Left Ventricular Involvement in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Assessed by Echocardiography Predicts Adverse Clinical Outcome

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Background: Among studies describing the phenotype of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), significant discrepancy exists regarding the extent and impact of left ventricular (LV) involvement. The capability of conventional and new quantitative echocardiographic techniques to accurately detect LV involvement in ARVD/C remains unknown. The aim of this study was to test the hypothesis that accurate detection of LV involvement on echocardiography identifies patients at additional risk for cardiac events during follow-up.

Methods: Thirty-eight patients with ARVD/C, 16 pathogenic mutation–positive relatives, and 55 healthy control subjects were prospectively enrolled. Conventional echocardiography with additional deformation imaging was performed in all subjects to detect LV involvement. In a subgroup (n = 27), cardiac magnetic resonance imaging was performed with late enhancement. All patients and relatives were prospectively followed for events (sustained ventricular tachycardia, appropriate implantable cardioverter-defibrillator intervention, sudden cardiac death, and heart transplantation).

Results: Conventional echocardiography detected LV involvement in 32% of patients with ARVD/C and in none of the relatives. Deformation imaging revealed LV involvement in 68% of patients with ARVD/C and 25% of relatives and was correlated closely with late enhancement on cardiac magnetic resonance imaging. During a mean follow-up period of 5.9 ± 2.3 years, 20 patients with ARVD/C (53%) experienced events, and no events occurred in the relatives. LV involvement detected by deformation imaging (hazard ratio, 4.9; 95% CI, 1.7–14.2) and right ventricular outflow tract enlargement (hazard ratio, 1.2; 95% CI, 1.1–1.3) were the only independent predictors of outcomes.

Conclusions: Deformation imaging detected a high incidence of LV involvement in patients with ARVD/C and their relatives. Compared with conventional echocardiography, deformation imaging is superior in detecting minor LV involvement. LV involvement and an enlarged right ventricular outflow tract are independent prognostic markers of outcomes. (J Am Soc Echocardiogr 2015;■:■-■.)

Keywords: ARVD/C, Arrhythmogenic right ventricular cardiomyopathy, Echocardiography, Deformation imaging, LV involvement, Prognosis

Arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy characterized by fibrofatty myocardial replacement, predominantly affecting the right ventricle.[1] However, left ventricular (LV) involvement has been demonstrated across a broad spectrum of disease severity.[2-4] Detection of LV involvement is important because these patients seem to experience more potentially lethal ventricular arrhythmias than those with apparently isolated RV disease.[5,6] Noninvasive diagnostic modalities enabling the detection of LV involvement in patients with ARVD/C could therefore be of value in risk stratification in individual patients. Cardiac magnetic resonance (CMR) imaging has taken a prominent role, whereby late enhancement (LE) detects structural LV abnormalities (myocardial fibrosis) associated with ARVD/C.[7,8] Unfortunately, the limited availability, high cost, and inability to evaluate patients with implantable cardioverter-defibrillators (ICDs) render this technique unsuitable for serial evaluation in this specific patient population. Conventional echocardiography is often unable to detect minor LV pathology detected on CMR imaging, because these abnormalities are usually not associated with wall motion abnormalities.[7,9] However, echocardiographic deformation imaging enables

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Abbreviations

ARVD/C = Arrhythmogenic right ventricular dysplasia/cardiomyopathy

CMR = Cardiac magnetic resonance

FAC = Fractional area change

ICD = Implantable cardioverter-defibrillator

LE = Late enhancement

LV = Left ventricular

LVEF = Left ventricular ejection fraction

RV = Right ventricular

RVOT = Right ventricular outflow tract

TAPSE = Tricuspid annular plane systolic excursion

the objective quantification of regional myocardial function,[10] which correlates closely with LE on CMR imaging with regard to fibrotic segments in patients with nonischemic heart disease, and can even detect regional abnormalities before the appearance of CMR LE in the left ventricle.[9,11] Previously, we reported a case in which deformation imaging was able to unmask LV involvement in a patient with ARVD/C with preserved LV systolic function and no regional wall motion abnormalities.[9] The capability of deformation imaging to detect LV involvement in a large cohort of patients with ARVD/C and their relatives remains unknown.

We hypothesized that echocardiographic deformation imaging is more sensitive than conventional echocardiographic parameters to detect LV wall motion abnormalities in patients with ARVD/C. The aim of this study therefore was to detect LV involvement in patients with ARVD/C and mutation-carrying relatives using echocardiographic deformation imaging and to explore the extent of LV dysfunction across a wide spectrum of ARVD/C severity. Second, we explored the predictive value of parameters derived from conventional and deformation imaging parameters in the occurrence of future cardiac events.

METHODS

Study Design

Between 2006 and 2008, consecutive individuals aged >18 years were prospectively enrolled for echocardiographic examination: (1) those with either known or suspected ARVD/C, (2) family members of patients with ARVD/C, and (3) healthy control subjects.

Group classification was established according to major and minor criteria as defined by the current 2010 ARVD/C diagnostic task force[12] and the results of deoxyribonucleic acid analysis of ARVD/C-associated genes, performed as described previously.[13,14] Figure 1 demonstrates, in detail, the group classification on the basis of clinical assessment and genetic testing. Three groups were specified: (1) patients with ARVD/C (n = 38), (2) relatives of patients with ARVD/C carrying pathogenic mutations (n = 16), and (3) control subjects (n = 55) free of any cardiovascular disease.

End point data were obtained directly from patients or relatives during periodic evaluations at the outpatient clinic or hospital admissions until September 2014. The outcome measure was a composite of end points: spontaneous sustained monomorphic ventricular tachycardia, sudden cardiac death, aborted sudden cardiac death, appropriate ICD intervention for a ventricular arrhythmia, and heart transplantation. Outcome definitions are available in Supplemental Table 1. In case of reaching multiple clinical events during the follow-up period, the first event was considered the end point. Subsequent events were registered but were not included in further analysis.

The study protocol was carried out with the approval of the Ethics Committee of the University Medical Center Utrecht, and all patients gave informed consent.

Standard Echocardiographic Study

The echocardiographic examination was performed with the subject at rest, in the left lateral decubitus position, using a Vivid 7 scanner (GE Vingmed Ultrasound AS, Horten, Norway) equipped with an M3S broadband transducer. A complete echocardiographic study was performed, with two-dimensional (B-mode) and Doppler tissue imaging recorded in both parasternal and apical views. Additional recordings of the three conventional apical views were recorded with the implementation of dual focus to optimize wall motion assessment. Special care was taken to avoid recording the right ventricle in any of these views for optimal blinding during postprocessing. According to the 16-segment model of the American Society of Echocardiography, regional LV wall motion was designated as normokinetic, hypokinetic, akinetic, dyskinetic, or not interpretable, after consensus was reached by two blinded experienced observers. From this the wall motion score index was calculated as the sum of scores divided by the total number of analyzed segments.

Conventional echocardiographic measurement of both LV and RV dimensions was performed (see "Results").[15] All dimensions were corrected for body surface area. RV function was measured by tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC).[16] Global LV function was measured by LV ejection fraction (LVEF) using the Simpson biplane method. Pulsed Doppler imaging was used to measure diastolic function.[17] A full description of the echocardiographic measurements is available as Supplemental Data.

Deformation Imaging

We previously described our methods for image acquisition and postprocessing with commercially available software (EchoPAC PC version 11.2; GE Vingmed Ultrasound AS) for two-dimensional speckle-tracking analysis.[10,18] More details according to the acquisition and processing of tissue deformation imaging are available in the Supplemental Files. The following parameters were measured in the basal, middle, and apical segment of each wall (a total of 18 segments): systolic peak strain and strain rate, defined as the maximum negative value between aortic valve opening and closure (in case values were positive during systole, the end-systolic value was measured). Averaging systolic peak strain values over 18 LV segments resulted in the mean systolic peak strain. Postsystolic shortening was defined as 100 × [(peak strain value − end-systolic value)/end-systolic value].

CMR Imaging

A subgroup of 19 patients with ARVD/C and eight relatives underwent CMR imaging as part of their clinical workup on a 1.5-T magnetic resonance imaging scanner (Achieva; Philips Healthcare, Best, The Netherlands) according to standard ARVD/C protocols.[19,20] All CMR examinations were performed within 12 months of the echocardiographic studies. LE of intravenously administered gadolinium was used to identify areas within the left ventricle with myocardial fibrosis using the 16-segment model of the American Society of Echocardiography. The presence of gadolinium LE on CMR imaging was determined by consensus reading of two blinded