
Male	205 (62%)	115 (64%)	90 (60%)	18 (43%)	0.019[a]	0.015[a]	0.053	0.516
BSA, m^2	1.5 (1.0-1.7)	1.4 (1.0-1.7)	1.6 (1.2-1.8)	1.6 (1.3-1.8)	0.044[a]	0.003[a]	0.535	<0.001[a]
Heart rate, beats/min	82 (70-93)	85 (72-95)	78 (67-89)	80 (67-90)	0.611	0.165	0.552	0.002[a]
Mean BP, mm Hg	76 (70-84)	74 (68-82)	79 (72-87)	82 (71-87)	0.087	0.008[a]	0.670	<0.001[a]

Values are median (IQR) or n. [a]$P < 0.05$.

BP = blood pressure; BSA = body surface area; CMR = cardiac magnetic resonance; LV = left ventricle; RV = right ventricle.

TABLE 3 Conventional CMR Data for all Fontan Patients, RV Group, LV Group, and Controls

	Groups				*P* Value			
	All Fontan Patients (N = 329)	RV (N = 180)	LV (N = 149)	Control LV (N = 42)	All Fontan vs Control	RV vs Control	LV vs Control	LV vs RV
EDV_i, mL/$BSA^{1.3}$	97 (80-121)	109 (90-136)	85 (70-101)	72 (64-80)	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
ESV_i, mL/$BSA^{1.3}$	45 (34-63)	53 (41-70)	38 (29-48)	27 (23-33)	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
$Mass_i$, g/$BSA^{1.3}$	49 (42-62)	50 (42-67)	48 (41-59)	45 (37-48)	<0.001[a]	<0.001[a]	0.001[a]	0.240
EF, %	53 (47-58)	51 (45-56)	55 (50-60)	60 (56-66)	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
>Mild AR (n = 296)	5/296 (1.7%)	3/165 (1.8%)	2/131 (1.5%)	0 (0%)	<0.001[a]	1.000	1.000	0.847
> Mild AVVR (n = 301)	46/301 (15%)	38/166 (23%)	8/135 (6%)	0 (0)	<0.001[a]	<0.001[a]	0.201	<0.001[a]
Stroke volume, ml	77 (58-99)	78 (55-99)	75 (59-99)	77 (66-95)	0.753	0.820	0.703	0.950
Indexed stroke volume, ml/$BSA^{1.3}$	50 (42-62)	54 (46-66)	46 (39-54)	44 (40-49)	0.001[a]	<0.001[a]	0.385	<0.001[a]
Aortic flow, L/min/m^2 (n = 284)	3.1 (2.6-3.7)	3.1 (2.7-3.9)	3.0 (2.4-3.5)	3.6 (3.1-3.8)	0.006[a]	0.060	<0.001[a]	0.009[a]
GCS, %	−15.2 (−17.2 to −12.5)	−13.6 (−15.6 to −11.3)	−16.7 (−18.7 to −14.6)	−17.9 (−19.8 to −17.0)	<0.001[a]	<0.001[a]	0.002[a]	<0.001[a]

Values are median (IQR) or n (%). [a]Indicates $P < 0.05$. Aortic flow, AR, and AVVR data not available for all patients.

AR = aortic regurgitation; AVVR = atrioventricular valve regurgitation; BSA = body surface area; CMR = cardiac magnetic resonance; EDV_i = indexed ventricular end-diastolic volume; EF = ejection fraction; ESV_i = indexed ventricular end-systolic volume; GCS = global circumferential strain; LV = left ventricle; RV = right ventricle.

underwent transplantation. Those with the composite outcome were younger, had a higher EDV_i, higher ESV_i, lower EF, higher indexed ventricular mass, worse GCS, and more AVVR (Table 5). Among rotational measurements, those with the composite outcome were more likely to have negative torsion, less apical rotation, lower twist, lower torsion, and a lower torsional gradient. Table 5 presents HRs based on univariable Cox regression analysis for the composite outcome. A multivariable Cox regression model was constructed including EDV_i, age at CMR, ventricular morphology, and EF. On this analysis, EDV_i per 10 ml increase/$BSA^{1.3}$ (HR: 1.15; 95% CI: 1.11-1.19; $P < 0.001$) and RV morphology (HR: 2.45; 95% CI: 1.06-5.65; $P = 0.036$) were independently associated with the composite outcome. A second multivariable Cox regression model including torsion, EDV_i, and ventricular morphology showed that torsion is not an independent predictor of the composite outcome (HR: 1.8; 95% CI: 0.84-3.86; $P = 0.129$).

Within the RV group, those with torsion >0.45 deg/cm (mean -2 SD for control group; n = 115, 64%) had a lower prevalence of the composite outcome (7%) compared to those with torsion ≤0.45 deg/cm (20%, $P = 0.014$). Figure 3 depicts torsion quartiles for left and RVs and the rate of composite outcome in each

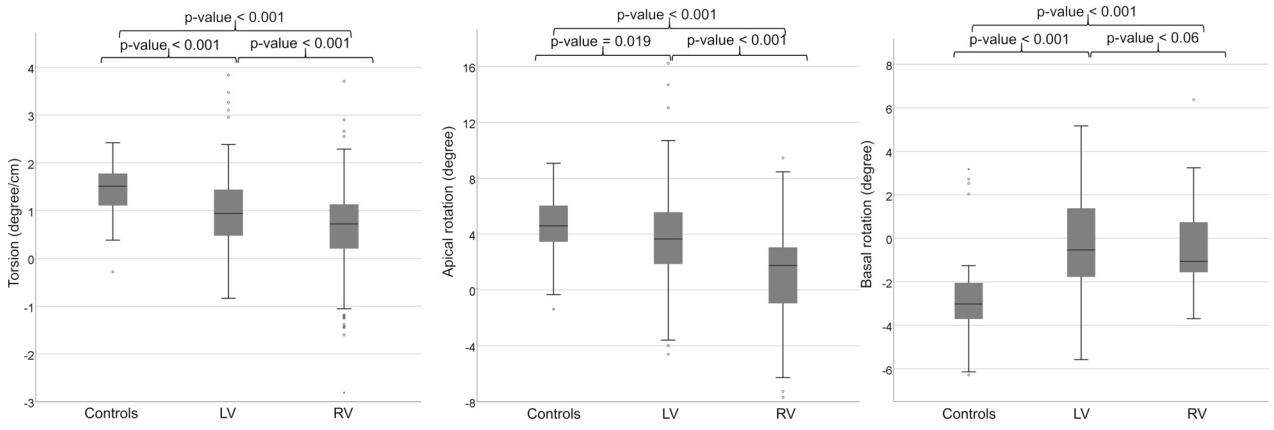
TABLE 4 CMR Rotational Ventricular Mechanics

	Groups				*P* Value			
	All Fontan Patients (N = 329)	RV (N = 180)	LV (N = 149)	Control LV (N = 42)	All Fontan vs Control	RV vs Control LV	LV vs Control LV	LV vs RV
Direction of rotation								
Basal slice clockwise rotation	206 (62%)	127 (71%)	79 (53%)	39 (93%)	<0.001[a]	0.003[a]	<0.001[a]	0.001[a]
Apical slice counterclockwise rotation	253 (77%)	123 (68%)	130 (87%)	40 (95%)	0.004[a]	<0.001[a]	0.173	<0.001[a]
Torsion positive	269 (82%)	138 (77%)	131 (88%)	42 (100%)	0.001[a]	<0.001[a]	0.015[a]	0.010[a]
Rotation degrees								
Peak basal rotation (deg)	−0.87 (−1.6 to 1.2)	−1.1 (−1.6 to 0.7)	−0.54 (−1.8 to 1.4)	−3.0 (−3.8 to −2.1)	<0.001[a]	<0.001[a]	<0.001[a]	0.060
Peak apical rotation (deg)	2.4 (0.92-4.3)	1.8 (−1.0-3.1)	3.6 (1.8-5.5)	4.6 (3.5-6.1)	<0.001[a]	<0.001[a]	0.019[a]	<0.001[a]
Twist (deg)	2.7 (0.99-4.5)	2.0 (−0.9-3.6)	3.5 (2.1-5.8)	6.9 (4.8-8.5)	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
Torsion (deg/cm)	0.82 (0.38-1.3)	0.72 (0.2-1.1)	0.94 (0.5-1.5)	1.5 (1.1-1.8)	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
Torsional gradient (deg/slice)	0.63 (0.21-1.03)	0.50 (0.02-0.93)	0.74 (0.39-1.15)	1.26 (0.94-1.72)	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
Torsional concordance	0.65 (0.24-0.83)	0.55 (0.16-0.79)	0.72 (0.37-0.88)	0.75 (0.56-0.86)	0.010[a]	<0.001[a]	0.394	0.001[a]
Torsion rates								
Systolic rate (deg/sec)	8 (−5.2-12.6)	7.5 (−6.7-12.7)	9 (3.7-12.7)	9.9 (7.6-13.3)	0.108	0.052	0.307	0.132
Diastolic rate (deg/sec)	−8.4 (−13.1 to −3.6)	−8 (−12.6 to 4.4)	−8.7 (−13.7 to −4.9)	−12 (−15.9 to −8.8)	<0.001[a]	<0.001[a]	0.002[a]	0.215

Values are median (IQR) or n (%). [a]Indicates $P < 0.05$.

CMR = cardiac magnetic resonance; LV = left ventricle; RV = right ventricle.

FIGURE 1 **Boxplots Illustrating Abnormal Rotational Parameters in Fontan Patients Compared to Control LVs**



Boxplot comparison of torsion, apical rotation, and basal rotation between control left ventricles, single left ventricles, and single right ventricles. Rotational parameters differ between Fontan patients compared to control left ventricles with a more pronounced abnormality in the right ventricular group. LV = left ventricle; RV = left ventricle.

quartile. In the RV group there is a linear decreasing trend in the prevalence of the outcome along the rising quartiles ($P = 0.005$). In the LV group the lowest torsion quartile has the highest rate of composite outcome; however, a trend similar to the RV group was not present ($P = 0.747$).

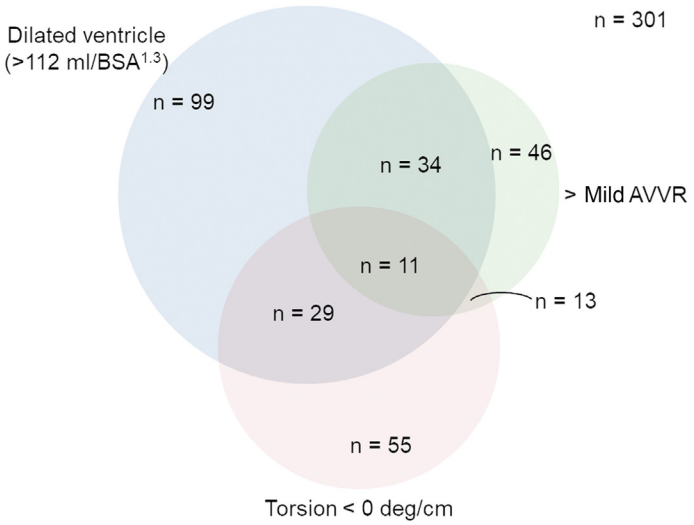
Kaplan-Meier estimates for event-free survival, stratified by presence of positive or negative torsion, are shown in **Central Illustration A**. Those with positive torsion had a higher freedom from composite outcome (mean, 14.3 years; 95% CI: 13.6-15.0 years) compared to those with negative torsion (mean, 11.3 years; 95% CI: 9.4-13.2 years, $P = 0.004$). **Central Illustration B** shows that when patients were stratified into 4 categories using ventricular morphology as well as positive torsion, the LV group with positive torsion had the highest freedom from the composite outcome. LV group patients with negative torsion had a similar survival when compared to RV group.

Table 6 and **Figure 4** demonstrate results of interobserver and intraobserver reliability analysis. For both interobserver and intraobserver analyses, reliability was excellent for GCS and good for torsion, twist, torsional gradient, and torsional concordance.

DISCUSSION

This CMR-based retrospective analysis demonstrates that SVs with a Fontan circulation, regardless of ventricular dominance, have reduced torsion compared to normal LVs and that an abnormal rotational pattern is associated with death or need for heart transplantation. Torsional abnormalities are more severe in morphologic RVs as compared to LVs, with a more pronounced reduction in basal and apical rotation. Patients with RV morphology and abnormal direction of torsion experience the highest rate of

FIGURE 2 **Venn Diagram Capturing the Overlap Between Patients With Ventricular Dilation, AVVR, and Torsion**



Notable overlap exists for patients with ventricular dilation, negative torsion, and significant atrioventricular valve regurgitation. Of the 301 patients with atrioventricular valve regurgitation data, 99 were dilated, 55 had negative torsion and 46 had >mild atrioventricular valve regurgitation. AVVR = atrioventricular valve regurgitation; BSA = body surface area.

TABLE 5 Comparison Between Fontan Patients With and Without Composite Outcome With Univariate Cox Regression Analysis for Composite Outcome

	No Outcome (N = 298)	Outcome (N = 31)	*P* Value	HR (95% CI)	*P* Value
Male, %	61	74	0.176	0.56 (0.25-1.25)	0.157
Age (y)	15.2 (10.5-20.8)	10.3 (7.7-16.8)	0.008[a]	0.94 (0.90-0.99)	0.016[a]
RV morphology, %	53	68	0.134	2.58 (1.21-5.51)	0.014[a]
EDV_i, mL/$BSA^{1.3}$	95 (79-117)	159 (89-230)	<0.001[a]	1.15 (1.11-1.19)	<0.001[a]
ESV_i, mL/$BSA^{1.3}$	45 (34-61)	81 (44-146)	<0.001[a]	1.16 (1.12-1.21)	<0.001[a]
$Mass_i$, g/$BSA^{1.3}$	49 (41-60)	61 (47-82)	0.005[a]	1.18 (1.06-1.30)	0.002[a]
EF %	54 (47-58)	49 (36-58)	0.004[a]	0.94 (0.91-0.97)	<0.001[a]
> Mild AVVR % (n = 301)	13	43	<0.001[a]	4.30 (2.03-9.10)	<0.001[a]
Aortic flow, L/min/m^2	3.1 (2.6-3.7)	3.3 (2.7-4.0)	0.104	1.31 (1.00-1.72)	0.046[a]
GCS, %	−15.3 (−17.3 to −12.8)	−12.3 (−16 to −8.7)	0.001[a]	1.26 (1.15-1.38)	<0.001[a]
Direction of rotation					
Basal slice clockwise rotation	187 (63%)	19 (61%)	0.848	1.00 (0.49-2.07)	0.995
Apical counterclockwise rotation	233 (78%)	20 (65%)	0.114	2.46 (1.18-5.15)	0.017[a]
Torsion positive	248 (83%)	21 (68%)	0.048[a]	2.87 (1.34-6.12)	0.006[a]
Rotation degrees					
Peak basal rotation (deg)	−0.9 (−1.7 to 1.1)	−0.9 (−1.4 to 2.1)	0.301	1.07 (0.89-1.28)	0.487
Peak apical rotation (deg)	2.5 (1.1-4.4)	1.6 (−1.0-2.6)	0.019[a]	0.85 (0.77-0.94)	0.001[a]
Twist (deg)	3.0 (1.3-4.6)	1.0 (−1.6-3.1)	0.003[a]	0.83 (0.74-0.92)	<0.001[a]
Torsion (deg/cm)	0.8 (0.4-1.3)	0.4 (−0.4-0.9)	0.005[a]	0.52 (0.35-0.75)	<0.001[a]
Torsional gradient (deg/slice)	0.66 (0.25-1.05)	0.22 (−0.17-0.80)	0.003[a]	0.44 (0.27-0.72)	0.001[a]
Torsional concordance	0.66 (0.27-0.84)	0.29 (0.12-0.81)	0.057	0.29 (0.10-0.81)	0.019[a]
Torsion rates					
Systolic rate (deg/sec)	8.2 (−4.8 to 13)	5.6 (−6.9 to 10.9)	0.187	1.00 (0.99-1.01)	0.700
Diastolic rate (deg/sec)	−8.5 (−13.3 to −4.1)	−7.3 (−10.4 to 9.6)	0.067	1.03 (1.01-1.06)	0.006[a]

Values are median (IQR) or n (%). [a]$P < 0.05$.

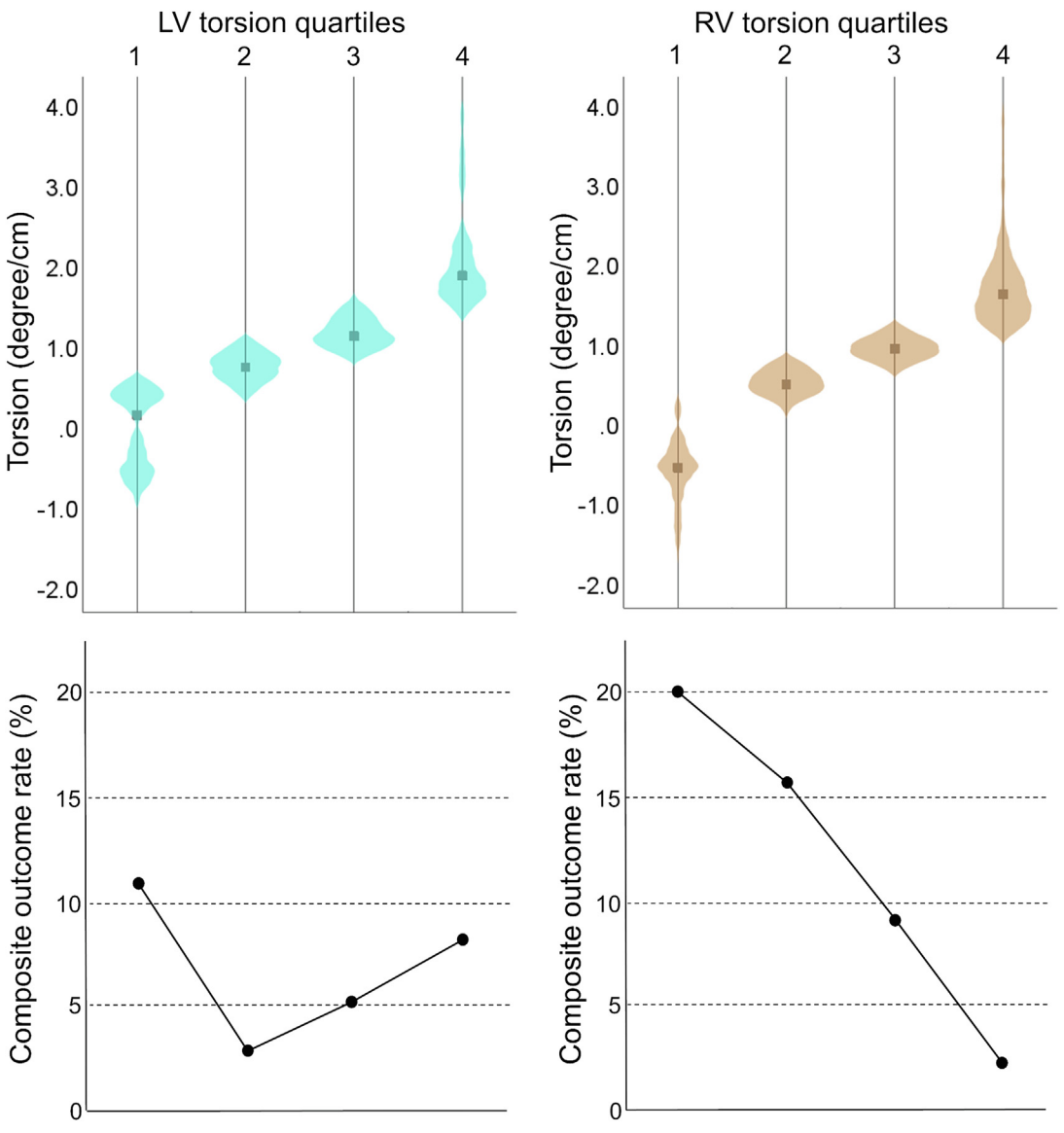
AVVR = atrioventricular valve regurgitation; BSA = body surface area; EDV_i = indexed ventricular end-diastolic volume; EF = ejection fraction; ESV_i = indexed ventricular end-systolic volume; GCS = global circumferential strain; RV = right ventricle.

adverse outcomes. These findings add to the growing understanding that suboptimal ventricular adaptation in patients with a Fontan circulation contribute to morbidity and mortality in this vulnerable population.

Data regarding contraction patterns in SVs with a Fontan circulation are growing, but remain to be fully elucidated.[6,8,16,17] Meanwhile, the mechanism for normal LV contraction has been well described. A normal LV has a wringing or helical contraction pattern that is important for pressure generation.[18] In Fontan patients, however, the current study observed an abnormal pattern and a reduced magnitude of torsion. These findings are consistent with previous studies, which have shown global abnormalities in ventricular rotation, with a heterogenous pattern of clockwise and counterclockwise apical and basal rotation.[11,19,20] Not surprisingly, the abnormalities were more pronounced in patients with a RV morphology. In contrast to LV contraction, RV ejection is thought to result from longitudinal myofibril shortening. Although there remains some degree of controversy with regards to the anatomic basis of contraction in both ventricles,[16,21] it is noteworthy that a nontrivial proportion of morphologic RVs had a torsional pattern similar to normal LVs. This is in contrast to systemic RVs in a biventricular setting (eg, after atrial switch operation), wherein the RVs have been shown to lack torsional contraction.[22] The absence or near-absence of a septum in single RVs may, in part, explain our findings. Furthermore, changes in ventricular geometry through staged palliation lead to an increased circumferential mode of RV contraction, likely related to myocyte alterations.[23,24] Bundle branch abnormalities were also more common in patients with RV morphology (12%) compared to LV morphology (2%) and likely contributed to an abnormal contraction pattern. It remains unknown, however, why certain RVs are better able to adapt to the demands of the systemic circulation.[20]

Impaired ventricular function, ventricular dilation, and RV morphology are established risk factors for poor clinical outcomes in patients with a Fontan

FIGURE 3 **Torsion Quartiles for Left and Right Ventricles and the Rate of Composite Outcome in Each Quartile**



Violin plots with medians show the distribution of torsion within each quartile by ventricular morphology and below **(dots with lines)** depicts the proportion of patients with the composite outcome. In the right ventricular group there is a linear decreasing trend in the prevalence of the outcome along the rising quartiles ($P = 0.005$). In the left ventricular group the lowest torsion quartile has the highest rate of composite outcome; however, a trend similar to the right ventricular group was not present ($P = 0.747$). LV = left ventricle; RV = right ventricle.

circulation.[25-28] This study reaffirmed these associations, but also demonstrated a higher prevalence of torsion abnormalities in the death/transplant group. Interestingly, younger age at CMR was associated with death/transplantation. This may be due to a combination of factors, including a referral bias for sicker children and the younger age of the RV group in this study. Multivariable analysis showed that the relationship between adverse outcomes and torsion was not independent of ventricular morphology

TABLE 6 Interobserver and Intraobserver Reliability Analysis

	N (Pairs)	Obs 1	Obs 2	Mean Difference (95% CI)	ICC (95% CI)
Interobserver reliability					
Torsion (deg/cm)	25	0.80 ± 0.84	0.72 ± 0.83	−0.08 (−0.25-0.10)	0.88 (0.74-0.94)
Twist (deg)	25	3.2 ± 3.4	2.8 ± 2.5	−0.38 (−1.23-0.47)	0.83 (0.65-0.92)
GCS (%)	25	−14.1 ± 3.2	−14.8 ± 3.6	−0.73 (−1.17-−0.28)	0.95 (0.89-0.98)
Torsional gradient (deg/slice)	25	0.63 ± 0.56	0.66 ± 0.61	−0.03 (−0.26-0.23)	0.90 (0.79-0.96)
Torsional concordance	25	0.62 ± 0.29	0.62 ± 0.25	0.02 (−0.14-0.18)	0.82 (0.63-0.92)
Intraobserver reliability					
Torsion (deg/cm)	25	0.88 ± 0.82	0.77 ± 0.93	0.11 (−0.11-0.32)	0.83 (0.65-0.92)
Twist (deg)	25	3.5 ± 3.6	3.1 ± 3.8	0.38 (−0.53-1.29)	0.83 (0.65-0.92)
GCS (%)	25	−15.2 ± 3.6	−14.8 ± 3.4	−0.40 (−0.84-0.04)	0.96 (0.91-0.98)
Torsional gradient (deg/slice)	25	0.63 ± 0.59	0.64 ± 0.56	−0.08 (−0.34-0.18)	0.89 (0.69-0.86)
Torsional concordance	25	0.59 ± 0.29	0.61 ± 0.25	−0.06 (−0.21-0.09)	0.80 (0.61-0.90)

GCS = global circumferential strain; ICC = intraclass correlation coefficient.

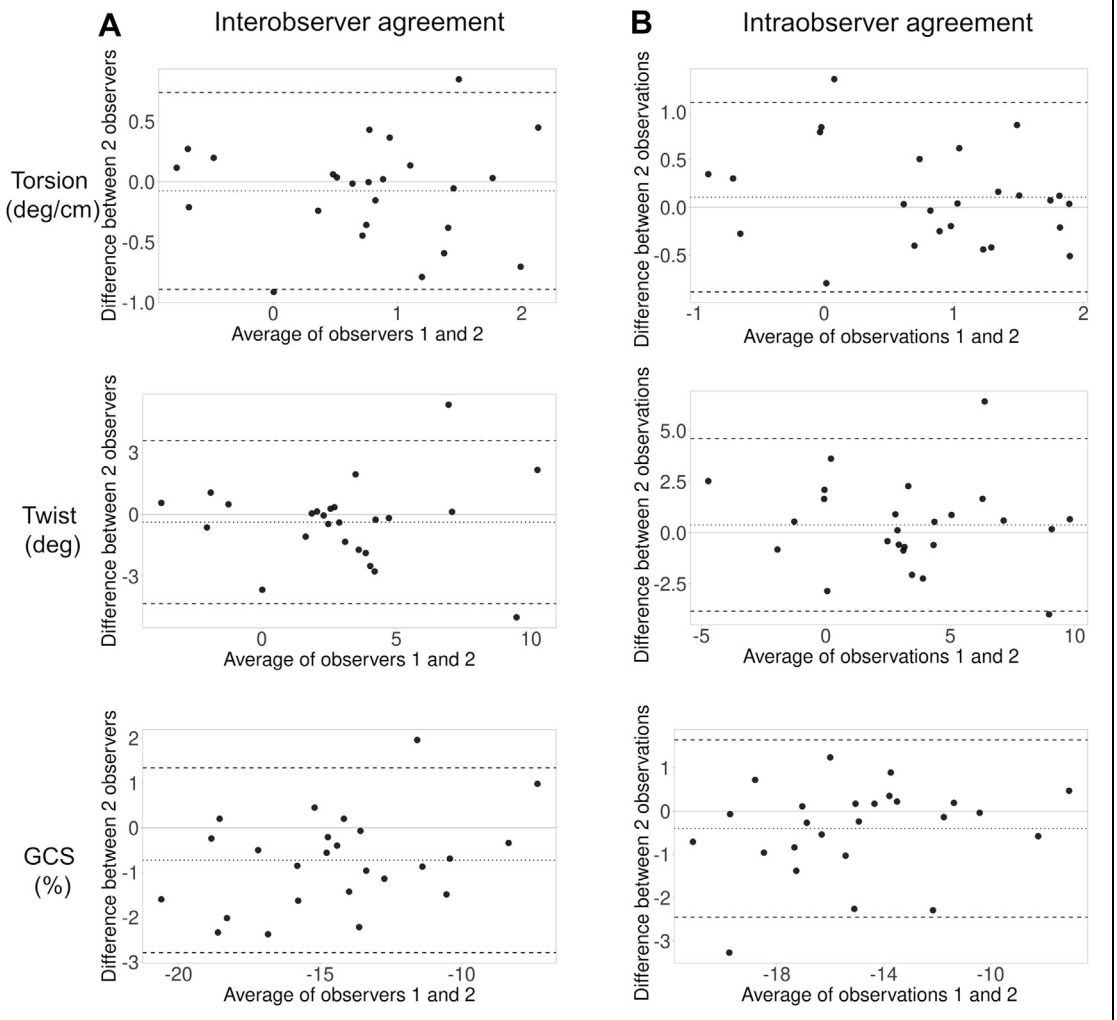
when analyzed for the whole cohort. On stratified survival analysis, LVs with abnormal torsion and RVs, regardless of torsional pattern, had worse outcomes compared to LVs with normal torsion. This suggests that while ventricular dominance is a valuable predictor of outcomes, torsion may have additive value in risk stratifying Fontan patients with LV morphology.

Torsion abnormalities correlated with conventional ventricular measures such as ventricular volumes and EF. Similar associations have been shown in LVs in biventricular hearts with dilated cardiomyopathy; in particular, forfeiture of apical counterclockwise rotation.[29] This is thought to result from the loss of oblique myofibril architecture, possibly due to dilation, leading to a closer resemblance to the transverse fibers of the basal portion of the LV. Perturbation from the normal gradual shift from basal clockwise rotation to apical counterclockwise rotation is reflected in lower torsional concordance and torsional gradient parameters estimated in this study. These findings suggest significant disruption of myofiber arrangement in Fontan hearts, even in those with LV morphology. Substantial but incomplete remodeling occurs after Fontan palliation, with increasing risk for ventricular hypertrophy, fibrosis, dilation, and dysfunction over time.[8,17,26] Although, torsion is associated with the adverse outcome, its relationship to the outcome is not independent of ventricular dilation which remains the strongest predictor. Failure of the ventricular pump in the Fontan circulation is likely multifactorial including effects of AVVR, aortopulmonary collateral flow, myocardial scarring, electrical and mechanical dyssynchrony, and disruption of the normal torsional contraction pattern. Faster rate of ventricular dilation is associated with worse outcomes and future studies may focus on understanding the mechanisms that lead to progressive dilation and eventual dysfunction and poor clinical outcomes.[30]

Although there was no correlation between torsion and age in our cohort, this must be viewed in light of the relatively narrow age range in this study. Nonetheless, a prior study in young Fontan patients (median age 4.0 years) with normal systolic function, found an unexpected preserved overall torsion, mainly because of maintained or increased apical rotation.[20] Perhaps there is age-related adverse remodeling paralleling the increased ventricular dilation, systolic dysfunction, and loss of apical rotational mechanics seen in our study and other studies looking at older SV populations.

This study has several limitations. While there is an increasing trend toward using CMR for routine follow-up of patients with a Fontan circulation, imaging in this study was at the provider's discretion and not standardized. Referral bias for CMR testing may lead to older, sicker, and more symptomatic patients being overrepresented in the cohort while patients with pacemakers and defibrillators were excluded. As the primary goal of this study was to analyze rotational mechanics, only circumferential variables were quantified. As a result, the study does not provide a more global assessment of contraction patterns in SVs, particularly in the RV group. Underlying factors for ventricular dilation and dysfunction such as collateral flow and presence of myocardial scar were also not analyzed. The study aimed to

FIGURE 4 **Bland Altman Plots Depicting Results of Interobserver and Intraobserver Reliability Analysis**



Interobserver **(A)** and intraobserver **(B)** reliability was assessed for torsion, twist, and global circumferential strain using a random set of 25 patients. LV = left ventricle; NS = non-significant; RV = right ventricle.

include patients with exclusive or nearly exclusive RV or LV morphology and hence, excluded patients with a nondominant ventricle comprising >20% of the total ventricular volume. While this was necessary to perform valid comparisons between LV and RV cohorts, Fontan patients with 2 significantly sized ventricles, such as patients with unbalanced atrioventricular canal defects, are underrepresented. It should also be acknowledged that patients with single RV and LV were compared exclusively to control LVs as the presence of a ventricular septum in control RVs make it even more challenging to compare to a single RV. Relatively low rate of composite outcomes in LV and RV subgroups precluded multivariate modeling and assessment of incremental value of torsion over conventional measures. While FT provides insights into ventricular contraction, it does not reliably assess all drivers of the contraction including presystolic state of the myofibers.

CONCLUSIONS

This study presents a comprehensive analysis of rotational ventricular mechanics in the largest cohort of Fontan patients and controls. It shows that systemic ventricles in the Fontan circulation

exhibit abnormal torsional mechanics, which are more pronounced in hearts with RV morphology. Patients with RV morphology, regardless of torsional pattern, and LV morphology with negative torsion were associated with adverse clinical outcomes. RV morphology and ventricular dilation are independently associated with death or need for heart transplantation. Patients with LV morphology and positive torsion exhibit the highest transplant-free survival and torsion may offer incremental prognostic value in the LV cohort.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: SVs in the Fontan circulation exhibit abnormal torsional mechanics and these abnormalities are associated with death or need for heart transplantation. RV morphology and ventricular dilation are independently associated with death or need for heart transplantation.

TRANSLATIONAL OUTLOOK: Underlying mechanisms for ventricular failure in the Fontan circulation remain to be fully elucidated. Large-scale longitudinal data would likely be needed to understand these mechanisms and discover the potential role of therapeutic interventions.

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