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Right Ventricular Imaging and Computer Simulation for Electromechanical Substrate Characterization in Arrhythmogenic Right Ventricular Cardiomyopathy

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ABSTRACT

BACKGROUND Previous studies suggested that electrical abnormalities precede overt structural disease in arrhythmogenic right ventricular cardiomyopathy (ARVC). Abnormal RV deformation has been reported in early ARVC without structural abnormalities. The pathophysiological mechanisms underlying these abnormalities remain unknown.

OBJECTIVES The authors used imaging and computer simulation to differentiate electrical from mechanical tissue substrates among ARVC clinical stages.

METHODS ARVC desmosomal mutation carriers (n = 84) were evaluated by electrocardiography (ECG), Holter monitoring, late-enhancement cardiac magnetic resonance imaging, and echocardiographic RV deformation imaging. Subjects were categorized based on the presence of 2010 International Task Force criteria: 1) subclinical stage (n = 21); 2) electrical stage (n = 15); and 3) structural stage (n = 48). Late enhancement was not present in any subclinical or electrical stage subjects.

RESULTS Three distinctive characteristic RV longitudinal deformation patterns were identified: type I: normal deformation (n = 12); type II: delayed onset of shortening, reduced systolic peak strain, and mild post-systolic shortening (n = 35); and type III: systolic stretching with large post-systolic shortening (n = 37). A majority (69%) of structural staged mutation carriers were type III, whereas a large proportion of both electrical and subclinical stage subjects (67% and 48%, respectively) were type II. Computer simulations demonstrated that the type II pattern can be explained by a combination of reduced contractility and mildly increased passive myocardial stiffness. This evolved into type III by aggravating both mechanical substrates. Electrical activation delay alone explained none of the patterns.

CONCLUSIONS Different ARVC stages were characterized by distinct RV deformation patterns, all of which could be reproduced by simulating different degrees of mechanical substrates. Subclinical and electrical staged ARVC subjects already showed signs of local mechanical abnormalities. Our novel approach could lead to earlier disease detection and, thereby, influence current definitions of electrical and subclinical ARVC stages. (J Am Coll Cardiol 2016;68:2185–97)

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ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

CMR = cardiac magnetic resonance

ECG = electrocardiogram

LV = left ventricle/ventricular

RV = right ventricle/ventricular

RVOT = right ventricular outflow tract

TFC = International Task Force criteria

Arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by ventricular arrhythmias and progressive RV dysfunction (1,2). Presently, an ARVC-causing mutation can be identified in 60% of index patients (3). Familial ARVC is associated with reduced penetrance and variable disease expression (3), ranging from sudden cardiac death in young individuals to lifelong absence of any phenotype (4). ARVC is characterized histopathologically by fibrofatty replacement of the myocardium, forming a substrate for conduction delay as well as both regional and global RV dysfunction (1). Accumulating evidence suggests that this structural disease is preceded by electrical abnormalities (5–7). Therefore, ARVC is currently divided into 3 consecutive clinical stages: 1) subclinical (concealed), with neither electrical nor structural abnormalities; 2) electrical, with only electrocardiographic (ECG) abnormalities; and 3) structural, with both electrical and structural abnormalities (7–9).

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Echocardiographic deformation (or strain) imaging can quantify regional myocardial deformation and has been used to detect regional functional abnormalities in ARVC (10,11). Deformation imaging revealed abnormal deformation throughout all clinical ARVC stages, including the early subclinical stage in which conventional diagnostic techniques detected neither structural nor electrocardiographic abnormalities (12–15). The pathophysiological mechanisms underlying these regional functional abnormalities in the early stages of ARVC remain unknown.

We hypothesized that the observed abnormal deformation patterns in early ARVC stages are explained by an electrical substrate, such as activation delay, rather than regional contractile dysfunction; and the abnormal deformation patterns in the advanced structural stage result from regional contractile dysfunction and increased myocardial stiffness in addition to electrical activation delay.

To assess our hypotheses, we examined a cohort of desmosomal ARVC mutation carriers using both RV echocardiographic deformation imaging and conventional ARVC diagnostic criteria. After subdividing the cohort based on their RV deformation patterns, we examined the distribution of these patterns in each clinical ARVC stage. Finally, we used computer simulations to understand the electromechanical tissue abnormalities underlying these characteristic RV deformation patterns.

METHODS

This retrospective study was conducted at the University Medical Center Utrecht in the Netherlands between 2006 and 2015, and approved by the local institutional ethics review board. During this period, 87 subjects carrying a pathogenic plakophillin-2 (*PKP2*) or desmoglein-2 (*DSG2*) mutation (54 index patients and 33 relatives) were sent for echocardiographic examination including RV deformation imaging; 3 were excluded due to inadequate image quality.

All mutation carriers underwent ECG, Holter monitoring, and cardiac imaging according to the diagnostic work-up as stated in the 2010 International Task Force criteria (TFC) (9). Definite diagnosis requires either 2 major, 1 major and 2 minor, or 4 minor criteria.

Eighty-four healthy unrelated age- and sex-matched controls were included to obtain normal RV deformation patterns.

ARVC stage classification was based on the presence of subsets of the 2010 TFC (7–9) (**Figure 1**). Subclinical ARVC stage was defined as the absence of any 2010 TFC, except for harboring a desmosomal ARVC pathogenic mutation. Electrical ARVC stage was defined as the presence of a major or minor criterion for depolarization, repolarization, or history of ventricular arrhythmias and the absence of structural abnormalities on imaging. Structural ARVC stage was defined as the presence of a major or minor TFC for structural abnormalities on noninvasive imaging, regardless of the history of ventricular arrhythmias or presence of ECG or Holter abnormalities.

IMAGING PROTOCOLS. Our echocardiographic protocol has been detailed elsewhere (10). Briefly, all data were obtained on a Vivid 7 or Vivid E9 ultrasound machine (General Electric, Milwaukee, Wisconsin) using a broadband M3S transducer. All echocardiographic studies were analyzed for fulfilling 2010 TFC for structural abnormalities (9). Conventional measurements included the end-diastolic diameter of the RV outflow tract in both the parasternal long- and short-axis view and RV fractional area change in the apical 4-chamber view (11). Left ventricular (LV) systolic function was measured by LV ejection fraction using Simpson's biplane measurement.

The RV focused apical 4-chamber view, after narrowing its sector width to optimize temporal resolution, was used to visualize the RV lateral free wall and stored for offline analysis (10).

RV deformation patterns were classified based on the longitudinal strain curve of the RV basal lateral