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LETTERS TO THE EDITOR

Spectrum of Biventricular Involvement on CMR Among Carriers of ARVD/C-Associated Mutations

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a rare cardiomyopathy characterized by myocardial fibro-fatty replacement predominantly affecting the RV. However, several studies have demonstrated a high incidence of biventricular or even isolated left ventricular (LV) abnormalities (1,2). To date, the incidence and spectrum of biventricular abnormalities among ARVD/C patients with pathogenic mutations and at-risk mutation carriers is not well defined in the North American population. Therefore, our aim was to evaluate the incidence and extent of biventricular abnormalities on cardiac magnetic resonance (CMR) in subjects with ARVD/C-associated mutations.

We identified 78 patients who had positive genetic test for an ARVD/C-associated mutation and CMR. We included affected, borderline, and unaffected (mutation carriers) subjects as diagnosed by the 2010 Task Force Criteria (TFC) (3). CMR exams were obtained on 1.5-T scanners and included double-inversion recovery fast spin echo images, cine functional images, and late gadolinium enhancement images. Quantitative analysis was performed using QMASS (Medis, Leiden, the Netherlands). Qualitative assessment was performed by consensus of 3 expert readers. Each CMR was scored for the presence of the CMR-specific TFC as well for the presence of fatty infiltration and late gadolinium enhancement of both ventricles. Locations of regional findings were recorded using an anatomical 17-segment LV model and 5-segment RV model (4). Continuous and categorical variables were compared using the independent Student *t* test, Fisher exact test, or Mann-Whitney *U* test, where appropriate. Statistical analyses were performed using SPSS version 20 (IBM, Armonk, New York) and STATA version 12 (Stata Corp., College Station, Texas).

All 78 subjects included carried a pathogenic ARVD/C mutation (83% *PKP2*). Of those 78, 40 had normal CMR exams. Among subjects with an abnormal CMR, the majority (55%) had LV abnormalities, of whom 19 of 21 (90%) had biventricular disease and 2 (9%) had isolated LV abnormalities (**Table 1**). Seventeen individuals had isolated RV involvement. Comparing subjects with LV abnormalities (inclusive of subjects with isolated LV or both LV and RV abnormalities), to those with isolated RV abnormalities, there were no significant differences in demographic, qualitative, or quantitative findings in the RV or LV. Subjects with isolated RV disease were significantly more likely to be plakophilin-2 (*PKP2*) mutation carriers than patients with LV with or without RV abnormalities ($p = 0.012$). This difference was in part driven by the isolated LV group ($n = 2$), of whom none carried a *PKP2* mutation (1 *DSP* mutation carriers and 1 *pln* mutation carrier). Individuals with LV abnormalities were equally as likely as those with isolated RV involvement to meet either CMR TFC or global TFC. Wall motion abnormalities were uncommon and observed in only 7 subjects. Among the 21 subjects with LV abnormalities, LV size and function were relatively preserved.

TABLE 1 Comparison Between Patients With Isolated RV Abnormalities and Those With LV Abnormalities*

	Abnormal CMR (n = 38)	RV Only Abnormality (n = 17)	LV* Involvement (n = 21)	p Value
Demographics				
Age, yrs	39 (27-49)	43 (20-50)	28 (23-41)	0.088
Male	26 (68)	14 (82)	12 (57)	0.161
Proband	21 (55)	7 (41)	14 (67)	0.190
Definite ARVD/C at last follow-up	34 (89)	15 (88)	19 (90)	0.770
PKP2 mutation carrier	28 (74)	16 (94)	12 (57)	0.012
Qualitative findings				
RV WMA	34 (50)	16 (94)	18 (86)	0.613
RV fat	13 (34)	8 (47)	5 (24)	0.178
RV LGE	7 (18)	3 (18)	4 (19)	1.000
LV WMA	7 (18)	–	7 (33)	–
LV fat	16 (42)	–	16 (76)	–
LV LGE	18 (47)	–	18 (86)	–
Quantitative findings				
RV ESVI, ml/m^2	66 ± 27	59 ± 22	71 ± 30	0.199
RV EDVI, ml/m^2	105 ± 33	98 ± 28	109 ± 36	0.343
RV EF, %	39 ± 9	42 ± 9	37 ± 10	0.100
LV ESVI, ml/m^2	41 ± 12	39 ± 11	42 ± 13	0.434
LV EDVI, ml/m^2	84 ± 18	86 ± 18	84 ± 19	0.888
LV EF, %	52 ± 7	54 ± 7	50 ± 7	0.144
CMR task force criteria				
Any criterion	27 (68)	11 (65)	16 (76)	0.491
Major criterion	24 (60)	8 (47)	16 (76)	0.094
Minor criterion	3 (8)	3 (18)	0 (0)	0.081

Values are median (interquartile range), n (%), or mean ± SD. *This group includes subjects with biventricular involvement and LV-only involvement.

ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy; CMR = cardiac magnetic resonance; EDVI = end-diastolic volume indexed; EF = ejection fraction; ESVI = end-systolic volume indexed; LGE = late gadolinium enhancement; LV = left ventricle; *PKP2* = plakophilin-2; RV = right ventricle; WMA = wall motion abnormality.

This study describes the spectrum of CMR findings in a cohort of ARVD/C-associated mutation carriers, including first-degree relatives of ARVD/C patients who were "at risk" of disease. Our study has several important findings. First, in ARVD/C mutation carriers with structural disease on CMR, biventricular abnormalities were seen with similar frequency to isolated RV disease. Involvement of the LV in subjects with ARVD/C has been increasingly recognized, with prevalence reported in up to 80% of ARVD/C patients in several European populations (1,2) and 40% in a cohort of North American and Dutch patients (4). Our study confirms the high prevalence of biventricular disease in North American patients with structurally abnormal hearts and genetic predisposition to ARVD/C. Interestingly, though, LV abnormalities were not detrimental to cardiac function with no significant differences between groups with and without LV involvement. Furthermore, demographic and RV findings were similar between individuals with isolated RV disease and those with biventricular disease, suggesting that LV abnormalities may occur at any stage of RV disease and are not limited only to subjects with advanced RV disease. This finding argues against the traditional notion that LV abnormalities are a late complication of the disease (5). More likely, there is a spectrum of the disease process that varies from patient to patient, extending across both ventricles. Finally, the only finding significantly different between subjects with isolated RV disease and those with LV abnormalities was genotype, suggesting an association between genotype and structural phenotype in ARVD/C mutation carriers.

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Variability of Tricuspid Annulus Diameter Measurement in Healthy Volunteers

Tricuspid valve (TV) anatomy and function play an important prognostic role in several heart diseases and in the development of functional tricuspid regurgitation. According to current guidelines for management of heart valve disease, the tricuspid annulus (TA) diameter measured by 2-dimensional transthoracic echocardiography (2DE) should be used to define the need of an associated TA annuloplasty in patients undergoing cardiac surgery for left-sided heart valve diseases (1,2). However, the timing during the cardiac cycle when the TA should be measured remains to be established. Moreover, normative data about TA diameter and function are limited (3–5).

Therefore, we designed a prospective cross-sectional study of 219 normal volunteers (age 43 ± 15 years; 57% female; body mass index <30 kg/m^2) to assess the variability of TA diameter measurement in 2DE 4-chamber view (4CH) in relation to timing during the cardiac cycle.

The TA diameter was obtained from the apical right ventricular (RV)-focused 4CH using a Vivid E9 (GE Vingmed, Horten, Norway) equipped with M5S probe and measured as the distance between the insertion points of the TV leaflets (inner edge to inner edge) at 5 time points during the cardiac cycle. The times during the cardiac cycle were determined using both electrocardiogram and valve dynamic visualization: TV closure (end-diastole—the first frame after the TV closure), mid-systole (beginning of T-wave), end-systole (end of T-wave), TV opening early filling (as the frame with the TV wide open during passive flow), TV opening late filling (as the frame with the TV wide open during active flow—after P-wave).