Left Ventricular Function in Children and Adolescents With Arrhythmogenic Right Ventricular Cardiomyopathy

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The aim of this study was to determine if left ventricular (LV) contractility is reduced in children with arrhythmogenic right ventricular cardiomyopathy (ARVC). For this retrospective study, children and adolescents undergoing a workup for ARVC were characterized according to the revised Task Force Criteria (rTFC). LV strain, rotation, and torsion were measured by feature-tracking cardiovascular magnetic resonance imaging (CMR). Of 142 pediatric patients, 41% had no, 23% possible, 20% borderline, and 16% definite ARVC. LV ejection fraction (EF) did not differ between rTFC categories. Patients in higher rTFC categories had lower right ventricular (RV) EF z-scores (Z-), higher Z-RV end-diastolic volumes (EDVs) and larger Z-LVEDVs ($p < 0.001$, $p = 0.002$ and 0.013, respectively). LV global circumferential strain was lower in higher rTFC categories ($p = 0.018$). Z-LVEDV correlated with Z-RVEDV, and Z-LVEF correlated with Z-RVEF ($r = 0.69$ and $r = 0.55$, both $p < 0.001$). Z-LVEF and Z-RVEF correlated with LV global circumferential strain ($r = 0.48$ and $r = 0.46$, both $p < 0.001$). Forty-eight patients (34%) underwent follow-up CMR investigations after a mean of 3.2 ± 1.9 (0.4 to 8.4) years. A decrease of Z-LVEF over time correlated with that of Z-RVEF ($r = 0.35$), and Z-LVEDV increase correlated with Z-RVEDV increase ($r = 0.57$). In conclusion, LV myocardial dysfunction is present in young patients with suspected ARVC. Progressive LV dysfunction assessed by conventional CMR and feature-tracking and enlargement over time parallel adverse remodeling of the RV. **(Am J Cardiol 2016;■:■−■)**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined, progressive condition and a cause of potentially fatal tachyarrhythmia. As suggested by its name, ARVC has traditionally been regarded as a predominantly right ventricular (RV) disease. However, involvement of the left ventricle (LV) is increasingly recognized in adults with ARVC[1,2] in whom LV dysfunction appears to be a risk factor for heart failure and ventricular arrhythmias.[3,4] In contrast, it is unclear whether pediatric patients are affected.[5,6] Signs and symptoms of ARVC are generally less advanced in children compared with adults.[7] We hypothesized that children with ARVC harbor abnormalities of LV systolic function and that the detection of these abnormalities require more sensitive measures of myocardial contractility than ejection fraction (EF). The objective of this study was to assess LV global function and myocardial mechanics in children who underwent a diagnostic workup for ARVC and to assess whether they predict adverse ventricular remodeling in the future.

Methods

This retrospective study was approved by the institutional research ethics board and complies with the Declaration of Helsinki.

The data of consecutive children and adolescents who underwent a workup for ARVC at a single institution from 2005 to 2009 were reviewed for this retrospective study. Using the patients' family history, results of cardiovascular magnetic resonance imaging (CMR), electrocardiogram (ECG), signal-averaged ECG, echocardiogram, Holter monitoring, endomyocardial biopsy, and genetic test results, patients were classified as having "no," "possible," "borderline," or "definite" ARVC according to the revised Task Force Criteria (rTFC).[8] Patients with concomitant congenital heart disease other than a hemodynamically insignificant interatrial communication and those with insufficient axial or short-axis cine imaging were excluded. Patients who lacked information in more than 2 of the rTFC criteria categories were also excluded. Some of the results in this cohort were previously published under a different objective.[9] The family history and genetic information was updated following our previous report on this cohort, leading to recategorization in a small number of patients. Forty-eight patients (34%) of study patients underwent repeat CMR examinations and were reviewed for a change in LV/RV EF and end-diastolic volumes (EDVs).

CMR scans were performed on a 1.5-T CMR scanner (Signa CV/I; General Electric Medical Systems, Milwaukee, Wisconsin or Avanto; Siemens Medical Solutions, Erlangen, Germany). Details regarding the scan protocol can be found elsewhere.[10,11] In summary, the protocol included

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See page 6 for disclosure information.

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Table 1
Right and left ventricular function

Variable	All N=142	No ARVC N=56 (39%)	Possible N=33 (23%)	Borderline N=29 (20%)	Definite N=24 (18%)	P value across all groups (ANOVA)	P value ('no' versus 'definite' ARVC)
Z-RVEDV	0.2±1.6	-0.3±1.3	-0.1±1.8	0.8±1.4	1.0±1.7	**<0.001**	**0.001**
Z-LVEDV	0.3±1.8	0.02 ±1.5	-0.04±2.0	1.0±1.7	0.4±2.1	0.052	0.422
Z-RVEF	-1.5±1.7	-1.1±1.7	-1.4±1.5	-1.3±1.2	-2.7±2.1	**0.002**	**0.003**
Z-LVEF	-0.4±1.5	-0.3±1.5	-0.4±1.5	-0.05±1.24	-0.9±1.8	0.251	0.192
Presence of RV RWMAs (%)	52 (36.6)	9 (16)	10 (30.3)	14 (48.3)	19 (79.2)	**<0.001**	**<0.001**
PR at apex(°)*	10.3 (4.4-21.6)	10.6 (5.5-27.6)	10.2 (4.9-21.1)	9.4 (4.4-21.0)	9.4 (5.1-20.8)	0.392	0.210
PR at base(°)*	-8.5±4.7	-8.8±4.9	-8.4±4.5	-8.9±5.7	-7.4±2.4	0.811	0.349
GCS (%)	-24.7±4.3	-25.3±4.5	-25.5±4.0	-24.8±3.8	-22.1±4.1	**0.01**	**0.004**
- base	-23.5±3.5	-24.0±3.4	-23.7±2.7	-24.4±3.4	-21.0±4.2	**0.006**	**0.01**
- mid	-22.1±3.9	-22.6±4.3	-22.4±2.8	-22.7±3.4	-19.8±4.0	**0.018**	**0.008**
- apex	-28.2±7.2	-29.7±8.2	-28.8±5.6	-27.2±6.9	-24.8±6.0	**0.037**	**0.005**
- IVS	-24.2±3.8	-24.7±3.6	-24.5±2.8	-24.2±3.9	-21.3±4.3	**0.02**	**0.05**
- FW	-26.1±5.0	-26.9±4.9	-27.0±5.0	-25.8±5.0	-23.3±5.3	**0.042**	**0.016**
GCS rate (%/s)	-1.6±0.4	-1.6±0.4	-1.6±0.3	-1.6±0.3	-1.4±0.4	0.058	**0.024**
- base	-1.4±0.3	-1.4±0.3	-1.4±0.3	-1.4±0.3	-1.2±0.3	0.080	**0.019**
- mid	-1.3±0.3	-1.4±0.4	-1.4±0.3	-1.4±0.3	-1.2±0.2	**0.049**	**0.003**
- apex	-2.0±0.8	-2.1±0.8	-2.0±0.8	-1.9±0.6	-1.7±0.8	0.157	**0.045**
- IVS	-0.9±0.7	-1.0±0.9	-1.0±0.6	-1.0±0.7	-0.8±0.7	0.726	0.389
- FW	-1.8±0.5	-1.6±0.4	-1.8±0.4	-1.9±0.4	-1.9±0.5	0.062	0.061
Torsion (°)	8.4±3.0	8.8±3.4	8.2±2.6	8.0±2.8	8.3±3.2	0.829	0.639

The statistically significant p values are in bold.

EDV = end-diastolic volume; EF = ejection fraction; FW = LV free wall; GCS = global circumferential strain; IVS = intraventricular septum; LV = left ventricle; PR = peak rotation; RV = right ventricle; RWMAS = regional wall motion abnormalities; Z = z-score.

* Higher values denote greater counterclockwise rotation. Lower (more negative) values reflect stronger clockwise rotation.

ECG-gated cine imaging in the axial, short axis, and 2-chamber planes using the steady-state free precession (SSFP) technique, with a temporal resolution sufficient to acquire 20 true phases per cardiac cycle. Ventricular volumes and EFs were derived from a cine short-axis stack in the routine clinical fashion, using commercially available software (Mass Analysis; Medis Medical Imaging Systems, Leiden, the Netherlands). EDVs and EFs of both ventricles were converted into Z-scores (Z-) according to published normative data for different ages and genders.[12] The differences between the initial and the last available CMR Z-scores were divided by the follow-up duration to obtain the rates of progression.

Left ventricular (LV) myocardial mechanics were quantified using the aforementioned standard SSFP cine images and feature-tracking software (2D Cardiac Performance Analysis MR; TomTec, Unterschleissheim, Germany). The feature-tracking approach is described in detail elsewhere.[13] In brief, the endocardium/blood border was manually defined at one phase within the cardiac cycle. This contour was then propagated to the remaining cardiac phases using an automated border-tracking algorithm.[13] LV global circumferential strain (GCS) and strain rate were measured at 3 short-axis levels. Rotation was quantified at the basal and apical levels. By convention, clockwise rotation is expressed as negative angles and counterclockwise rotation as positive angles.[14] The base typically rotates clockwise and the apex counterclockwise. Torsion was calculated as follows[15]: Torsion = $(PR_{apex} - PR_{base}) \times (r_{apex} + r_{base})/(2\ L)$ where PR = peak rotation at the basal and apical levels, L = LV length (measured in the 2-chamber view at end diastole) and r = LV radius at the basal and apical levels (measured in short axis at end diastole). Gadolinium was administrated for enhancement imaging to assess for myocardial scars.

Continuous variables are presented as means ± SDs if distributed normally and as medians and ranges otherwise. Normality of distribution was tested using the Shapiro-Wilk test. Categorical data are reported as n (%). Continuous variables were compared across 4 diagnostic categories by analysis of variance and by Kruskal-Wallis tests for normally and nonnormally distributed data, respectively. Categorical variables were compared using the chi-square test. Correlation was assessed by the Pearson and Spearman rank correlation coefficient if distributed normally and not normally, respectively. Patients in the "possible" and "borderline" rTFC categories may or may not have ARVC, potentially blurring the differences between health and disease. Therefore, patients with "no" ARVC according to the rTFC were contrasted to the ones with "definite" ARVC using unpaired Student *t* tests. For all analyses, p values <0.05 were regarded as statistically significant. SPSS version 20.0 (IBM, Armonk, New York) was used for all statistical analyses.

Results

The diagnostic tests of 213 consecutive patients referred for the first time evaluation ARVC, including CMR, were reviewed. Twenty-eight patients were excluded because of