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Morphologic Variants of Familial Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

A Genetics–Magnetic Resonance Imaging Correlation Study

Darshan Dalal, MD, MPH,* Harikrishna Tandri, MD,* Daniel P. Judge, MD,* Nuria Amat, MS,* Robson Macedo, MD,† Rahul Jain, MD,* Crystal Tichnell, MGC,* Amy Daly, MS,* Cynthia James, PHD, SCM,* Stuart D. Russell, MD,* Theodore Abraham, MD,* David A. Bluemke, MD, PHD,‡ Hugh Calkins, MD*

Baltimore and Bethesda, Maryland

Objectives The purpose of this study was to determine the extent of left ventricular (LV) involvement in individuals predisposed to developing arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), and to investigate novel morphologic variants of ARVD/C.

Background The discovery of desmosomal mutations associated with ARVD/C has led researchers to hypothesize equal right ventricular (RV) and LV affliction in the disease process.

Methods Thirty-eight (age 30 ± 17 years; 18 males) family members of 12 desmosomal mutation-carrying ARVD/C probands underwent genotyping and cardiac magnetic resonance imaging (CMR). The CMR investigators were blinded to clinical and genetic data.

Results Twenty-five individuals had mutations in *PKP2*, *DSP*, and/or *DSG2* genes. RV abnormalities were associated with the presence of mutation(s) and with disease severity determined by criteria (minor = 1; major = 2) points for ARVD/C diagnosis. The only LV abnormality detected, the presence of intramyocardial fat, was present in 4 individuals. Each of these individuals was a mutation carrier, whereas 1 had no previously described ARVD/C-related abnormality. On detailed CMR, a focal "crinkling" of the RV outflow tract and subtricuspid regions ("accordion sign") was observed in 60% of the mutation carriers and none of the noncarriers ($p < 0.001$). The sign was present in 0%, 37%, 71%, and 75% of individuals who met 1, 2, 3, and 4+ criteria points, respectively ($p < 0.01$).

Conclusions Despite a possible LV involvement in ARVD/C, the overall LV structure and function are well preserved. Independent LV involvement is of rare occurrence. The accordion sign is a promising tool for early diagnosis of ARVD/C. Its diagnostic utility should be confirmed in larger cohorts. (J Am Coll Cardiol 2009;53:1289–99) © 2009 by the American College of Cardiology Foundation

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a familial cardiomyopathy characterized clinically by right ventricular (RV) dysfunction and ventricular tachycardia (1–4) and histopathologically by fibrofatty replacement of the myocardium (5). Recent literature has demonstrated the role of mutations in genes encoding cardiac desmosomal proteins such as desmoplakin, plakoglobin, plakophilin-2, and desmoglein-2 in the development of ARVD/C (6–17). Although ARVD/C has been considered primarily as a right-sided cardiomyopathy, the growing evidence supporting the desmosomal origin of ARVD/C has led investigators to hypothesize a concomitant

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From the *Division of Cardiology, Department of Medicine, and †Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; and ‡Radiology and Imaging Sciences, National Institutes of Health Clinical Center, Bethesda, Maryland. The Johns Hopkins ARVD Program is supported by the Bogle Foundation, the Campanella family, the Wilmerding Endowments, and Healing Hearts; this work was also supported by grants from the Donald W. Reynolds Foundation; and the W.W. Smith Charitable Trust. Dr. Abraham has received honoraria and research support from GE Healthcare. Dr. Tandri is supported by a grant from the National Heart, Lung, and Blood Institute (HL093350). Drs. Dalal and Tandri contributed equally to this work.

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Abbreviations and Acronyms

ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy
CMR = cardiac magnetic resonance imaging
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
LV = left ventricle/ventricular
ROC = receiver-operating characteristic
RV = right ventricle/ventricular
RVOT = right ventricular outflow tract

or independent left ventricular (LV) involvement in these patients (18). The Task Force criteria that are widely applied to ascertain the diagnosis of ARVD/C were published in 1994 and were designed to specifically exclude LV disease (19).

The purpose of this study was 2-fold. First, our study was aimed at determining the presence and extent of LV involvement in individuals predisposed to developing ARVD/C. The hypothesis of the study was that family members carrying mutations in genes encoding desmosomal proteins would be equally likely to develop right- or left-sided cardiomyopathy. The secondary aim of the study was to identify the early morphologic variants of ARVD/C and to examine their incremental value in the diagnosis of ARVD/C. Cardiac magnetic resonance imaging (CMR), which has been developed as an important tool for the noninvasive evaluation of the disease, was used to ascertain the morphologic variants of both ventricles (20–23).

Methods

Patient recruitment, evaluation, and diagnosis. The study population was identified from the Johns Hopkins ARVD Registry. The Johns Hopkins ARVD Registry was established in 1999 with the goal of gaining insights into the diagnosis, genetic basis, and clinical course of patients with known or suspected ARVD/C. All patients included in this registry provided written informed consent to participate in clinical and research genetic screening. The study protocol was approved by the Johns Hopkins Medicine Institutional Review Board. As a routine protocol of the registry, after diagnosis of an ARVD/C patient, all family members of the patient are invited to undergo a screening protocol for ARVD/C. The screening protocol includes obtaining relevant medical history, noninvasive clinical testing for ascertainment of the Task Force criteria, and genetic sequencing to identify possible mutations in 1 or more genes encoding desmosomal proteins.

For the purpose of the present study, family members of probands with 1 or more mutations in genes encoding plakophilin-2 (*PKP2*), desmoplakin (*DSP*), and/or desmoglein-2 (*DSG2*), were included. The probands were only used for the purpose of identifying the family members, and were excluded in all further analyses. Families in which none of the family members underwent CMR were excluded.

Patients were evaluated as described previously (4). For each patient, medical history and family history were obtained. Subsequently, each patient underwent noninvasive clinical testing, including electrocardiogram, signal-averaged electrocardiogram, Holter monitoring, and CMR. Diagnosis of ARVD/C was established based on the criteria set by the Task Force of the Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology (19).

CMR. A detailed CMR was performed for the entire study population irrespective of their genetic or clinical findings. CMRs were performed according to standard protocols for diagnosis of ARVD/C (22). All CMR datasets were obtained on a 1.5-T scanner (CV/i, GE Medical Systems, Waukesha, Wisconsin) and included both fast spin-echo and gradient-echo sequences. Fat- and nonfat-suppressed fast spin-echo sequences were acquired in the axial and short-axis planes with breath-hold double-inversion recovery blood suppression pulses. The repetition time was 1 or 2 R-R intervals, and the time to excitation was 10 ms. The slice thickness was 5 mm and slice gap 5 mm. The matrix and field of view were 256 × 256 and 24 cm, respectively. Gradient echo sequences were acquired in the axial and short-axis planes using breath-hold steady-state free precession imaging. The flip angle was 40°, and time to excitation was set to minimum. For steady-state free precession imaging, the slice thickness was 8 mm with a slice gap of 2 mm. The matrix and field of view were 256 × 160 and 36 cm, respectively. A phased array cardiac coil was used for all the studies. The datasets were transferred to an Advantage Windows workstation (GE Medical Systems) for analysis. Gadolinium-enhanced CMRs were reviewed for evidence of delayed enhancement in any of the RV or LV segments. After intravenous administration of a CMR contrast agent (0.2 mmol/kg of gadodiamide [Omniscan, Amersham Health, Princeton, New Jersey]), inversion recovery prepared breath-hold cine gradient-echo images were obtained 20 min after contrast agent injection. Breath-hold 2-dimensional imaging (7.2/3.2; inversion time optimized 150 to 200 ms; flip angle, 25°; slice thickness, 8 mm; slice gap, 2 mm; number of excitations, 2; matrix, 256 × 192; and field of view, 360 × 270 mm) scans were obtained in the short-axis and axial planes at 10-mm intervals covering the entire RV and LV.

Quantitative analysis was performed using the software program MASS (Medis, Leiden, the Netherlands). End-systolic image was defined visually as the one with the smallest ventricular cavity size and end-diastolic image, as the first image after the R-wave trigger. Quantitative CMR parameters included end-systolic volume (ESV), end-diastolic volume (EDV), and ejection fraction (EF) of both ventricles.

For qualitative assessment, the RV was divided into 4 regions: 1) base; 2) mid-cavity; 3) apex; and 4) right ventricular outflow tract (RVOT). The LV was divided into 4 regions based on the 17-segment model (24), so that segments 1 to 6 represented the base, segments 7 to 12 represented the midcavity, segments 13 to 16 represented