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Longitudinal sequential biventricular assessment in adults with transposition of the great arteries and relationship with adverse outcomes

M. Riahi, A. Claman, M. Kiess, M. Orgad, D. Human, S. Chakrabarti, J. Leipsic, J. Grewal *

Pacific Adult Congenital Heart Disease Clinic, Division of Cardiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

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ABSTRACT

Background: In a cohort of congenitally corrected transposition of the great arteries (cc-TGA) and transposition of the great arteries after atrial switch procedure (d-TGA) the study objectives were: 1) to assess the change of quantitative systemic right ventricle (sRV) parameters over time and; 2) to examine the relationship of quantitative sRV parameters with adverse clinical outcomes.

Methods and results: Single-center cohort study that included 49 (39%) cc-TGA and 76 (61%) d-TGA patients >18 years who had at least one MUGA sRV assessment, 18/39 had more than one respectively. The primary clinical endpoint was all-cause mortality, heart transplantation and/or heart failure hospitalization. At a median clinical follow-up of 7 years following the first MUGA, the primary endpoint occurred more often in cc-TGA versus d-TGA patients (18 (36.7%) vs. 9 (11.8%), $p = 0.03$). Median time between the MUGA assessments was 5.8 (cc-TGA) and 4.9 years (d-TGA). At last MUGA follow-up: 6 (33%) cc-TGA/14 (36%) d-TGA patients showed a significant decline in sRVEF (>5%); 6 (33%) cc-TGA/17 (44%) d-TGA patients had a significant increase in sRVEDVi; and 7 (39%) cc-TGA/19 (49%) PA-TGA patients had a significant increase in sRVESVi. Baseline sRV parameters were not associated with the primary end point or sRV changes over time.

Conclusions: An important proportion of both patient cohorts demonstrated a significant change in sRV parameters over time and these are likely related to multiple factors that vary between individuals given population heterogeneity. The TGA patients have distinct clinical trajectories with increased adverse heart failure outcomes in the cc-TGA population and sRV parameters were not related to adverse heart failure events in either group.

1. Introduction

The morphologic systemic right ventricle (sRV) delivers blood to the systemic circulation in two instances of biventricular physiology in congenital heart disease: congenitally corrected transposition of the great arteries (cc-TGA) and transposition of the great arteries after atrial switch procedure (d-TGA). Previous reports have shown that sRV systolic dysfunction becomes increasingly prevalent with age in both cc-TGA and d-TGA populations [1–4]. A number of factors have been proposed to explain the vulnerability of the sRV [5–7]. Several reports have found that systemic atrioventricular valvular regurgitation (SAVVR) is associated with sRV dysfunction and congestive heart failure [6,8]. However, whether there is indeed a causal relationship remains unclear [9]. Due to its wide availability, low-cost and ease of use, two-dimensional transthoracic echocardiography has been used as the primary imaging modality for serial sRV assessment. However, due to the unique RV geometry and lack of echocardiographic validated quantitative measurements, sRV echo evaluation remains largely qualitative [10,11]. Cardiac magnetic resonance (CMR) and radionuclide ventriculography or multi-gated acquisition (MUGA) can provide accurate quantitative evaluation of the sRV ejection fraction and volumetric measurements [12,13]. Adverse events such as congestive heart failure, arrhythmias and premature cardiac death have also been shown to occur at later stages of adult life in this group of patients, however the relationship sRV systolic function or volumes with clinical events is unclear [14,15].

Given the paucity of quantitative sRV data over time and relationship with clinical outcomes, we performed a single-center prospective cohort study of cc-TGA and d-TGA patients with the following study objectives: 1) to assess the change of quantitative sRV parameters over time and; 2) to examine the relationship of quantitative sRV parameters with adverse clinical outcomes.

2. Methods

2.1. Study population

The study group consisted of consecutive patients ≥18 years of age with either cc-TGA or d-TGA followed at the Pacific Adult Congenital Heart Clinic in Vancouver, B.C. between

* Corresponding author at: St. Paul's Hospital, Rm 448-1081 Burrard St., Vancouver, B.C. V6Z 1Y6, Canada.
E-mail address: jasmine.grewal@vch.ca (J. Grewal).

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January 1995 and December 2014. This clinic is the referral center for adult congenital heart patients in the province of British Columbia. All patients included had at least one MUGA assessment to quantify sRV volumes and ejection fraction. It should be noted that since all of these patients are followed only in the PACH clinic on a yearly or bi-yearly basis, minimal patients were lost to follow-up. Patient charts were reviewed to confirm the diagnosis, record any associated abnormalities, document operative history and medication use. The institutional research ethics board approved the study protocol.

2.2. Study endpoints

The primary clinical endpoint was a composite endpoint of all-cause mortality, heart transplantation and/or hospitalization due to heart failure. All clinical endpoints were assessed for between time of first MUGA evaluation and last clinical contact. The primary imaging endpoint was the occurrence of significant sRV systolic function deterioration as defined by a decrease of sRVEF ≥ 5% on MUGA. The secondary imaging endpoints were an increase of sRV indexed end diastolic volume (sRVEDVi) of >20 cm^3/m^2 and/or increase of sRV indexed end systolic volume (sRVESVi) of >10 cm^3/m^2.

2.3. Echocardiography

Two-dimensional transthoracic echocardiogram studies performed within 6 months of MUGA assessment were reviewed. Right ventricular systolic function was graded as normal, mildly, moderately or severely impaired. Pulmonary stenosis was deemed significant if continuous Doppler interrogation indicated a peak systolic gradient of at least 30 mm Hg. The method to estimate SAVVR severity was as follows: Mild: no sRV enlargement and regurgitant jet <5cm^2; Moderate: sRV enlargement and regurgitant jet 5 to 8 cm^2; Severe: sRV enlargement and regurgitant jet >8 cm^2 and presence of pulmonary vein systolic flow reversal.

2.4. Multi-gated acquisition scan

The patient's red blood cells were labeled with Technetium-99m using an Ultratag RBC kit. The Tc-99m labeled red blood cells were injected into an antecubital vein and the cardiac output was calculated (area under the curve) from a non gated first pass acquisition (94 × 0.5 second frames followed by a 60 second frame) performed in the anterior projection. Thirty minutes later, a multi-gated 16 frame acquisition (MUGA) was performed using a 64 × 64 matrix for a total of 5000 counts in the anterior, modified left anterior oblique (best angle to separate the two ventricles), and shallow left posterior oblique projections. In most of the studies, a small field-of-view, single crystal camera with a multi-purpose, low energy collimator was used. The more recent studies were performed with a large field of view, single crystal camera (Siemens Symbia) with a low energy, high resolution collimator. Time activity curves were obtained from regions of interest placed over the systemic and subpulmonic ventricles. Background-subtracted end-diastolic and end-systolic counts were obtained from manual regions of interest applied to the end-diastolic and end-systolic frames and the ejection fractions of the both ventricles were performed. Using the stroke volume from the first pass acquisition (CO=HRXSV) and the sRVEF calculated from the MUGA, the sRVEDV and sRVEDV were calculated.

2.5. Statistical analysis

Continuous data are presented as mean ± SD, or median with interquartile range (IQR) according to data distribution. Categorical variables are presented as frequencies and percentages. For comparison of continuous variables between independent groups, the Student's unpaired *t*-test was used. For paired groups, the paired Student's *t*-test or Wilcoxon signed-rank test were performed. Frequencies of unpaired data were compared with use of the Chi square test or Fisher's exact test when applicable, and for paired data the McNemar test was used. To determine correlations between two variables, the Pearson correlation test or Spearman correlation test was used. Univariate logistic regression models were built for the imaging and clinical primary binary outcomes. A multivariate logistic regression model was not built due to limited patient numbers and outcomes. A cut off p-value of 0.05 was considered significant. The R version 3.2.2 Statistical software package (The R Foundation for Statistical Computing, 2014) was used for the analysis.

3. Results

Among the 125 patients included in this study, 49 (39%) were cc-TGA and 76 (61%) were d-TGA. The cc-TGA patients were significantly older and consequently had their first MUGA assessment at a later age (Table 1). The cc-TGA population also had higher rates of heart block, sub-pulmonary obstruction, LV-to-PA conduits and more intensive baseline heart failure therapy as compared to the d-TGA population. Baseline echocardiography at study entry showed no significant difference in rates of SAVVR. MUGA assessment showed similar sRV and spLV volumes and function between the two groups.

Eighteen (37%) cc-TGA and thirty-nine (51%) d-TGA patients had at least one repeat MUGA assessment. Median time between the first and last MUGA was 5.8 (range 2.7 to 9.5) years for cc-TGA and 4.9 (range 3.7 to 7.8) years for d-TGA patients. There was no significant difference in baseline clinical characteristics and MUGA findings between TGA patients who had a repeat MUGA versus those who did not. At last MUGA assessment cc-TGA patients showed no significant overall change in sRV ejection fraction, end-diastolic or end-systolic volumes or cardiac output. Similarly, d-TGA patients showed no overall significant change in sRV ejection fraction or cardiac output, however sRV volumes did increase significantly over this time period (Table 2). Six (33%) cc-TGA and fourteen (36%) d-TGA patients showed a significant decline

Table 1
Patient characteristics at study entry.[a]

	cc-TGA (49)	d-TGA	p-Value
Age, years	46.8 ± 17.4	36.1 ± 7.8	0.01
Age at first MUGA study, years	36.9 ± 12.2	25.1 ± 6.3	0.01
Male	31 (63%)	41 (54%)	0.40
Left ventricle to pulmonary conduit	13 (26%)	1 (1.3%)	0.01
Third degree heart block	15 (30%)	8 (10%)	0.01
Atrial fibrillation/flutter	17 (35%)	20 (26%)	0.59
Ventricular tachycardia	5 (10%)	4 (5.3%)	0.31
Pacemaker	20 (41%)	20 (26%)	0.11
Biventricular device	0 (0)	1 (1.3%)	1
Echocardiographic findings			
Moderate SAVVR	8 (16%)	9 (12%)	0.59
Severe SAVVR	8 (16%)	9 (12%)	0.59
Right ventricular dilatation[b]	12 (24%)	26 (34%)	0.26
RVOT peak gradient ≥ 30 mm Hg	15 (31%)	5 (6.5%)	<0.01
Medications			
ACEI/ARB	25 (51%)	20 (26%)	0.01
Beta blocker	17 (34%)	22 (29%)	0.78
Diuretic	11 (22%)	3 (4%)	<0.01
Digoxin	7 (14%)	1 (1.3%)	<0.01
Aspirin	11 (22%)	9 (11%)	0.24
Coumadin	13 (26%)	7 (9%)	0.01
MUGA findings			
sRVEF, %	48 (42–52)	50 (45–53)	0.34
sRVEDVi, ml/m^2	104 (82–140)	99 (81–130)	0.16
sRVESVi, ml/m^2	56 (45–74)	52 (39–66)	0.32
CO, L/min at rest	5.4 (4.4–6.9)	5.9 (4.4–7.1)	0.23
CI, L/min/m^2 at rest	3.0 (2.4–3.7)	3.2 (2.4–3.9)	0.06
spLVEF,%	45 (37–52)	51 (45–54)	0.02

RVOT = right ventricular outflow tract, SAVVR = systemic atrioventricular valvular regurgitation; ACE = angiotensin converting enzymes inhibitors, ARB = angiotensin receptor blocker, sRVEF = systemic right ventricle ejection fraction, spLVEF = subpulmonic left ventricle ejection fraction, sRVEDVi = systemic right ventricle end diastolic volume index, sRVESVi = systemic right ventricle end systolic volume index, CO = cardiac output, CI = cardiac index.

[a] All variables reported as mean ± SD, N(%) or median (range).

[b] Moderate to severe.

Table 2
Change over time of systemic right ventricular parameters.[a]

	Baseline	Last	p-Value
cc-TGA (n = 18; TIME between sequential MUGA assessment = 5.8 [2.7–9.5] years)			
sRVEF,%	49 (45–50)	47 (41–53)	0.29
sRVEDVi, ml/m^2	123 (78–148)	113 (97–127)	0.99
sRVESVi, ml/m^2	58 (44–75)	60 (48–68)	0.47
CO, L	6.1 (4.5–8.9)	6.0(4.9–7.0)	0.59
CI, L/m^2	3.6 (2.4–4.8)	3.1 (2.6–3.7)	0.37
d-TGA (n = 39; TIME between sequential MUGA assessment = 4.9 [3.7–7.8] years)			
sRVEF,%	50 (47–55)	50 (47–54)	0.19
sRVEDVi, ml/m^2	100 (84–124)	113 (101–147)	0.02
sRVESVi, ml/m^2	50 (40–66)	55 (46–85)	0.01
CO, L	5.8 (4.5–7.3)	6.5 (5.2–4.5)	0.19
CI, L/m^2	3.4 (2.5–4.1)	3.5 (3.0–4.3)	0.32

sRVEF = systemic right ventricle ejection fraction, spLVEF = subpulmonic left ventricle ejection fraction, sRVEDVI = systemic right ventricle end diastolic volume indexed, sRVESVI = systemic right ventricle end systolic volume indexed, CO = cardiac output, CI = cardiac index.

[a] All variables reported as median (range).

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