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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