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Exercise Testing in Asymptomatic Gene Carriers Exposes a Latent Electrical Substrate of Arrhythmogenic Right Ventricular Cardiomyopathy

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Objectives The aim of this study was to determine if exercise testing could expose a latent electrical substrate of arrhythmogenic right ventricular cardiomyopathy (ARVC) in asymptomatic gene carriers.

Background Management of asymptomatic ARVC gene carriers is challenging because of variable penetrance of disease and the recognition that sudden cardiac death may be the first clinical manifestation.

Methods Exercise-induced abnormalities during exercise treadmill testing (ETT) were initially compared in 60 subjects: 30 asymptomatic ARVC gene carriers and 30 healthy controls. In phase 2 of the study, ETT results of 25 patients with ARVC with histories of sustained ventricular arrhythmia or cardiac arrest were evaluated to determine if ETT abnormalities in asymptomatic gene carriers were common to patients with a malignant electrical form of the disease.

Results Depolarization abnormalities during ETT were found to develop more frequently in asymptomatic gene carriers compared with healthy controls: epsilon waves appeared in 4 of 28 (14%) compared with 0 of 30 (0%) ($p = 0.048$), premature ventricular contractions in 17 of 30 (57%) compared with 3 of 30 (10%) ($p = 0.0003$), and new QRS terminal activation duration $\geq$55 ms in 7 of 22 (32%) compared with 2 of 29 (7%) ($p = 0.03$). Superior axis premature ventricular contractions occurred only in gene carriers. In the second phase of the study, the frequency of these abnormalities was found to be high in patients with symptomatic ARVC: new epsilon waves appeared in 3 of 18 (17%), superior axis premature ventricular contractions in 21 of 25 (84%), and new terminal activation duration $\geq$55 ms in 8 of 12 (67%).

Conclusions Exercise testing exposes a latent electrical substrate in asymptomatic ARVC gene carriers that is shared by patients with ARVC with histories of ventricular arrhythmia. ETT may be useful in guiding treatment decisions, exercise prescription, and prioritizing medical surveillance in asymptomatic ARVC gene carriers. (J Am Coll Cardiol 2013;62:1772–9) © 2013 by the American College of Cardiology Foundation

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically mediated disease. The advent of clinical genetic testing for ARVC now allows the identification of causal genetic mutations in up to 50% of patients (1). Consequently, the 2010 revised task force criteria (TFC) for ARVC (2) include a pathogenic mutation as a major criterion for the diagnosis. After the identification of a culprit gene in an index patient, current guidelines recommend genetic screening of family members, who are typically asymptomatic of the disease (1,3).

The management of asymptomatic patients with ARVC mutations can be challenging: clinical penetrance of the disease is highly variable, and many gene carriers enjoy active lifestyles and normal life spans. Of concern, however, is that the earliest "latent" stage of ARVC is characterized by normal electrocardiographic (ECG) findings with undetectable structural heart disease but a risk for sudden cardiac death that may be highest during exercise (4). Therefore, testing that is able to identify a developing electrical substrate for ventricular arrhythmia in asymptomatic,

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genotype-positive individuals may be beneficial in guiding exercise prescription and medical surveillance.

We hypothesized that exercise testing might be used to expose a latent electrical substrate of ARVC in asymptomatic gene carriers with resting ECG results absent of major criteria for the disease. In the first phase of this study, we sought to identify and evaluate the frequency of electrical abnormalities induced on exercise treadmill testing (ETT) in asymptomatic patients with ARVC mutations compared with healthy age-matched and sex-matched controls. In phase 2 of this study, we expanded our testing cohorts and also assessed whether identified exercise abnormalities in asymptomatic gene carriers may correlate with arrhythmia risk by evaluating the results of ETT in a cohort of patients with ARVC with histories of sustained ventricular arrhythmia or cardiac arrest.

Methods

Asymptomatic patients with ARVC genotypes were identified from 3 inherited arrhythmia clinics after cascade family genetic screening following the identification of an affected ARVC proband.

In the first study phase, 60 subjects were compared. This cohort consisted of 30 asymptomatic ARVC gene carriers and 30 age-matched and sex-matched healthy subjects.

Each gene carrier harbored a pathogenic mutation predicted to cause ARVC according to the TFC (2) (Online Table 1). Asymptomatic gene carriers underwent resting 12-lead electrocardiography, signal-averaged electrocardiography, 24-h Holter monitoring, and magnetic resonance imaging or echocardiography. By study design, the resting electrocardiograms of all asymptomatic ARVC gene carriers exhibited no major criteria for ARVC per the TFC (2).

ETT was performed in all gene carriers and controls. Abnormalities of depolarization and repolarization were recorded. Depolarization abnormalities included new epsilon waves in leads V_1 and V_2, premature ventricular contractions (PVCs) categorized as superior or inferior or indeterminate axis, and prolonged QRS terminal activation duration (TAD) $\geq$55 ms in leads V_1 and V_2. Repolarization abnormalities analyzed included new T-wave inversion (TWI) beyond lead V_2 and new ST-segment elevation $\geq$0.1 mV in either lead V_1 or lead V_2.

In phase 2 of the study, the ETT results of 25 patients with ARVC and a history of sustained ventricular arrhythmia and/or cardiac arrest were evaluated to determine the frequency of the ETT observations in this cohort. In addition, we expanded our ETT observations in asymptomatic ARVC gene carriers by 17 patients, for a total of 47 patients, and evaluated the ETT results of an additional 40 controls, for a total of 70 healthy individuals, to more accurately determine the specificity of exercise abnormalities identified in phase 1.

Details of analyses and statistical methods are available in the Online Appendix.

Abbreviations and Acronyms

ARVC = arrhythmogenic right ventricular cardiomyopathy
ECG = electrocardiographic
ETT = exercise treadmill test
PKP2 = plakophilin-2
PVC = premature ventricular contraction
RBBB = right bundle branch block
TAD = terminal activation duration
TFC = task force criteria
TWI = T-wave inversion

Results

ETT in asymptomatic ARVC gene carriers and healthy controls.

BASELINE CHARACTERISTICS. The mean age of the asymptomatic ARVC gene carrier cohort was 39.6 $\pm$ 18.9 years, and the mean age of the healthy control group was 38.4 $\pm$ 10.7 years ($p = 0.80$).

Of gene carriers, 27 of 30 (90%) harbored plakophilin-2 (*PKP2*) mutations (Table 1). The *PKP2* mutations were "radical" in 24 of 27 (90%). Digenic heterozygosity was present in 2 subjects (#12 and #13). Both patients harbored rare missense *PKP2* and desmoglein 2 mutations. A single subject (#14) was heterozygous for the Val56Met missense mutation in desmoglein-2. This variant segregated with 2 affected family members, including an identical twin diagnosed with ARVC at necropsy after sudden death. This variant has been reported in numerous ARVC cohorts.

The revised ARVC task force score was calculated for each gene-positive patient (2). "Definite" diagnoses of ARVC were present in 3 patients; the remainder were either "borderline" (n = 9) or "possible" diagnoses (n = 18). We also summarized the burden of disease in our cohort by calculating the task force score excluding section VI ("family history"). Twenty-four of 30 subjects (80%) were now considered "negative" for ARVC (i.e., lacking a recognized phenotype of the disease) (Table 1).

Resting ECG abnormalities. By study design, no asymptomatic gene carrier had a major ECG criterion for the diagnosis of ARVC. On analysis, no healthy control had a major criterion for ARVC on resting electrocardiography. However, 1 of 30 (3%) healthy controls had TAD $\geq$ 55 ms (a minor criterion in the TFC) on resting electrocardiography. This finding was present in 6 of 28 (21%) asymptomatic gene carriers ($p = 0.05$; 2 had resting right bundle branch block [RBBB] and were excluded from this analysis). No subject in either group had TWI reaching minor criterion status.

In asymptomatic gene carriers, signal-averaged ECG results were positive in at least 1 of 3 criteria in 9 of 25 (36%) (Table 2). Although signal-averaged electrocardiography was not performed in healthy subjects, the largest study to date examining the utility of signal-averaged ECG criteria for the diagnosis of ARVC reported specificity of 92% for $\geq$1 of 3 criteria (5).