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Myocardial fibrosis and its relation to adverse outcome in transposition of the great arteries with a systemic right ventricle

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ABSTRACT

Background: Myocardial dysfunction has been implicated in gradual heart failure in transposition of the great arteries (TGA) with a systemic right ventricle (RV). Fibrosis can be assessed using the extracellular volume fraction (ECV). Our aim was to measure ECV and determine its associations with clinical findings and outcomes.
Methods: We prospectively measured ECV in systemic RV subjects (either D-loop after atrial switch or L-loop) and healthy controls. T_1 measurements for a single mid-ventricular short-axis plane before and 3, 7, and 15 min after gadolinium contrast were used to quantify systemic ventricular ECV. Individuals with elevated ECV were compared to those without.
Results: In 53 TGA subjects (age 34.6 ± 10.3 years, 41% female) the mean ECV for the systemic RV (28.7 ± 4.4%) was significantly higher than the left ventricle in 22 controls (26.1 ± 2.8%, $P = 0.0104$). Those with an elevated ECV ($n = 15$, 28.3%) had a higher b-type natriuretic peptide (BNP) ($P < 0.011$) and a longer 6-min walk distance ($P = 0.021$), but did not differ by age, arrhythmia history, ventricular volume, function, or circulating collagen byproducts. At follow-up (median 4.4 years), those experiencing major cardiovascular endpoints (new arrhythmia, arrhythmia device, heart failure hospitalization, listing for transplantation, mechanical support, or cardiovascular death, $n = 14$) had a higher ECV. ECV, age, and BNP were independent predictors of cardiac events in Cox-proportional hazard models.
Conclusions: Myocardial fibrosis is common in the systemic RV and associated with a higher BNP. Elevated CMR-derived ECV was associated with adverse clinical outcome. The findings suggest a role of diffuse myocardial fibrosis in clinical deterioration of the systemic RV.

1. Introduction

There is growing recognition that myocardial preservation, not just anatomic correction, is paramount to long-term survival in adults with congenital heart disease (ACHD). Specifically, patients with transposition of the great arteries (TGA) who have a systemic right ventricle (RV), either in the setting of D-loop TGA after an atrial switch palliation, or L-loop TGA (congenitally corrected TGA), are both expected to develop myocardial dysfunction over time with important clinical consequences.

Myocardial fibrosis, as demonstrated by cardiovascular magnetic resonance (CMR), has been described in the systemic RV and is associated with age, ventricular size and function, and prior atrial arrhythmia [1,2]. Newer methods measuring diffuse fibrosis using T_1 measurements to calculate the extracellular volume fraction (ECV) have also shown changes in a number of different pathologic states as well as in congenital heart disease [3–9], detecting fibrosis beyond that appreciable by LGE alone [3].

To study the relationship between diffuse fibrosis and heart failure manifestations and outcomes, we sought to measure ECV prospectively in a larger cohort of systemic RV patients. Despite recognized differences between D and L-loop transposition, because both share the problems of a vulnerable systemic RV we included both groups in our study. We hypothesized that ECV would be higher in TGA compared to healthy individuals, correlate with circulating collagen peptide fragments, exercise capacity, and arrhythmia history, and be associated with adverse clinical outcomes.

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2. Methods

2.1. Patient selection

Outpatients age ≥ 18 years with TGA and a systemic RV (L- or D-loop TGA) were prospectively recruited. Patients with an implanted pacemaker or cardioverter-defibrillator (ICD), creatinine >1.5 mg/dl, or severe claustrophobia were excluded. Healthy control subjects (non-smokers without known heart disease, diabetes, or hypertension) were also studied, and their data have been reported previously [10]. The study protocol was approved by the institutional review board at both participating institutions, and all subjects gave written, informed consent.

2.2. Study protocol

An intravenous cannula was placed in each subject and blood samples were drawn for measurement of blood count, blood chemistries and b-type natriuretic peptide (BNP). Additional blood samples were spun, and serum placed in frozen storage for additional biomarker assays. Surgical history and medications were obtained from medical records. CMR was then performed, followed by a six-minute walk test (6MWT) in which distance, heart rate, and oxygen saturation were recorded immediately upon completion.

2.3. CMR protocol

CMR was performed on a 1.5 Tesla scanner (Philips 1.5 Achieva or Integra). Standard cine acquisitions included a short-axis stack (30 phases, 7 mm thickness with 3 mm gap) for RV and left ventricle (LV) volume and function. Thereafter, a single mid-ventricle short-axis plane Look-Locker sequence was prescribed 3 cm apically from the atrioventricular valves viewed in 4 chamber view (8 mm thickness, 16–21 phases, TR/TE 8/2.5 ms, temporal resolution 40 ms). The Look-Locker method allowed for analysis of each phase to provide better scrutiny of avoiding trabecular pooling and makes no assumptions about interphase registration. Following gadolinium contrast administration (0.15 mmol/kg), the sequence was repeated at 3, 7, and 15 min post-injection. To allow for full relaxation between inversion pulses, the expected heart rate was set to 20–30 bpm on the scanner, and the repetition time for inversion was set to ~4 s for pre-contrast T_1 measurements and ~2 s post-contrast accounting for shorter T_1 times. The inversion time increments in the Look-Locker read-out were approximately 120 ms for pre-contrast and 90 ms for post-contrast sequences, changed by adjustment of the segmentation factor. Late gadolinium enhancement imaging followed the final Look-Locker acquisition.

2.4. CMR analysis

CMR studies were analyzed using QMass software (Medis, Leiden, The Netherlands) for all patients at a single institution. End-diastolic volume (EDV), end-systolic volume (ESV), and mass, each indexed to body surface area, and EF were measured for both the RV and LV by contouring short-axis sequences. Trabeculations were included as part of the myocardium. Wall stress was calculated as systolic blood pressure x end-systolic volume/mass.

For ECV quantification, each Look-Locker phase was used to trace the systemic ventricle along endo- and epicardial borders, divided into 6 equal segments (2 for septum, 4 for free wall). Care was taken to exclude non-compacted myocardium or trabeculations to avoid blood pooling, as well as epicardial fat. A region of interest was also placed in the RV lumen avoiding trabeculations or papillary muscles. All contours were manually traced and reviewed by two physicians. Signal intensity vs. time curves for myocardium and blood were plotted to quantify T_1 through exponential fitting, and its reciprocal, R_1. This was done for each acquisition pre- and post-contrast. The slope of the linear relationship between R_1 for myocardium vs. blood before and after gadolinium administration (4 data points) defined the partition coefficient for gadolinium (lambda) [11]. Values for all six myocardial segments were averaged in each subject. The partition coefficient was multiplied by (1-hematocrit/100) to obtain the extracellular volume of distribution of gadolinium, also referred to as ECV.

2.5. Collagen peptide fragments and related enzymes

Stored serum samples were thawed for batched analysis of collagen byproducts and other protein assays relevant to collagen turnover and myocardial fibrogenesis including pro-collagen 1 N-terminal peptide (PC1NP) and pro-collagen 3 N-terminal peptide (PC3NP) using commercially available assays (Orion Diagnostica Oy, Espoo, Finland). Additional assays included aldosterone (Alpco, Salem, NH), matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1, R and D Systems, Minneapolis, MN). Each assay was run with appropriate quality controls by personnel blinded to any other imaging or clinical data.

2.6. Follow-up

Clinical follow-up was obtained through clinic visits or review of available electronic medical records by an experienced ACHD provider blinded to all other variables. Patients who did not have recent follow-up were contacted by phone. Major clinical events were those related to either arrhythmia or congestive heart failure (CHF). Arrhythmia events included new atrial arrhythmia (found clinically or during 48-hour ambulatory ECG monitoring ordered for symptom evaluation, or requiring intervention such as cardioversion or ablation) in those without prior arrhythmia, ventricular arrhythmia, or new indications for pacemaker or ICD implantation given their potential relationship with fibrosis. CHF events included heart failure hospitalization (non-elective admission for intravenous diuretics), ventricular assist device (VAD) placement, listing for heart transplantation, or cardiovascular death. Those with events were compared to those without.

2.7. Statistical analysis

Study data were collected and managed using the REDCap electronic data capture tools [12]. Elevated ECV was defined as >1.96 SD above the mean for healthy controls according to gender to account for gender differences in healthy controls [10,13,14]. Appropriate comparisons were made using a two-tailed Student's *t*-test, Mann-Whitney *U* test, chi-squared or Fisher's exact test as appropriate, with $P < 0.05$ considered statistically significant. Univariate correlation of ECV with other parameters was done using Pearson's correlation coefficient. Natural log transformation of BNP was used to account for its non-normal distribution.

Kaplan-Meier survival curves were used to estimate event-free survival distributions based on a normal vs. elevated ECV, and distributions were compared using the Log-Rank test. Time zero was defined as the date of CMR study. For patients with multiple outcome events, the time to first event was used. Cox proportional hazards analyses were also conducted to test for interaction between ECV and other variables that differed between those with and without events. Because of the limited sample size, only bivariate analyses were used. Beta coefficients with 95% confidence intervals and *P* values were calculated for each significant variable. For all statistical tests, two-tailed *P* values <0.05 were considered statistically significant. Analyses were done using SPSS (version 22.0, IBM, Armonk, NY). Results are presented as mean ± SD, median [interquartile range] for non-normal variables, or N (%) for categorical variables.

3. Results

A total of 53 TGA subjects were studied (age 34.6 ± 10.3 years, 41% female, 10 L-loop TGA). Of all TGA subjects, 14 (26%) had moderate or severe tricuspid valve regurgitation, 18 (34%) had a history of prior atrial arrhythmia, one had diabetes and one had been treated for hypertension. There were 16 former smokers and 6 current smokers. None had known coronary atherosclerosis or prior myocardial infarction. Eleven were taking a beta-blocker, 15 an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and 14 a loop diuretic. In addition, 22 healthy controls (40.2 ± 11.9 years, 41% female) were enrolled.

3.1. TGA vs. control subjects

Comparisons between TGA and controls are shown (Table 1). TGA subjects were younger (34.6 ± 10.3 vs. 40.2 ± 11.3 years, $P = 0.042$) but did not differ by gender, heart rate, blood pressure, or oxygen saturation. Systemic ventricular EF was lower in TGA than controls (51.1 ± 10.8% vs. 68.6 ± 6.4%, $P < 0.001$).

ECV was 28.7 ± 4.4% in the TGA subjects, and 26.1 ± 2.8% in controls ($P = 0.0104$). T_1 value 15 min after contrast was shorter in TGA (397 ± 110 vs. 508 ± 45 ms, $P < 0.001$). ECV was higher in women than men in controls (28.1 ± 0.3 vs. 24.0 ± 1.62%, $P < 0.001$) but not in TGA (28.9 ± 2.8 vs. 28.4 ± 5.2% respectively). ECV values by segment ranged from 29.4 ± 4.8% in the anterior septum to 26.6 ± 4.5% in the anterolateral free wall. There was no statistical difference between segments, including specifically no difference between the septum and free wall.

BNP was higher in TGA than controls ($P < 0.001$), and correlated with ECV ($R = 0.44$ for ln BNP, $P < 0.001$). PC3NP was higher in TGA (4.4 ± 2.1 vs. 2.8 ± 0.6 μg/l, $P = 0.0015$) but PC1NP was not statistically different (53.6 ± 23.7 vs. 44.7 ± 16.6 μg/l, $P = 0.11$). MMP-2 was higher (243 ± 54 vs. 182 ± 28 ng/ml, $P < 0.001$) as was TIMP-1 (146 ± 31 vs. 130 ± 27 ng/ml, $P = 0.033$). The MMP/TIMP ratio was also higher than controls (1.71 ± 0.35 in TGA vs. 1.48 ± 0.42, $P = 0.021$). Aldosterone did not differ.

3.2. Normal vs. elevated ECV

Among the TGA subjects, 15 of 53 (28.3%, 95% CI 18%–42%) had an elevated ECV value based on gender-specific cutoffs for the healthy controls (>28.9% for males and >31.4% for females). By univariate analysis

for TGA subjects, ECV was associated with lnBNP ($r = 0.423$ $P < 0.001$) and weakly associated with systolic blood pressure ($r = -0.302$, $P = 0.025$) but not associated with age, RV volumes, RVEF, RV mass index, mass/volume ratio, 6MWT distance, or collagen byproducts.

Comparisons of those with an elevated ECV to those with normal ECV are shown (Table 2). Those with elevated ECV did not differ by height, weight, smoking history, or resting heart rate. Those with an elevated ECV tended to be older though not significantly (38.1 ± 5.4 vs. 33.3 ± 11.5 years, $P = 0.13$). There was no difference in RV volume or EF. BNP was higher in the elevated ECV group, which also showed a longer 6MWT distance (546 ± 89 vs. 457 ± 118 m, $P = 0.021$). Frequency of medication use, smoking, and arrhythmia history were similar in both groups. Procollagen fragments, TIMP-1, MMP-2, and aldosterone were not different. Because others have previously reported difficulty measuring ECV in the systemic RV free wall [5], we repeated our analysis using septal ECV only, and found no change in the statistical significance of any comparison.

LGE anywhere in the heart was evident in 8 patients (15%, 2 with abnormal ECV and 6 with normal ECV, two with L-loop TGA, one of which had prior valve replacement), all in small quantities. No large transmural enhancement was seen. The presence of LGE did not differ in those with elevated ECV vs. normal ECV, nor correlate with ECV.

3.3. Follow-up events

Median follow up time was 4.4 years, range 1.0–8.1 years. All but one subject was accounted for at least one year following the baseline visit. Fourteen patients had a major event, 6 (16%) in those with a normal ECV and 8 (53%) in those with an elevated ECV ($P = 0.006$). Events in those with a normal ECV included 5 subjects with new arrhythmia event (three cardioversions, one with isolated symptomatic supraventricular tachycardia found during a 48-hour ambulatory electrocardiogram, and one required a pacemaker). One subject developed worsening heart failure leading to VAD placement followed by heart transplant. There were two non-cardiovascular deaths in this group which were not included as adverse events.

Among subjects with an elevated ECV, two experienced a new arrhythmia event alone (ablation for new atrial flutter in one and NSVT found on a Holter monitor leading to ICD implant in another). Six had a CHF event, all but two of whom also had a new atrial arrhythmia. These six included two subjects with multiple hospital admissions leading eventually to death from heart failure, two who have been referred and listed for transplant, one who has received a VAD and now awaits transplant, and one who was hospitalized for CHF necessitating diuresis. CHF events alone were more prevalent in the elevated ECV group (40% vs. 5%, $P = 0.002$), while arrhythmia events alone were not statistically significant (33% vs. 14%, $P = 0.10$).

Comparisons among those with vs. without events are shown (Table 3). Those with events differed by age, ECV, systolic blood pressure, RVESVi, RVEF, oxygen saturation after 6MWT, serum sodium, and ln BNP. Lambda and post-contrast T1 were also different. Other variables did not differ. Outcome data did not differ when device implant was omitted as an outcome variable. By Kaplan-Meier analysis (Fig. 1) using time to first event with abnormal ECV as the comparison factor, ECV was discriminatory (mean event-free survival 4.2 ± 0.7 years vs. 6.5 ± 0.5 years, median survival 3.7 vs. 5.9 years, log-rank statistic $P = 0.002$).

By Cox-Regression analysis (forward stepwise conditional) using only two comparators in each model, only ECV remained a significant predictor in comparisons with 6MWT post-walk saturation, systolic blood pressure, RVESVi and RVEF. In bivariate models with ECV and either age or lnBNP, both variables remained significant. Of these, ECV was the only variable that remained independently predictive in a trivariate model together with age and lnBNP (Beta coefficient ECV 1.4 (95%CI 1.16–1.68, $P = 0.001$)).

3.4. L-loop vs. D-loop TGA

ECV was not statistically different in L-loop TGA ($N = 10$) vs. D-loop TGA ($N = 43$). Of the L-loop subjects, five had prior surgeries; three for tricuspid valve replacement, one for VSD closure, and one with severe PS requiring an aortopulmonary shunt followed by VSD closure and an LV-PA conduit. The later subject had an elevated ECV, others did not. All D-TGA subjects had undergone an atrial switch palliation. In addition, one had also undergone a surgical septostomy, and one had undergone tricuspid valve replacement later in life, both of whom had a normal ECV.

To explore the impact of our decision to include L-loop transposition in the cohort, we repeated the analysis using only the 43 D-loop patients. Our findings were essentially unchanged. Significant variables in D-loop included higher ECV, longer 6MWT distance, larger RV volumes, lower RVEF, higher BNP and other biomarkers than controls. Significant variables in those with an elevated ECV included a higher 6MWT distance, higher BNP, and lower LVEF as well as a higher rate of events in follow up. D-loop subjects who experienced events ($N = 11$) still had a higher ECV, higher NYHA class, lower 6MWT oxygen saturation, lower RVEF and RVESVi, and lower sodium.

Table 1
Transposition patients compared to healthy controls.

	TGA ($N = 53$)	Controls ($N = 22$)	P
Age (years)	34.6 ± 10.3	40.2 ± 11.3	0.0422
Female	22 (42%)	9 (41%)	0.94
Height (in)	67.3 ± 4.1	66.8 ± 4.3	0.65
Weight (kg)	85.8 ± 17.0	72.5 ± 14.3	0.002
BSA (m^2)	1.97 ± 0.21	1.83 ± 0.22	0.011
Hemoglobin (g/dl)	14.5 ± 1.16	14.1 ± 1.2	0.21
Hematocrit (%)	42.2 ± 3.1	41.4 ± 3.4	0.13
Sodium (mmol/l)	139 ± 2	139 ± 2	0.30
BUN (mg/dl)	14.2 ± 4.0	12.8 ± 4.8	0.19
Creatinine (mg/dl)	0.82 ± 0.16	0.90 ± 0.11	0.068
6-minute walk distance (m)	480 ± 117	639 ± 79	<0.001
CMR findings			
Systemic EDVi (ml/m^2)	102 ± 27	80 ± 25	<0.001
Systemic ESVi (ml/m^2)	52 ± 25	25 ± 6	<0.001
Pulmonic EDVi (ml/m^2)	81 ± 22	88 ± 14	0.16
Pulmonic ESVi (ml/m^2)	34 ± 16	34 ± 8	0.99
RV ejection fraction (%)	52% ± 11%	69% ± 6%	<0.001
LV ejection fraction (%)	59% ± 9%	62 ± 56	<0.001
15 min postcontrast T1 (ms)	397 ± 110	508 ± 45	<0.001
Lambda	0.495 ± 0.070	0.445 ± 0.041	0.002
ECV (%)	28.7% ± 4.5%	26.1% ± 2.8%	0.010
Biomarker analysis			
b-type natriuretic peptide (pg/ml)	94 [162]	19.5 [18]	0.012
ln BNP	4.69 ± 1.17	2.92 ± 0.61	<0.001
Aldosterone (pg/ml)	179 ± 95	181 ± 67	0.94
PC1NP (μg/l)	53.6 ± 23.7	44.7 ± 16.6	0.11
PC3NP (μg/l)	4.4 ± 2.1	2.8 ± 0.6	0.001
TIMP-1(ng/ml)	146 ± 31	130 ± 27	0.033
MMP-2 (ng/ml)	244 ± 53	182 ± 28	<0.001
MMP2/TIMP1 ratio	1.71 ± 0.35	1.48 ± 0.42	0.021

Values are given as N (%), mean ± SD, or median [interquartile range]. LV = left ventricular, RV = right ventricular, ECV = extracellular volume fraction. Lambda is the partition coefficient of gadolinium. PC1NP = procollagen 1 N terminal peptide, PC3NP = procollagen 3 N terminal peptide, MMP-2 = matrix metalloproteinase 2, TIMP-1 = tissue inhibitor of matrix metalloproteinase-1.

4. Discussion

Elevated ECV, a measure of diffuse myocardial fibrosis, is associated with an increased risk of CHF and arrhythmia in TGA patients with a systemic RV. Despite a lack of association with other indicators of cardiovascular function, ECV appears to discriminate event-free survival in this cohort. Events in those with elevated ECV tended to occur early, and be more related to CHF, whereas events in the normal ECV group

Table 2
Comparisons between those with or without elevated ECV.

	Normal ECV ($N = 38$)	Elevated ECV ($N = 15$)	*P*
Age (years)	33.2 ± 11.5	38.1 ± 5.4	0.13
Female gender	19 (50%)	3 (20%)	0.046
Current smoker	2 (5%)	3 (20%)	0.09
Smoker ever	11 (29%)	4 (27%)	0.94
Prior atrial arrhythmia	11 (29%)	7 (47%)	0.22
Prior heart surgery	31 (82%)	15 (100%)	0.074
Beta blocker	8 (21%)	3 (20%)	0.93
ACE/ARB	10 (26%)	5 (33%)	0.32
Spironolactone	1 (3%)	1 (7%)	0.13
Diuretic	10 (26%)	3 (20%)	0.98
QRS duration (ms)	103 ± 30	93 ± 48	0.73
L-loop TGA	9 (24%)	1 (7%)	0.15
Height (in)	67.4 ± 4.6	68.0 ± 2.2	0.49
Weight (kg)	85.8 ± 17.9	85.1 ± 18.0	0.99
BSA (m^2)	2.0 ± 0.2	2.0 ± 0.2	0.76
Heart rate (bpm)	70.2 ± 14.3	73.9 ± 15.1	0.41
Systolic blood pressure (mmHg)	123 ± 12	116.3 ± 7.9	0.022
Diastolic blood pressure (mmHg)	69 ± 10	66.5 ± 10.7	0.27
Oxygen saturation (%)	96.2 ± 2.3	96.6 ± 2.1	0.42
Hemoglobin (g/dl)	14.6 ± 1.1	14.2 ± 1.2	0.27
Hematocrit (%)	42.6 ± 3.2	40.9 ± 2.8	0.14
Sodium (mmol/l)	139 ± 2.3	137 ± 1.8	0.026
BUN (mg/dl)	13.8 ± 4.3	15.1 ± 3.0	0.29
Creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.1	0.77
6-minute walk distance (m)	457 ± 117	546 ± 89	0.021
NYHA class	1.7 ± 0.7	1.4 ± 0.7	0.93
CMR findings			
RVEDVi (ml/m^2)	101 ± 27	106 ± 30	0.58
RVESVi (ml/m^2)	51 ± 22	59 ± 90	0.34
LVEDVi (ml/m^2)	78 ± 21	91 ± 26	0.12
RV mass index (g/m^2)	89 ± 21	90 ± 14	0.69
Mass/volume ratio	0.91 ± 0.26	0.91 ± 0.17	0.95
RVSV (ml/m^2)	49.2 ± 11.6	45.5 ± 9.8	0.29
LVSV (ml/m^2)	47.9 ± 9.1	46.5 ± 11.6	0.64
RV ejection fraction (%)	52 ± 10	53 ± 15	0.38
LV ejection fraction (%)	62 ± 8	53 ± 9	0.006
Tricuspid Regurg (mod-sev)	7 (18%)	7 (47%)	0.036
Pre contrast T1 (ms)	949 ± 197	1001 ± 179	0.37
15 min postcontrast T1 (ms)	410 ± 112	365 ± 102	0.19
lambda	0.463 ± 0.045	0.575 ± 0.058	<0.001
ECV (%)	26.6 ± 2.8	33.9 ± 3.2	<0.001
Biomarker analysis			
b-type natriuretic peptide (pg/ml)	151.3 [173.7]	456.5 [650.4]	0.009
ln BNP	4.5 ± 1.1	5.3 ± 1.3	0.024
Aldosterone (pg/ml)	178 ± 94	181 ± 99	0.94
PC1NP (μg/l)	54.8 ± 21.6	50.9 ± 29.1	0.60
PC3NP (μg/l)	4.5 ± 1.1	4.1 ± 3.3	0.59
TIMP-1(ng/ml)	143 ± 31	152 ± 30	0.38
MMP-2 (ng/ml)	238 ± 51	258 ± 59	0.24
MMP2/TIMP1 ratio	1.7 ± 0.4	1.7 ± 0.3	0.94

Values are given as *N* (%), mean ± SD, or median [interquartile range]. SBP = systolic blood pressure. DBP = diastolic blood pressure. LV = left ventricular, RV = right ventricular, ECV = extracellular volume fraction. SV = stroke volume. Lambda is the partition coefficient of gadolinium. PC1NP = procollagen 1 N terminal peptide, PC3NP = procollagen 3 N terminal peptide, MMP-2 = matrix metalloproteinase 2, TIMP-1 = tissue inhibitor of matrix metalloproteinase-1.

occurred later and were most often atrial arrhythmias. ECV was associated with serum BNP, another important predictor of health outcomes in ACHD.

The relationship of ECV to cardiovascular outcome is important since the mechanistic links between myocardial dysfunction and clinical heart failure in TGA have been elusive in prior research. Proposed predictors of outcome have included severe TR [15,16], atrial arrhythmia [17], and BNP [18], though not all studies concur. The largest long-term atrial switch follow-up study (60% of 468 patients survived after 30 years) found no outcome differences related to age, comorbid conditions, or arrhythmia [19]. There is lack of congruity between functional decline and change in EF or BNP [20]. In fact, self-assessment has been more predictive of clinical deterioration than objective parameters [21].

Table 3
Comparison of baseline variables between subject with or without a major outcome event.

Variable	No Event	Event	*P*
	$N = 38$	$N = 14$	
Age (years)	32.7 ± 9.8	39.4 ± 10.7	0.038
Female	17 (45%)	4 (29%)	0.29
ECV (%)	27.6 ± 3.5	31.8 ± 5.3	0.002
Elevated ECV	7 (18%)	8 (57%)	0.005
Lambda	0.479 ± 0.056	0.543 ± 0.085	0.003
Native T1 (ms)	952 ± 183	984 ± 235	0.61
Post contrast T1 (ms)	425 ± 110	316 ± 67	0.001
Hematocrit (%)	42.3 ± 3.2	41.6 ± 3.1	0.49
Congenitally-corrected TGA	6 (16%)	3 (21%)	0.63
Prior atrial arrhythmia	11 (29%)	6 (43%)	0.34
Beta blocker use	9 (24%)	2 (14%)	0.46
ACEi/ARB use	9 (24%)	6 (43%)	0.18
Aldosterone inhibitor use	1 (3%)	2 (14%)	0.11
Loop diuretic use	8 (21%)	5 (36%)	0.28
QRS duration (ms)	99 ± 40	108 ± 11	0.57
Baseline heart rate (bpm)	69 ± 14	76 ± 16	0.12
Baseline O_2 saturation (%)	97 ± 2	96 ± 3	0.29
Systolic blood pressure (mmHg)	122 ± 11	115 ± 10	0.051
6MWT post-heart rate (bpm)	105 ± 26	104 ± 22	0.89
6MWT post-O_2 saturation (%)	96 ± 4	91 ± 5	0.007
6MWT distance (m)	484 ± 120	471 ± 111	0.76
Body surface area (m^2)	1.97 ± 0.22	1.96 ± 0.23	0.73
RVEDVi (ml/m^2)	99 ± 25	112 ± 31	0.18
RVESVi (ml/m^2)	47 ± 20	66 ± 32	0.013
RVEF (%)	54 ± 9	43 ± 11	0.002
Moderate-severe TR	9 (24%)	5 (36%)	0.39
RV mass index (g/m^2)	88.1 ± 19.7	91.5 ± 19.6	0.62
LGE present	6 (16%)	1 (7%)	0.43
Sodium (mmol/l)	139 ± 2	137 ± 2	0.002
Creatinine (mg/dl)	0.83 ± 0.16	0.85 ± 0.13	0.53
ln BNP	4.48 ± 1.07	5.23 ± 1.34	0.047

Values are given as *N* (%), mean ± SD, or median [interquartile range]. TGA = transposition of the great arteries. ECV = extracellular volume fraction. Lambda is the partition coefficient of gadolinium. ACEi = angiotensin converting enzyme inhibitor. ARB = angiotensin receptor blocker. 6MWT = six-minute walk test. RVEDVi = RV end-diastolic volume index, RVESVi = RV end-systolic volume index. BNP = b-type natriuretic peptide.

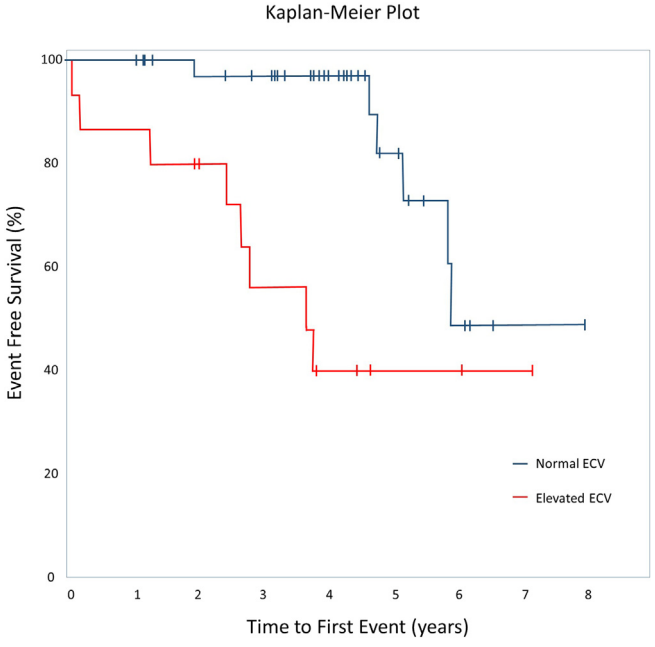

Fig. 1. Kaplan-Meier Plot showing event-free survival curves for patients with a normal ECV vs. elevated ECV. Vertical bars indicate time of last follow up. $P = 0.001$ log-rank statistic.

Hence, although our findings need confirmation with larger populations, they are an important step towards understanding deterioration of myocardial function and clinical heart failure. The data are generally in harmony with others who reported an association between LGE and a composite clinical endpoint (mainly atrial arrhythmia) [22]. Comparisons of the two studies are worth consideration. Their cohort similarly consisted of 55 subjects, though slightly younger (age 29 years), with a slightly lower RVESVi, (39 ml/m^2), higher RVEF (59%), fewer atrial arrhythmias ($N = 12$), and less moderate or severe TR ($N = 2$). They were followed for a longer period (median 7.8 years), finding 19 atrial arrhythmias, 3 ventricular arrhythmias, 1 transplant and 1 cardiovascular death. Both studies show a link between myocardial fibrosis and adverse outcome. As well, both studies show the importance of atrial arrhythmia as a frequent antecedent event to CHF. LGE was found in 31 subjects (56%), compared to ECV elevation in 15 subjects (29%) in our study. This discrepancy could be due to the fact that LGE assessment typically covers the entire myocardium whereas ECV here was from a single short axis plane. Since ECV acquisitions took priority during post-contrast imaging in our study, LGE acquisitions lacked the uniformity and completeness needed for a comparison of LGE vs. ECV as event predictors. Still, the message of both studies is consistent; myocardial fibrosis is an important harbinger of adverse cardiovascular outcome in the systemic RV.

Considering ECV as a discriminator of those with future events, as our study suggests, it follows that pharmacotherapy targeted at myocardial fibrosis would be beneficial. Yet there is much uncertainty regarding the role of CHF pharmacotherapy for the systemic RV. Studies, though small, have repeatedly not shown favorable differences from standard CHF pharmacotherapy [23–26]. Beta-blockers may be protective of appropriate ICD shock in those with devices [27], but there is as yet no demonstrated improvement in outcome from ICD implants [27–30], despite being used in those with severely reduced systolic function who go on to eventual transplantation [31]. The use of ECV as an objective means to both detect and quantify fibrosis may be an important surrogate in studying this process further.

We found diffuse fibrosis in 28% of systemic RV patients and abnormal patterns of collagen turnover, consistent with other studies [5,23,32]. Yet this percentage of affected individuals is lower than that suggested by LGE studies. Some, but not all, previous studies in comparably-sized cohorts have shown LGE in 40–60% of systemic RV patients [1,2,22,33]. Diffuse fibrosis is typically more abundant than that suggested by LGE [3,32]. LGE in TGA has been found to be associated with age, QRS duration, EF, prior arrhythmia and/or syncope [1], reduced exercise capacity [2], and ventricular dyssychrony [33]. However such correlations with ECV were not found.

Several possibilities for the lower fibrosis prevalence could be considered. Foremost, we studied a single representative myocardial plane, not the entire myocardium. Most LGE studies evaluate the entire heart, giving additional sensitivity, which would have been impractical with our methods; the Look-Locker sequences yield more phases but are time consuming to analyze. Yet LGE findings vary considerably between publications; some show LGE in only 0–5% of systemic RVs despite poor systolic function [5,34,35], in deference to 40–60% in others. [1,2,33]. The range could reflect either methodologic or cohort differences between publications. Also, since histologically fibrosis has been shown to be diffuse in the systemic RV [32], our ECV findings may not have differed if additional planes were included. Cohorts may differ in severity. For example, in our previous study the 12 TGA patients referred for CMR had a lower RVEF ($46 \pm 11\%$ compared to $54 \pm 11\%$ in the present study, $P = 0.036$) despite a comparable age distribution [3]. Yet the present cohort had a significant number of adverse events including death/transplant in 4 years of follow up, so it is hard to explain our lower prevalence based on inclusion of a healthier cohort alone.

Our findings harmonize well with the first investigation of ECV in TGA [5]. Using different methods in 14 TGA adults, these authors reported that ECV of the septum was higher than controls and correlated with BNP but not with RVEF or RV volumes, which our data confirm. Also similar, none of the subjects had demonstrable LGE. In light of their findings, we reanalyzed our data using only ECV of the septum, and our results were unchanged.

Considering the bulk of evidence thus far reported, fibrosis consistently appears to be a plausible indicator of a failing systemic RV, despite the lack of association between ECV and ventricular size or function. The later may simply indicate that fibrosis in this context evolves independently of ventricular remodeling. Furthermore, measuring the RV can be a challenge, even with CMR, which may explain why systemic RV EF has been insensitive as a marker of clinical deterioration in this and other studies. Global longitudinal strain (GLS) [36,37] may be more sensitive to differences in those with fibrosis, but we did not measure this in our cohort. Although prior cardiopulmonary bypass at the time of surgery has been theorized as a potential cause of myocardial damage, prior surgeries, in either our D- or L-loop subjects, did not appear to have a relationship with detectable fibrosis.

4.1. Limitations

It is difficult to define "normal" for a systemic RV. By necessity we used healthy controls with a systemic LV to define cut points for ECV elevation, but acknowledge the inherent limitations of this application. Our necessary exclusion of pacemakers may be relevant, as pacing is associated with poorer long-term survival [19,38]. There are unique features of L-loop TGA vs. D-loop TGA [39] that we did not explore given the cohort size, though we did not find significant differences in our analysis even when L-loop subjects were excluded. Different methodologies for T_1 quantification exist [40,41], yet our T_1 values were similar to other published data both in patients and healthy controls [8,42,43]. We used identical methodology in tetralogy of Fallot with significant associations [10]. We acknowledge this is a CMR-derived measure of fibrosis. Histologic validation was impractical in our study, though has been done by others [44].

As is common in TGA, our sample size limits statistical power; a larger cohort may be able to unmask differences that we could not demonstrate. T_1 may be altered in acute necrosis or inflammatory states [45], but such states are not likely in these chronic patients. We paradoxically found a higher 6MWT in those with higher ECV, even after excluding outliers. Given the limited dataset, it is difficult to speculate on the significance of this finding; whether it represents a sampling error or whether there could be some functional advantage to a degree of RV fibrosis. We did not perform cardiopulmonary exercise testing, which may have been more sensitive than 6MWT to a relationship between fibrosis and functional capacity [22]. Finally, our use of bivariate regression, mandated by our sample size, is less robust than multivariate models that would be performed in a larger cohort. Therefore our data provide less certainty that ECV is independent.

5. Conclusions

TGA patients with a systemic RV showed CMR evidence of diffuse myocardial fibrosis and altered collagen metabolism. ECV identified patients at high risk for arrhythmia or heart failure. This confirms the role of fibrosis in the gradual development of clinical heart failure, presenting a potential target for therapeutic study.

Disclosures

Authors have no relevant financial relationships to disclose regarding this work. All authors assume responsibility for the data integrity and have reviewed and agree to the manuscript as written.

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