Early Detection of Regional Functional Abnormalities in Asymptomatic ARVD/C Gene Carriers

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Background: The overt stage of arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy (ARVD/C) is preceded by a concealed stage with minor or no signs of disease. However, sudden death may occur in this early phase. Deformation imaging may contribute to early diagnosis. The aims of this study were to compare the diagnostic accuracy of the conventional (1994) versus the recently published (2010) new echocardiographic criteria for ARVD/C and to evaluate the additional value of echocardiographic tissue deformation imaging to detect subclinical RV functional abnormalities in asymptomatic carriers of pathogenic ARVD/C mutations.

Methods: Fourteen asymptomatic first-degree relatives of ARVD/C probands (the ARVD/C-r group; mean age, 38.0 ± 13.2 years) with a pathogenic plakophilin-2 mutation and a group of age-matched controls (n = 56; mean age, 38.2 ± 12.7 years) were included at a 1:4 ratio. A complete echocardiographic evaluation (dimensions, global systolic parameters, and visual assessment and deformation imaging of the RV free wall including Doppler tissue imaging and two-dimensional strain echocardiography) was obtained. Peak systolic strain less negative than −18% and/or postsystolic shortening (postsystolic index > 15%) in any RV segment was considered abnormal.

Results: RV dimensions in the ARVD/C-r group were similar to those in controls (RV outflow tract, 15.4 ± 2.9 vs 14.4 ± 1.9 mm/m^2, P = NS; RV inflow tract, 18.6 ± 2.6 vs 19.1 ± 2.6 mm/m^2, P = NS), and global systolic parameters were moderately reduced (tricuspid annular plane systolic excursion, 20.0 ± 3.2 vs 23.9 ± 2.8 mm, P = .001; RV fractional area change, 40.3 ± 8.4 vs 40.6 ± 7.1, P = NS). According to task force criteria, 57% of the ARVD/C-r group and 29% of controls were classified as abnormal when applying the 1994 criteria and 29% and 4% when applying the 2010 criteria, respectively. Doppler tissue imaging and two-dimensional strain deformation (and strain rate) values were reduced in the ARVD/C-r group in the basal and mid RV segments compared with controls (P < .001). In the ARVD/C-r group, peak systolic strain less negative than −18% was seen in six patients (43%), postsystolic strain in nine (64%), and either abnormality in 10 (71%), almost exclusively in the basal segment; these findings were observed in none of the controls.

Conclusions: The 2010 criteria for ARVD/C improve specificity, whereas sensitivity is significantly reduced in this asymptomatic population. In contrast, echocardiographic deformation imaging detects functional abnormalities in the subtricuspid region in 71% of asymptomatic carriers of a pathogenic plakophilin-2 mutation, while regional deformation was normal in all control subjects, indicating superiority of both sensitivity and specificity with these new modalities. (J Am Soc Echocardiogr 2012;25:997-1006.)

Keywords: Echocardiography, Diagnosis, Cardiomyopathy, Deformation imaging

Arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy (ARVD/C) is a disease histopathologically characterized by fibrofatty alteration predominantly in the RV myocardium.[1-5] A molecular-genetic origin of this disease can be identified in up to 70% of patients with familial ARVD/C, with an autosomal dominant mode of inheritance[6] with incomplete penetrance.[2,7] Potentially lethal ventricular arrhythmias may be the first manifestation of this disease in previously healthy young individuals.[2,7] This emphasizes the importance of early recognition of this disease, for instance, in the family members of ARVD/C probands. Currently, the diagnosis is established using a composite of criteria proposed by a task force including electrocardiographic (ECG) disturbances, functional and morphologic abnormalities, and family history.[8] These criteria have recently been modified to increase the sensitivity of ARVD/C diagnosis.[9] Unfortunately, because the

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Abbreviations

ARVD/C = Arrhythmogenic right ventricular dysplasia/cardiomyopathy

ARVD/C-r = First-degree relatives of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy

DTI = Doppler tissue imaging

ECG = Electrocardiographic

ε = Strain

PKP2 = Plakophilin-2

PSI = Postsystolic strain index

RV = Right ventricular

RVOT = Right ventricular outflow tract

TAPSE = Tricuspid annular plane systolic excursion

TFC = Task force criteria

2DSE = Two-dimensional strain echocardiographic

pathognomonic characteristics on noninvasive imaging are often not present in the early stages of the disease, early detection remains cumbersome. This phase is often referred to as the concealed phase of the disease,[5] but it nevertheless carries the risk for sudden cardiac death.[10]

We hypothesized that an objective and regional approach to evaluate changes in RV function would improve the diagnostic accuracy of echocardiography and thus identify the phenotypic expression of the disease earlier in its course. We have previously shown that regional assessment using echocardiographic deformation imaging is able to accurately identify patients in whom ARVD/C has been diagnosed previously.[11] Using a cutoff value of −18% for peak systolic strain (ε) in any RV segment showed sensitivity of 97% and specificity of 91.2% in differentiating between patients with ARVD/C and healthy controls. The role of this technique in detecting functional abnormalities as an early manifestation of ARVD/C, however, remains unknown. The aim of this study was to evaluate the additional value of tissue deformation imaging included in the echocardiographic examination to detect subclinical RV functional abnormalities in asymptomatic carriers of a pathogenic ARVD/C mutation. A secondary goal of this study was to compare the recently published updated guidelines[9] with the conventional 1994 task force criteria (TFC) for ARVD/C in this specific population.[8]

METHODS

Study Population

A total of 38 consecutive relatives, not fulfilling criteria for ARVD/C at the time of analysis, of ARVD/C probands referred for echocardiographic evaluation at our tertiary center were prospectively enrolled. All included individuals were first-degree relatives of 21 index patients in whom the diagnosis of ARVD/C was established as previously described.[11] All relatives underwent full echocardiographic examinations, as well as electrocardiography at rest, typically performed within 2 months of echocardiography. All included individuals were offered deoxyribonucleic acid analysis as part of our clinical workup if a disease-causing mutation had been found in the proband. All probands were tested for pathogenic desmosomal mutations in plakophilin-2 (*PKP2*), desmoglein-2, desmocollin-2, desmoplakin, and junction plakoglobin, whereas relatives were tested only for the mutation that was found in the proband. Of the initial cohort, 24 individuals were excluded because (1) no pathogenic mutation was found in the proband ($n = 11$) and thus no genetic testing was performed in the relative, (2) no pathogenic mutation was detected in the relative ($n = 6$), or (3) the subject refused to undergo genetic testing ($n = 7$). Thus, the study population consisted of 14 ARVD/C first-degree relatives of nine index-patients with disease-causing mutations (asymptomatic mutation carriers; the ARVD/C-r group). At the time of echocardiographic examination and data analysis, no member of the ARVD/C-r group fulfilled diagnostic criteria for ARVD/C, as established by the TFC valid at that time.[8] According to the modified TFC proposed in 2010,[9] however, six of 14 did fulfill the diagnostic criteria for ARVD/C. This higher yield was due not to phenotypic criteria but exclusively to the presence of a pathogenic mutation as a major criterion. Nevertheless, all 14 members of the ARVD/C-r group were included for final analysis in this study.

As reference group, a total of 56 age-matched healthy controls free of cardiovascular disease were included (ratio of first-degree relatives to controls, 1:4[12]) and subjected to the same echocardiographic protocol. No genetic analysis was performed in any of the control subjects. All included individuals were aged ≥ 18 years and in stable sinus rhythm. None of the controls were athletes, because of the impact of regular physical activity on RV geometry and function.[13] The local ethics committee approved study protocol, and consent was obtained before echocardiographic examinations.

Standard Echocardiographic Examination

The echocardiographic examination was performed with the subject at rest, lying in the left lateral decubitus position. Ultrasound data were acquired using a Vivid 7 scanner (GE Vingmed Ultrasound AS, Horten, Norway) equipped with an M3S broadband transducer. A complete echocardiographic study was performed in two-dimensional (B-mode) and Doppler tissue imaging (DTI) mode. Both standard parasternal and apical views were obtained,[14] as well as additional views as proposed by Foale *et al.*[15] of both the left and right ventricles.

Conventional measurements included RV outflow tract (RVOT) end-diastolic diameter in the parasternal long-axis and short-axis views. In addition, parasternal long-axis RVOT end-systolic diameter was measured, with which the fractional change was calculated as the percentage change. Left ventricular internal diameter at end-diastole was measured using M-mode echocardiography. In the apical four-chamber view, left ventricular and RV short-axis inflow tract end-diastolic diameters were measured at the level of the valve leaflet tips, while by measuring RV end-diastolic and end-systolic areas, RV fractional area change was calculated. Right atrial and left atrial single-plane areas were measured at end-systole. Additionally, all dimensions were corrected for body surface area. In the four-chamber view, tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode imaging. Pulsed Doppler imaging was used to interrogate transtricuspid and RVOT flow at end-expiration during breath hold for timing of cardiac events. By DTI, the systolic (s′) and diastolic, both early (e′) and late (a′), velocities were calculated in the basal segment of the RV free wall in addition to isovolumic acceleration. Color DTI was used to extract these velocity data.

Wall motion in the RV free wall was evaluated in the apical four-chamber view in the basal, mid, and apical segments. Wall motion was classified as normokinetic, hypokinetic, akinetic, dyskinetic, or uninterpretable. Finally, a major or a minor criterion was ascribed to the echocardiographic examination according to both the 1994 and 2010 modified TFC,[8,9] using all available echocardiographic data, with the exception of the results of the deformation analysis. Visual assessment was performed by two experienced observers, blinded to group, who had to reach consensus for both regional wall motion abnormalities and the assignment of TFC point(s).