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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).

Table 1 Clinical Characteristics and Exercise Results of Asymptomatic ARVC Gene Carriers

Patient #	Age (yrs)	Sex	2010 TFC	Modified 2010 TFC	MRI Results	Holter PVCs	SAECG	Affected Gene(s)	Coding	Protein Product	New Epsilon Waves	Superior-Axis PVCs	Inferior-Axis PVCs	TAD ≥55 ms	TWI Beyond Lead V_2	STE ≥0.1 mV
1	18	F	Possible	Negative	Normal	0	0	*PKP2*	c.1613G>A	Trp538X	N	N	N	N	N	N
2	42	F	Possible	Negative	Normal	48	0	*PKP2*	c.1912C>T	Gln638X	N	N	Y	N	Y	N
3	67	M	Possible	Negative	Normal	36	NA	*PKP2*	c.1912C>T	Gln638X	N	Y	Y	N	N	N
4	59	F	Possible	Negative	Normal	10	0	*PKP2*	c.1613G>A	Trp538X	N	N	N	N	N	N
5	24	F	Possible	Negative	Normal	93	0	*PKP2*	c.1912C>T	Gln638X	N	N	N	N	Y	N
6	17	F	Possible	Negative	Normal	0	0	*PKP2*	c.1912C>T	Gln638X	N	N	Y	Y	N	Y
7	19	M	Possible	Negative	Normal	0	Q	*PKP2*	c.1912C>T	Gln638X	Y	N	N	Y	N	N
8	48	F	Definite	Possible	Normal	1,469	Q, R	*TMEM43*	c.1073C>T	Ser358Leu	N	Y	N	Y	N	N
9	53	M	Borderline	Possible	Normal	1,526	Q, H, R	*PKP2*	c.1912C>T	Gln638X	Y	N	Y	Y	N	N
10	59	F	Possible	Negative	Normal	38	0	*PKP2*	c.1912C>T	Gln638X	N	N	Y	N	N	N
11	21	M	Borderline	Possible	Normal¶	4	Q	*PKP2*	c.1912C>T	Gln638X	Y	Y	N	—	N	N
12	28	F	Possible	Negative	Normal	0	0	*PKP2*, *DSG2*	c.1580T>C, c.3061_3062delAG	Leu527Pro, Ser1021X	N	N	Y	N	N	N
13	69	M	Borderline	Negative	Normal¶	258	H, R	*PKP2*, *DSG2*	c.2431C>A, c.1439C>T	Arg811Ser, Thr480Ile	N	Y‖	N	—	Y	N
14	59	F	Borderline	Negative	Normal	1,689‖	0	*DSG2*	c.166G>A	Val56Met	N	Y	Y	Y	N	N
15	31	M	Borderline	Possible	Minor	15	Q†	*PKP2*	c.2197_2202delinsG	His733fsX740	N	N	N	—	N	N
16	56	F	Borderline	Negative	Normal	0	R	*PKP2*	c.2197_2202delinsG	His733fsX740	N	N	Y	N	N	N
17	73	M	Borderline	Negative	Normal	181	H, R	*PKP2*	c.2197_2202delinsG	His733fsX740	N	N	N	N	N	N
18	24	F	Possible	Negative	Normal	11	0	*PKP2*	c.2197_2202delinsG	His733fsX740	N	N	N	N	Y	N
19	66	M	Definite	Definite	Major¶	713	Q, H, R†	*PKP2*	c.2146_1G>C	Mutant splice product	Y	N	Y	—	Y	N
20	48	F	Definite	Possible	Normal	9	0	*PKP2*	c.2216_2217delAT	His739fs	N	N	Y	Y	Y	N
21	34	F	Possible	Negative	Normal	71	0	*TMEM43*	c31073C>T	Ser358Leu	N	N	N	—	N	N
22	37	F	Borderline	Negative	Normal	1,268	H	*PKP2*	c.2216_2217delAT	His739fs	N	N	Y	N	N	N
23	43	F	Possible	Negative	Normal	11	0	*PKP2*	c.2216_2217delAT	His739fs	N	N	Y	N	N	N
24	50	M	Possible	Negative	Normal	10	Q, H, R†	*PKP2*	c.1378+1G>C	Mutant splice product	§	Y	N	§	N	N
25	17	M	Possible	Negative	Normal	0	0	*PKP2*	c.148_151delACAG	Ser50fsX110	N	N	N	N	N	N
26	55	M	Possible	Negative	Normal	184	0	*PKP2*	c.1643delG	Val548X	N	Y	Y	N	N	N
27	14	M	Possible	Negative	Normal	1	0	*PKP2*	c.148_151delACAG	Ser50fsX110	N	N	N	N	N	N
28	20	M	Possible	Negative	Normal	NA	0	*PKP2*	c.1643delG	Val548fsX562	Y	N	N	—	N	N
29	19	M	Possible	Negative	Normal	4	Q, H, R†	*PKP2*	c.2484C>T‡	Mutant splice product	§	N	N	§	N	N
30	21	M	Borderline	Negative	Normal	420	Q, L	*PKP2*	c.235C>T	Arg79X	N	N	N	Y	N	N

A modified 2010 TFC score was calculated, excluding section VI (family history), to more accurately summarize the burden of structural and electrical disease. A dash indicates that the abnormality was present on resting electrocardiography. *Axis could not be determined. †Baseline QRS duration ≥110 ms, therefore the results of SAECG were not interpretable (2010 TFC) (2). ‡Homozygous for mutation. §Right bundle branch block at baseline, therefore TAD was not interpretable (2010 TFC) (2). ||Nonsustained ventricular tachycardia. ¶Transthoracic echocardiography.

ARVC = arrhythmogenic right ventricular cardiomyopathy; *DSG2* = desmoglein 2; H = low-amplitude signal duration ≥38 ms; MRI = magnetic resonance imaging; N = no; NA = not available; *PKP2* = plakophilin-2; PVC = premature ventricular contraction; Q = filtered QRS ≥114 ms); R = root mean square voltage of terminal 40 ms ≤20 μV; SAECG = signal-averaged electrocardiography; STE = ST-segment elevation; TAD = terminal activation duration; TFC = task force criteria; *TMEM43* = transmembrane protein 43; TWI = T-wave inversion; Y = yes.

Table 2 Summary Data Comparing Asymptomatic Gene Carriers With Healthy Control Patients

Variable	Asymptomatic ARVC Gene Carriers (n = 30)	Healthy Controls (n = 30)	p Value
Age (yrs)	39.7 ± 18.9	38.4 ± 10.7	0.80
Men	15	15	1.00
Resting electrical abnormalities			
TWI in leads V_1 and V_2	0 (0%)	0 (0%)	1.00
TAD ≥55 ms	6/28 (21%)	1 (3%)	0.05
SAECG (≥1 criterion)	9/25 (36%)	—	—
Exercise-induced depolarization abnormalities			
Epsilon wave	4/28 (14%)	0 (0%)	0.048
PVCs			
Any	17 (57%)	3 (10%)	0.0003
Superior axis	7 (23%)	0 (0%)	0.01
TAD ≥55 ms	7/22 (31%)	2/29 (7%)	0.03
Exercise-induced repolarization abnormalities			
TWI beyond lead V_2	6/28 (21%)	4 (13%)	0.50
ST-segment elevation ≥0.1 mV	2 (7%)	2 (7%)	1.00

Values are mean ± SD, n, n (%), or n/N (%). When the denominator is <30, the abnormality was present at rest or else could not be assessed (e.g., resting QRS must be <110 ms to interpret the results of SAECG; see the Methods section).
Abbreviations as in Table 1.

New abnormalities of depolarization during ETT. EPSILON WAVES AND NEW PROLONGATION OF QRS TAD. Two asymptomatic gene carriers were excluded from the analysis of epsilon waves because of the presence of resting RBBB. In the remaining cohort, new epsilon waves appeared during ETT in 4 of 28 (14%) (Fig. 1). No healthy controls developed new epsilon waves (0 of 30 p = 0.048).

Resting QRS TAD ≥55 ms was present in 6 of 28 (21%) asymptomatic ARVC gene carriers (excluding 2 patients with RBBB). In the remaining subjects, 7 of 22 (32%) developed TAD ≥55 ms during ETT. In each case, TAD ≥55 ms was present during the recovery period. Resting TAD ≥55 ms was present in 1 healthy control and developed during exercise in another 2 of 29 (p = 0.03 vs. asymptomatic gene carriers).

PVCS. PVCs of any configuration were recorded during ETT in 17 of 30 (57%) asymptomatic gene carriers and 3 of 30 (10%) healthy controls (p = 0.0003). Superior-axis PVCs were seen in 7 of 30 (23%) asymptomatic gene carriers and were not observed in healthy controls (p = 0.01).

In 2 gene carriers, nonsustained ventricular tachycardia was noted during ETT: superior axis in 1 and inferior axis in the other. Nonsustained ventricular tachycardia was not recorded in healthy controls. Sustained ventricular tachycardia was not seen in either group.

Thus, among exercise-induced abnormalities of depolarization, new epsilon waves, new QRS TAD ≥55 ms, and

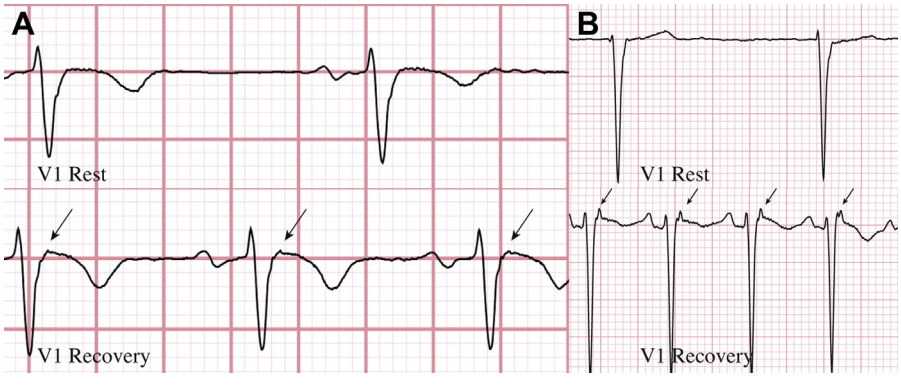

Figure 1 Epsilon Waves Appearing During Exercise

(A) An epsilon wave appeared during early exercise in subject #9 and persisted during the recovery period **(arrows)**. **(B)** In subject #7, a relatively large amplitude epsilon wave **(arrows)** was prominent late into the recovery period. Both asymptomatic subjects had normal results on rest electrocardiography and normal results on cardiac magnetic resonance imaging and harbored radical plakophilin 2 mutations.

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ventricular ectopic activity occurred with greater frequency in asymptomatic ARVC gene carriers. In addition, superior-axis PVCs were unique to asymptomatic ARVC gene carriers.

New abnormalities of repolarization during ETT. ST-SEGMENT ELEVATION. New ST-segment elevation ≥1 mV in the right precordial leads was noted in 2 of 30 (7%) asymptomatic gene carriers and 2 of 30 (7%) healthy controls (p = 1.00).

NEW TWI. TWI extending to lead V_3 or beyond developed in 6 of 28 gene carriers (21%; 2 had resting RBBB). However, 4 of 30 healthy controls (13%) developed TWI to lead V_3 or beyond (p = 0.50). TWI typically developed early in exercise and resolved at peak exercise in both groups.

Thus, both abnormalities of repolarization occurred with equal frequency between asymptomatic ARVC gene carriers and healthy controls.

Phase 2 study: ETT in TFC-positive patients with ARVC with histories of sustained ventricular tachycardia or cardiac arrest. BASELINE CHARACTERISTICS. The mean age of the symptomatic ARVC cohort was 40.7 ± 10.9 years, and 18 of 25 (72%) were men. In this phase, the ETT results of an additional 17 asymptomatic ARVC gene carriers were evaluated, for a total of 47 patients. The mean age of these 47 patients was 36.6 ± 18.1 years, and 18 of 47(38%) were men.

We applied modified TFC for the diagnosis of familial ARVC to this expanded asymptomatic gene carrier cohort (Online Table 2). These criteria, proposed by Hamid et al. (6), consider minor electrical and structural abnormalities identified in first-degree relatives of an ARVC proband as signs of early disease. We modified the original criteria of Hamid et al. to accommodate the now widespread availability of cardiac magnetic resonance imaging and defined "minor" abnormalities according to the minor ARVC criteria of the 2010 TFC (2). Consistent with Hamid et al., we also considered a PVC count >200 in 24 h as a sign of disease. In our asymptomatic cohort, only 21 of 47 (45%) were considered to have ARVC by the modified criteria of Hamid et al. Of note, 5 of the remaining 26 patients negative per the criteria of Hamid et al. had either superior-axis PVCs or new epsilon waves during exercise, suggesting incremental value to exercise-induced changes in identifying affected first-degree relatives. Including these exercise changes would increase the sensitivity of the modified criteria to 55% (26 of 47).

In addition, we evaluated the ETT results of a further 40 healthy controls, for a total of 70 healthy subjects. The additional healthy subjects were all gene-negative, first-degree relatives of probands diagnosed at an inherited arrhythmia clinic. The mean age of this expanded cohort was 35.8 ± 15.2 years, and 28 of 70 (40%) were men.

Resting ECG abnormalities. Major criteria for ARVC were present on resting electrocardiography in 12 of 25 (48%) patients with symptomatic ARVC. Resting epsilon waves and TWI reaching lead V_3 were present in 6 and 9 patients, respectively. Both abnormalities were present in 3 patients. By study design, no asymptomatic gene carrier had a major ECG criterion on resting electrocardiography. Minor criteria were present, however, in 11 of 47 (23%) asymptomatic ARVC gene carriers, consisting of QRS TAD ≥55 ms in 8 subjects and minor TWI criterion in 3 subjects.

New abnormalities of depolarization during ETT. During ETT, new epsilon waves appeared in 6 of 45 asymptomatic gene carriers (13%) and 3 of 18 subjects with symptomatic ARVC (17%). PVCs of any axis were recorded in 27 of 47 asymptomatic ARVC gene carriers (57%) and 23 of 25 patients with symptomatic ARVC (92%). Superior-axis PVCs were recorded in 10 of 47 asymptomatic gene carriers (21%) and 21 of 25 patients with symptomatic ARVC (84%) (Fig. 2).

In patients with symptomatic ARVC, the predominant configuration of superior-axis PVCs was left bundle branch block, identified in 17 of 21 subjects. The remaining 4 subjects had superior-axis PVCs of indeterminate configuration (PVCs not recorded in leads V_1 and V_2). Four symptomatic patients showed both RBBB and left bundle branch block superior-axis PVCs. In asymptomatic gene carriers, 9 of 10 displayed left bundle branch block or indeterminate-configuration superior-axis PVC configurations. RBBB configuration was also seen in 4 subjects and was the only configuration of superior-axis PVC in a single subject.

Overall, in the expanded healthy control cohort, 11 of 70 (16%) developed PVCs during ETT. One of the 70 (1.4%), a 63-year-old woman, developed superior-axis PVCs; the bundle branch configuration could not be determined. New epsilon waves were not seen in any healthy control (0 of 70).

Last, new prolonged QRS TAD ≥55 ms developed in 11 of 36 asymptomatic ARVC gene carriers (31%) and 8 of 12 patients with symptomatic ARVC patients (67%) (p = 0.04).

Thus, abnormalities seen in a proportion of asymptomatic ARVC gene carriers during ETT were also seen, albeit at a higher frequency, in patients with symptomatic ARVC with histories of sustained ventricular arrhythmia or cardiac arrest. These results are summarized in Table 3.

Discussion

The principal finding of this study is that exercise testing may expose a latent electrical substrate of ARVC in asymptomatic gene carriers that is absent from healthy subjects but shared by patients with symptomatic ARVC and histories of ventricular arrhythmia or cardiac arrest. Two abnormalities found in asymptomatic ARVC gene carriers, epsilon waves and superior-axis PVCs, were rare or absent in healthy controls. Furthermore, new epsilon waves and/or superior-axis PVCs appeared during ETT in 22 of 25 patients with ARVC (88%) with histories of sustained ventricular arrhythmia and/or cardiac arrest, indicating that these observations may be clinical markers of greater arrhythmic risk.

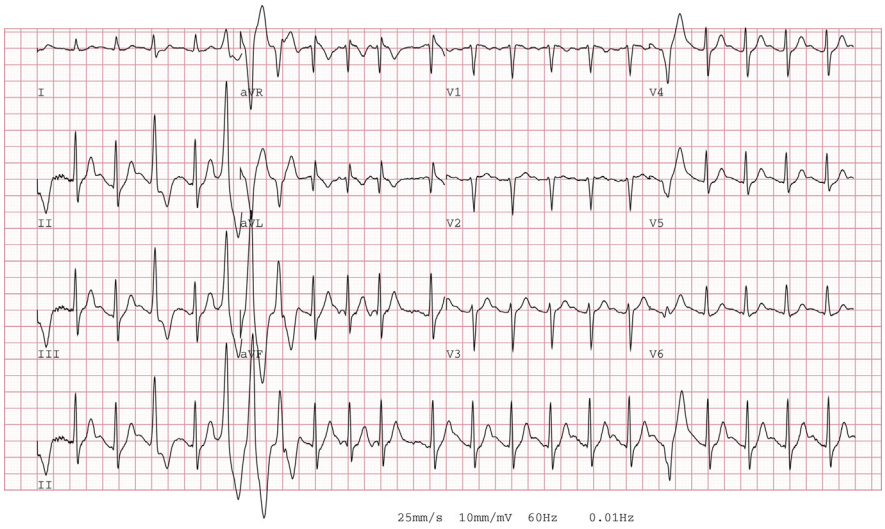

Figure 2 **PVCs During Exercise Treadmill Testing**

Electrocardiogram recorded during the recovery period of an exercise treadmill test in a 41-year-old man with arrhythmogenic right ventricular cardiomyopathy and a history of sustained ventricular arrhythmia. This patient was found to have a large deletion of plakophilin 2. A short triplet of premature ventricular contractions (PVCs) was recorded with an inferior (outflow tract–like) configuration. A single superior-axis PVC was noted later in the recording. PVCs were not seen at rest or during the exercise stage of the test.

A small number of studies have examined the effects of exercise in ARVC. Toyofuku et al. (7) evaluated 17 ARVC probands with histories of sustained ventricular tachycardia. During ETT, ST-segment elevation ≥0.1 mV developed in 11 of 17 (65%). Although not a focus of their study, ventricular ectopic activity and/or ventricular arrhythmia was noted in 14 of 17 (82%); this occurred despite a high rate of antiarrhythmic medication. Sequeira et al. (8) assessed ETT observations in a small study of 16 patients (age <18 years) with ARVC. The pattern and inducibility of ventricular ectopic activity were found to be variable. Consequently, the investigators urged caution in using ETT to rule in or out a diagnosis of ARVC. However, in contrast to our study, their patients were much younger, the proportion of patients with histories of sustained ventricular arrhythmia was not reported, and more than 50% of the treadmill tests were performed while on antiarrhythmic medications. Last, Furlanello et al. (9) studied 32 athletes with ARVC, including 20 with histories of sustained ventricular tachycardia. In the entire cohort, bicycle exercise–induced ventricular ectopic activity or tachycardia occurred in 69%. The correlation between exercise results and a history of sustained ventricular arrhythmia was not reported.

In this limited body of research, our study is unique for enrolling asymptomatic ARVC gene carriers. Consequently, manifest structural disease of the right ventricle was rare in our cohort: 2 of 47 met minor or major 2010 TFC. Furthermore, by study design, all subjects did not have major ECG criteria for ARVC. The small burden of disease in our cohort may be summarized by calculating a modified TFC 2010 score excluding genotype and family history. By this method, 40 of 47 (85%) were considered "negative" for ARVC (i.e., showing no or little manifestation of the disease). The low burden of disease identified in ARVC gene carriers identified through cascade family screening demonstrates that genetic defects do not in themselves constitute disease but are markers of risk. It is now common to identify genotype-positive relatives of a proband, both young and old, with active lifestyles and no overt manifestation of the disease. In our asymptomatic cohort, 11 of 47 were >50 years of age, but only 1 displayed overt structural cardiac disease. Given the low penetrance of symptomatic and overt structural disease in genotype-positive family members, the question arises as to how asymptomatic gene carriers should be managed; specifically, is it possible to risk-stratify who may be at higher risk for ventricular arrhythmia or sudden cardiac death?

Our symptomatic ARVC cohort exposes the problem of arrhythmia risk prediction on the basis of baseline testing performed at rest. Despite histories of sustained ventricular arrhythmia or aborted cardiac arrest, 9 of 25 (36%) did not have major or minor criteria for right ventricular disease on cardiac imaging, 13 of 25 (52%) had no major ECG criteria, and 6 of 25 (24%) had both normal cardiac imaging and no major ECG criteria. That is, a significant proportion did not have apparent structural or electrical phenotypes that would be predicted to predispose to their arrhythmia. In contrast, the response to exercise was significant: 22 of 25 (88%) developed superior-axis PVCs and/or new epsilon waves during exercise. The remaining 3 had resting epsilon waves. These same exercise abnormalities were identified in a subset of asymptomatic gene carriers: 15 of 47 (32%) developed

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Table 3 Summary Data Comparing Asymptomatic Gene Carriers With Patients With Symptomatic (VT) ARVC

Variable	Healthy Controls (n = 70)	Asymptomatic ARVC Gene Carriers (n = 47)	Patients With Symptomatic ARVC (n = 25)	p Value (Controls vs. Asymptomatic Gene Carriers)	p Value (Asymptomatic Gene Carriers vs. Patients With Symptomatic ARVC)
Age (yrs)	35.8 ± 15.2	36.7 ± 18.1	40.7 ± 10.9	0.78	0.24
Men	28 (40%)	18 (38%)	18 (72%)	1.00	0.01
Genotype					
PKP2	—	43 (91%)	19 (76%)	—	0.09
Structural RV abnormalities					
Major criterion	—	1 (2%)	16 (64%)	—	<0.0001
Minor criterion	—	1 (2%)	0 (0%)	—	1.00
Resting ECG abnormalities					
TWI in leads V_1 to V_3	0/70	0/45 (0%)	9 (36%)	1.00	<0.0001*
Epsilon waves	0/70	0/45 (0%)	6 (24%)	1.00	0.002*
TAD ≥55 ms	—	10/45 (22%)	11/24 (45)	—	0.06
SAECG (≥1 criterion)	—	10/41 (24%)	17/21 (81)	—	<0.0001
Exercise ECG abnormalities					
Epsilon waves	0/70	6/45 (13%)	3/18 (17%)	0.003	0.70
PVCs					
Any	11/70 (11%)	27 (57%)	23 (92%)	<0.0001	0.003
Superior axis	1/70 (1%)	10 (21%)	21 (84%)	0.0004	<0.0001
TAD ≥ 55 ms	—	11/36 (31%)	8/12 (67%)	—	0.04

Values are mean ± SD, n (%), or n/N (%). Where the denominator is <47 (asymptomatic gene carriers) or 25 (patients with symptomatic ARVC), the abnormality was present at rest or else could not be assessed (see the Methods section). *By study design, no subjects with resting major ECG criteria for ARVC were enrolled into the asymptomatic gene carrier cohort.

ECG = electrocardiographic; RV = right ventricular; other abbreviations as in Table 1.

superior-axis PVCs and/or new epsilon waves. Given a shared exercise phenotype between asymptomatic gene carriers and patients with symptomatic ARVC, we would suggest that asymptomatic patients showing these abnormalities are in transition to a stage of disease associated with a higher risk for ventricular arrhythmia. Specific cases from our cohort and the published research illustrate this concept. A 36-year-old male patient in our symptomatic cohort was initially diagnosed with benign syncope on the basis of clinical history, normal cardiac imaging results, and normal results on resting electrocardiography. Over the following year, the patient developed intractable ventricular arrhythmia and was diagnosed with ARVC on the basis of the 2010 TFC. Analysis of ETT results at initial evaluation revealed isolated superior-axis PVCs. Similarly, Sanatani et al. (10) described the case of an male adolescent who experienced sudden cardiac death during exercise and was diagnosed with ARVC at autopsy. Three years previously, he had received a diagnosis of benign syncope after normal investigations. However, retrospective analysis of his ETT results at initial evaluation revealed a single superior-axis PVC.

The management of asymptomatic ARVC gene carriers is uncertain. Current practice involves lifelong clinical assessment but at ill-defined time intervals and with no specific recommendations as to when any specific therapies might be considered. Furthermore, the issue of exercise restriction is challenging in asymptomatic gene carriers without symptoms or overt clinical disease. The European Society of Cardiology recommends against all competitive sports in ARVC gene carriers without clinical phenotypes of disease (11). The distinction between competitive and recreational sports is not clear in our minds; many subjects exert to high intensity even during "noncompetitive" sports. In contrast, the 36th Bethesda Conference allows participation in all sports when a phenotype of disease is absent (11). The psychological consequences of receiving a life-changing diagnosis coupled with major lifestyle changes should be considered. In our view, risk should be individualized on the basis of the burden of disease in an individual patient (structural disease, PVCs on Holter monitoring, and so on), with particular attention to exercise-induced abnormalities. Patients showing ventricular ectopic activity, especially of superior axis morphology, would be advised to avoid exercise intensity to a greater extent than other asymptomatic gene carriers with consistently normal treadmill exercise results. Consideration might be given to beta-blocker therapy or to specific heart rate limits during exercise to attenuate risk, rather than complete cessation of all activity. Although from our perspective, exercise prescription should be based on an assessment of the burden of disease in an individual patient, we would advise against high-intensity endurance exercise in all gene carriers, as animal models of ARVC suggest that endurance exercise may speed the development of the ARVC phenotype (12).

In addition to risk stratification in asymptomatic gene carriers, we can envisage several novel uses of ETT in the evaluation of suspected ARVC that will require validation in future studies. The demonstration of epsilon waves appearing during exercise is novel to our knowledge and

apparently infrequent, being absent from healthy controls. It is therefore a possible candidate to be included in future revisions of TFC. ETT may also be useful when screening the asymptomatic relatives of an ARVC proband when initial testing does not reveal a genetic cause. Furthermore, genetic testing is not routinely available in many countries or is prohibitively expensive. ETT, with other noninvasive modalities, may be used to identify a phenotype of disease in asymptomatic relatives. Exercise prescription could then be provided on the basis of the results of this testing.

Study limitations. Overall, about 90% of asymptomatic gene carriers in our study had *PKP2* mutations. The generalization of our findings to other genotypes may therefore be brought into question. The high rate of *PKP2* mutations resulted from an enrollment bias that all mutations be definitely pathogenic.

We did not demonstrate the reproducibility of ETT results in our patients. It is possible that ectopic activity and other abnormalities may be present in a higher proportion of subjects when serial testing is performed.

The reproducibility of TAD measurements was recently brought into question by Jain et al. (13). We found this measurement difficult and agree that its diagnostic usefulness is likely to be low in the absence of true blinding. Importantly, our discussion and conclusion do not rest on TAD but rather the appreciation of exercise-induced epsilon waves and ventricular ectopic activity.

We would advise caution in the application of our findings to large populations in which the pretest probability of ARVC is likely to be low, such as healthy athletes. Even uncommon exercise abnormalities such as superior-axis PVCs are more likely to be "normal" when the population incidence of ARVC is low (14).

Perhaps the most significant weakness of our study is the lack of long-term follow-up. A shared exercise phenotype between asymptomatic gene carriers and patients with symptomatic ARVC is suggestive of a vulnerability to arrhythmia in these patients; however, a definitive answer as to how vulnerable such patients are cannot be made at this time.

Conclusions

We performed ETT in asymptomatic ARVC gene carriers, age-matched and sex-matched healthy controls, and a cohort of patients with symptomatic (ventricular arrhythmia or cardiac arrest) ARVC. Our principal finding is that exercise can expose an electrical phenotype in asymptomatic ARVC gene carriers that is absent from healthy controls but shared by patients with manifest and symptomatic ARVC. In asymptomatic ARVC gene carriers, the results of exercise testing may be useful to identify a developing substrate of ARVC and thus prioritize medical surveillance and guide exercise prescription.

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REFERENCES

1. Gollob MH, Blier L, Brugada R, et al. Recommendations for the use of genetic testing in the clinical evaluation of inherited cardiac arrhythmias associated with sudden cardiac death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper. Can J Cardiol 2011;27:232–45.
2. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533–41.
3. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm 2011;8:1308–39.
4. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988;318:129–33.
5. Kamath GS, Zareba W, Delaney J, et al. Value of the signal-averaged electrocardiogram in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart Rhythm 2011;8:256–62.
6. Hamid MS, Norman M, Quraishi A, et al. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. J Am Coll Cardiol 2002;40:1445–50.
7. Toyofuku M, Takaki H, Sunagawa K, et al. Exercise-induced ST elevation in patients with arrhythmogenic right ventricular dysplasia. J Electrocardiol 1999;32:1–5.
8. Sequeira IB, Kirsh JA, Hamilton RM, Russell JL, Gross GJ. Utility of exercise testing in children and teenagers with arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol 2009;104:411–3.
9. Furlanello F, Bettini R, Bertoldi A, et al. Arrhythmia patterns in athletes with arrhythmogenic right ventricular dysplasia. Eur Heart J 1989;10 Suppl:16–9.
10. Sanatani S, Duncan W, Chan S. The challenge of diagnosing arrhythmogenic right ventricular cardiomyopathy in the young. Pediatr Cardiol 2008;29:800–3.
11. Pelliccia A, Zipes DP, Maron BJ. Bethesda Conference #36 and the European Society of Cardiology consensus recommendations revisited: a comparison of U.S. and European criteria for eligibility and disqualification of competitive athletes with cardiovascular abnormalities. J Am Coll Cardiol 2008;52:1990–6.
12. Kirchhof P, Fabritz L, Zwiener M, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. Circulation 2006;114:1799–806.
13. Jain R, Tandri H, Daly A, et al. Reader- and instrument-dependent variability in the electrocardiographic assessment of arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Cardiovasc Electrophysiol 2011;22:561–8.
14. Biffi A, Pelliccia A, Verdile L, et al. Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes. J Am Coll Cardiol 2002;40:446–52.

Key Words: arrhythmia ■ ARVC ■ exercise ■ genetics.

APPENDIX

For an expanded methods section and supplemental tables, please see the online version of this article.