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Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy–Associated Desmosomal Mutation Carriers

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Objectives This study sought to determine how exercise influences penetrance of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) among patients with desmosomal mutations.

Background Although animal models and anecdotal evidence suggest that exercise is a risk factor for ARVD/C, there have been no systematic human studies.

Methods Eighty-seven carriers (46 male; mean age, 44 ± 18 years) were interviewed about regular physical activity from 10 years of age. The relationship of exercise with sustained ventricular arrhythmia (ventricular tachycardia/ventricular fibrillation [VT/VF]), stage C heart failure (HF), and meeting diagnostic criteria for ARVD/C (2010 Revised Task Force Criteria [TFC]) was studied.

Results Symptoms developed in endurance athletes ($N = 56$) at a younger age (30.1 ± 13.0 years vs. 40.6 ± 21.1 years, $p = 0.05$); they were more likely to meet TFC at last follow-up (82% vs. 35%, $p < 0.001$) and have a lower lifetime survival free of VT/VF ($p = 0.013$) and HF ($p = 0.004$). Compared with those who did the least exercise per year (lowest quartile) before presentation, those in the second (odds ratio [OR]: 6.64, $p = 0.013$), third (OR: 16.7, $p = 0.001$), and top (OR: 25.3, $p < 0.0001$) quartiles were increasingly likely to meet TFC. Among 61 individuals who did not present with VT/VF, the 13 subjects experiencing a first VT/VF event over a mean follow-up of 8.4 ± 6.7 years were all endurance athletes ($p = 0.002$). Survival from a first VT/VF event was lowest among those who exercised most (top quartile) both before ($p = 0.036$) and after ($p = 0.005$) clinical presentation. Among individuals in the top quartile, a reduction in exercise decreased VT/VF risk ($p = 0.04$).

Conclusions Endurance exercise and frequent exercise increase the risk of VT/VF, HF, and ARVD/C in desmosomal mutation carriers. These findings support exercise restriction for these patients. (J Am Coll Cardiol 2013;62:1290–7)

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a heritable cardiomyopathy characterized by life-threatening ventricular arrhythmias, right ventricular (RV) dysfunction, and an increased risk of sudden cardiac death (1,2). Incomplete penetrance and variable phenotypic expression are characteristic of ARVD/C, suggesting a potential role for environmental influences (3–5). Many ARVD/C patients are highly athletic, and those who participate in competitive athletics have been found to have a 5-fold increased risk of sudden death compared with nonathletes (6). It is currently recommended that ARVD/C patients not participate in either competitive (7) or most recreational (8) sports, but no recommendations have been made for clinically unaffected mutation carriers.

Over the past decade, pathogenic ARVD/C-associated mutations have been identified in 5 desmosomal genes (*PKP2*, *DSG2*, *DSP*, *DSC2*, and *JUP*) (9–13). Cardiac desmosomes are specialized adhesion junctions composed

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of a symmetrical group of proteins—the cadherins, armadillo proteins, and plakins—that provide a mechanical connection between cardiac myocytes. Desmosomal mutations can now be identified in as many as 60% of ARVD/C patients (14,15). The appreciation that ARVD/C is in many cases a "disease of the desmosome" suggests potential mechanisms through which exercise, particularly endurance exercise, could be a risk factor for ARVD/C (16,17).

Kirchhof et al. (18) showed that endurance exercise accelerated the development of RV dysfunction and arrhythmias in a plakoglobin-deficient mouse model, but there are no systematic human studies.

Clinical genetic testing for ARVD/C is now routinely performed (19). Therefore, the clinician is now confronted not only with ARVD/C patients seeking advice on physical activity, but also with making recommendations for a growing group of clinically unaffected mutation carriers. Because familial ARVD/C is a clinically heterogeneous disorder with incomplete penetrance and variable expressivity (20,21), management of unaffected mutation carriers is challenging as the individualized risk of the disease developing is uncertain. Discerning whether lifestyle choices (exercise habits) can modify penetrance is critical. Therefore, we developed a study of ARVD/C-associated desmosomal mutation carriers to test the hypothesis that exercise influences age-related penetrance, arrhythmic risk, and progression to heart failure in ARVD/C.

Methods

Study population. The study population was recruited from the Johns Hopkins ARVD/C Registry, which prospectively enrolls ARVD/C patients and their family members. Participants are contacted and medical records are updated annually. Registry participants who carried a single copy of a pathogenic ARVD/C-associated desmosomal mutation, were 10 years of age or older, and could speak English were invited to participate in a detailed interview to document exercise history. Parents were co-informants for children younger than 18 years of age. All aspects of the study were approved by The Johns Hopkins School of Medicine Institutional Review Board.

Genotype. Genotype was derived from direct sequencing of the desmosomal genes *PKP2*, *DSG2*, *DSC2*, *DSP*, and *JUP* through either our research (14,20) or commercially available testing. Family members are screened only for mutations identified in the proband. Individuals with digenic or compound heterozygous mutations were excluded.

Clinical outcomes. Clinical and demographic data were drawn from the Johns Hopkins ARVD/C Registry. Baseline data included sex, date of birth, date and type of clinical presentation, family history, and results of noninvasive and invasive studies (12-lead electrocardiogram [ECG], exercise testing, 24-h Holter monitoring, 2-dimensional transthoracic echocardiography, cardiac magnetic resonance imaging, signal averaged ECG, RV angiogram). Clinical presentation was defined as the first medical visit for a cardiac symptom related to ARVD/C. Primary outcome measures included first sustained ventricular arrhythmia (ventricular tachycardia/ventricular fibrillation [VT/VF]), onset of stage C heart failure (HF), and diagnosis of ARVD/C at last follow-up (2010 Revised Task Force Criteria [TFC]). First sustained ventricular arrhythmia was a composite measure of the occurrence of spontaneous sustained VT, aborted sudden cardiac death, or appropriate implantable cardioverter-defibrillator (ICD) intervention. In patients without an ICD, VT/VF outcome was adjudicated based on reviewing ECGs and medical records; in patients with an ICD, the device stored ECGs were reviewed for appropriateness of ICD therapy. In patients with multiple endpoints, the first event was considered the censoring event. HF was defined using the American College of Cardiology/American Heart Association heart failure staging system (22), but required both evidence of structural heart disease including RV abnormalities and symptoms directly attributed to HF, as done previously (23). Heart failure was adjudicated independently by 2 members of the study team blinded to exercise history. The diagnosis of ARVD/C was based on the presence of major and minor diagnostic criteria according to the TFC (24).

Abbreviations and Acronyms

ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy
CI = confidence interval
ECG = electrocardiogram
HF = (stage C) heart failure
ICD = implantable cardioverter-defibrillator
IQR = interquartile range
OR = odds ratio
RV = right ventricular
TFC = 2010 Revised Task Force Criteria
VT/VF = ventricular tachycardia/ventricular fibrillation

Exercise interviews. Structured telephone or in-person interviews were conducted by 3 genetic counselors and 1 physician. During the interview, we prompted participants to list regular exercise done for leisure/recreation, work, and transportation since 10 years of age. Two aspects of each regularly performed exercise were collected: intensity and duration. Intensity of each activity was rated as light, moderate, or vigorous using language and definitions from the Multi-Ethnic Study of Atherosclerosis Typical Week Physical Activity Survey (25). To determine duration, participants were asked between which ages they had participated in each exercise activity. Then the participant was asked on average how many months of the year, days of the month, and hours per day that he or she did this activity at each relevant intensity level. Responses were transcribed on pre-prepared data collection sheets.

Exercise history analysis. In this study, we evaluated the influence of 2 aspects of exercise history: 1) aerobic intensity, defined as participation in vigorous-intensity endurance (aerobic) athletics; and 2) duration, defined as annual hours of all regular exercise. Endurance athletics were sports with a high dynamic demand (>70% maximum O_2), as defined by the 36th Bethesda Conference Classification of Sports (Task Force 8) (26), done for at least 50 h/year at vigorous intensity. Vigorous intensity had been self-rated during the

interview as described. Individuals meeting these criteria are referred to as endurance athletes throughout this paper. For exercise duration, average hours per year of all regular exercise were calculated for each participant both before and after clinical presentation.

Statistical analysis. Categorical variables are reported as frequency (%) and compared between groups by the chi-square or Fisher exact test. Continuous variables are summarized as either mean ± SD or median (interquartile range [IQR]) and compared across groups using a Student *t* or Mann-Whitney *U* test as appropriate. Median hours per year of exercise before and after presentation were compared by the Wilcoxon signed rank test. The likelihood of meeting TFC was estimated using multivariate logistic regression. Cumulative freedom from the composite arrhythmic outcome and HF outcome were determined by the Kaplan-Meier method. Differences in survival among groups were evaluated with a log-rank test. A p value <0.05 was considered significant. SPSS version 20.0 statistical software (SPSS Inc., Chicago, Illinois) was used.

Results

Population. Of 134 mutation carriers from 68 families invited to participate, 89 (66%) were interviewed. There was no difference in response rate by sex or whether an individual was a proband or family member. Two interviews were excluded from analysis, one in which a minor and her mother gave discordant responses and a second in which the participant was unable to attend to interview questions due to distress related to a change in her personal life.

The final study population included 87 individuals (46 male) from 51 families with a single copy of a pathogenic ARVD/C-associated desmosomal mutation (76 *PKP2*, 7 *DSG2*, 3 *DSP*, 1 *DSC2*) (Online Table 1). Age at interview ranged from 11 to 88 years (mean, 44 ± 18 years). Two individuals were of Asian ancestry. The remaining subjects were white. Approximately two thirds (57 of 87, 66%) met TFC and 45% (39 of 87) had experienced at least 1 life-threatening VT/VF episode at last clinical follow-up. In 10 (12%), HF had developed at last follow-up, and 2 (2%) had undergone cardiac transplantation, both for VT. Participants had 14 first-degree relatives who had died of ARVD/C-associated arrhythmias (13) or heart failure (1). Additional clinical characteristics are shown in Table 1.

Exercise history. Overall, 56 of 87 (64%) participants had been endurance athletes. The most common endurance sports were long- and middle-distance running (37 of 56, 66%), basketball (27 of 56, 48%), soccer (14 of 56, 25%), and competitive swimming (8 of 56, 14%). Other qualifying sports included distance cycling (5), lacrosse/field hockey (5), tennis/squash (4), rowing (1), and cross-country skiing (1). Some endurance athletes competed in multiple endurance sports. The median age at starting a first endurance sport was 14 years (range: 10 to 45 years; IQR: 10 to 18 years). Males were not significantly more likely to have been endurance athletes. There was no significant difference in the age at interview between endurance athletes and nonathletes.

Interviewees participated in a median of 284 h/year (range: 0 to 2,657 h/year; IQR: 135 to 509 h/year) of regular exercise of all types before presentation and a median 155 h/year (range: 0 to 1,658 h/year; IQR: 17 to 314 h/year) afterward ($p < 0.001$). Most individuals (61 of 87, 70%) decreased exercise after presentation, with no difference between athletes and nonathletes. Endurance athletes did more annual exercise before presentation (median: 404 h/year; IQR: 210 to 684 h/year) than nonathletes (median: 135 h/year; IQR: 38 to 243 h/year) ($p < 0.001$). There was no significant difference in annual exercise after clinical presentation between endurance athletes and nonathletes.

Influence of participation in endurance athletics on clinical course. As shown in Table 1, mutation carriers who were endurance athletes had a different presentation and clinical course than nonathletes. Endurance athletes were more likely to be probands (50% athletes vs. 26% nonathletes, $p = 0.028$) and to have cardiac symptoms (VT/VF, syncope, presyncope, palpitations, or chest pain) at presentation (68% athletes vs. 29% nonathletes, $p = 0.001$) and during follow-up (75% athletes years vs. 32% nonathletes, $p < 0.001$). Symptoms developed in endurance athletes at a younger age than nonathletes (30.1 ± 13.0 years vs. 40.6 ± 21.1 years, $p = 0.05$). Lifetime arrhythmic risk was higher among endurance athletes. Overall, 31 endurance athletes (55%) had experienced at least 1 sustained VT/VF at last follow-up compared with 8 (26%) nonathletes ($p = 0.008$) (Table 1). As shown in Figure 1A, cumulative lifetime event-free survival from VT/VF was significantly lower in endurance athletes ($p = 0.013$).

ARVD/C diagnosis. We evaluated the influence of both participation in endurance athletics and average annual duration of all exercise on likelihood of meeting diagnostic criteria (TFC) at last follow-up. Endurance athletes were more likely to meet both overall TFC (82% vs. 35%, $p < 0.001$) (Fig. 2) and criteria for each of the domains of the TFC (structural abnormality/dysfunction, repolarization abnormalities, depolarization abnormalities, arrhythmias) except family history/genetics (Table 1). The absence of a relationship with genetics is consistent with the entry criteria for this study requiring that all subjects have a pathogenic desmosomal mutation.

The amount of annual exercise was also positively correlated with an increasing likelihood of meeting TFC at last follow-up. Among those who participated in the fewest (lowest quartile) hours per year of exercise at presentation, 6 of 21 (29%) met TFC compared with 14 (64%) in the second quartile, 22 (82%) in the third quartile, and 19 (86%) among those in the top quartile ($p < 0.001$) (Fig. 2). Controlling for sex and age at last clinical follow-up, compared with those who did the least (lowest quartile) exercise, those in the second (odds ratio [OR]: 6.64; 95% confidence interval [CI]: 1.49 to 29.5, $p = 0.013$), third (OR: 16.7; 95% CI: 3.21 to 86.9, $p = 0.001$), and top (OR: 25.3; 95% CI: 4.21 to 153, $p < 0.0001$) quartiles of exercise per year before presentation were increasingly likely to meet TFC at the last follow-up.

Table 1 Association Between Clinical Characteristics and Participation in Endurance Athletics

	Overall (N = 87)	Endurance Athlete (n = 56)	Not Endurance Athlete (n = 31)	p Value
Male	46 (53)	32 (57)	14 (45)	NS
Proband	36 (41)	28 (50)	8 (26)	0.028
Age at interview, yrs	44 ± 18	42 ± 15	45 ± 22	NS
Presentation				
Age at clinical presentation, yrs	35 ± 17	32 ± 14	38 ± 20	NS
Type of presentation				
Symptomatic presentation	44 (51)	36 (64)	8 (26)	0.002
Resuscitated SCD	3 (3)	2(4)	1 (3)	
Asymptomatic	40 (46)	18 (45)	22 (71)	
Sustained VT/VF at presentation	26 (30)	18 (32)	8 (26)	NS
Stage C HF at presentation	0 (0)	0(0)	0(0)	NS
Age at first symptom, yrs	32 ± 15	30 ± 13	41 ± 21	0.05
Task Force Criteria at LFU, yes	56 (64)	46 (82)	11 (35)	<0.001
Structural alterations	30 (35) major 10 (12) minor	24 (44) major 8 (15) minor	6 (20) major 2 (7) minor	0.021
Repolarization abnormalities*	43 (50) major 15 (17) minor	34 (62) major 12 (22) minor	9 (29) major 3 (10) minor	<0.001
Depolarization abnormalities*	5 (6) major 35 (41) minor	5 (9) major 28 (51) minor	0 (0) major 7 (23) minor	0.003
Arrhythmias†	17 (21) major 30 (36) minor	13 (24) major 24 (44) minor	4 (14) major 6 (21) minor	0.011
Family history/genetics	87 (100) major	56 (100) major	31 (100) major	1.000
VT/VF at LFU (yes)	39 (45)	31 (55)	8 (26)	0.008
Type of arrhythmic event				
Sustained VT	29 (74)	22 (71)	7 (88)	NS
Aborted SCD/resuscitated SCD	3 (18)	2 (6)	1 (12)	
Appropriate ICD therapy	7 (8)	7 (23)	0 (0)	
Activity at first VT/VF				
Exercise	25 (64)	21 (68)	4 (50)	NS
Daily activity	10 (26)	6 (19)	4 (50)	
At rest	4 (10)	4 (13)	0 (0)	
Age first VT/VF, yrs	33 ± 12	32 ± 11	37 ± 16	NS
Stage C heart failure at LFU (yes)	10 (12)	10 (18)	0 (0)	0.012
Transplant at LFU	2 (2)	2 (4)	0 (0)	NS

Values are n (%) or mean ± SD. *One 11-year-old participant had no electrocardiogram available for review. Therefore, only 86 individuals were characterized for repolarization and depolarization abnormalities. †Three individuals had Holter monitoring performed, noting that premature ventricular complexes were present, but no count was provided, so these individuals were not included in the arrhythmias category.

HF = heart failure; LFU = last clinical follow-up; SCD = sudden cardiac death; VT/VF = composite measure of the occurrence of spontaneous sustained ventricular tachycardia/ventricular fibrillation, aborted SCD, SCD, or appropriate implantable cardioverter-defibrillator intervention for a ventricular arrhythmia.

Heart failure. We also evaluated the influence of both intensity (participation in endurance athletics) and duration (hours per year of all exercise) on the incidence of HF. None of our population had HF at presentation; HF developed in 12% during follow-up. Mean age at onset of HF was 42 ± 18 years (range: 19 to 74 years). HF developed only in endurance athletes (18% vs. 0%, p = 0.012). As shown in Figure 1B, cumulative lifetime survival free from HF onset was significantly lower among endurance athletes (p = 0.004).

HF was more likely to develop in participants who did more average annual exercise before presentation (8 of 44, 18% more hours of exercise vs. 2 of 43, 5% fewer hours, p = 0.048). Hours of annual exercise after presentation, sex, and age at presentation had no association with the development of HF.

Arrhythmic outcome. The relationship between exercise and development of a first sustained ventricular arrhythmia (VT/VF) during follow-up was evaluated in the subset of 61 subjects (70%) who did not present clinically with VT/VF. Thirty-eight of these 61 were endurance athletes (62%). This group of 61 decreased exercise from a median 242 h/year before presentation (range: 0 to 2,657 h/year; IQR: 119 to 516 h/year) to 212 h/year (range: 0 to 1,658 h/year; IQR: 16 to 425 h/year) afterward (p = 0.021).

Over a mean follow-up of 8.4 ± 6.7 years, 13 of these 61 subjects (21%) experienced a first VT/VF, including a resuscitated sudden cardiac arrest in 1 individual. The mean age at first VT/VF was 32.3 ± 7.8 years (range: 22 to 45 years). The mean VT cycle length was 282 ms (range: 240 to 394 ms). Events disproportionately occurred in younger individuals (p = 0.018). There was no difference by sex. Thirteen of the 38 endurance athletes (34%) experienced a first VT/VF during follow-up compared with none of the 23 nonathletes (0%) (p = 0.002).

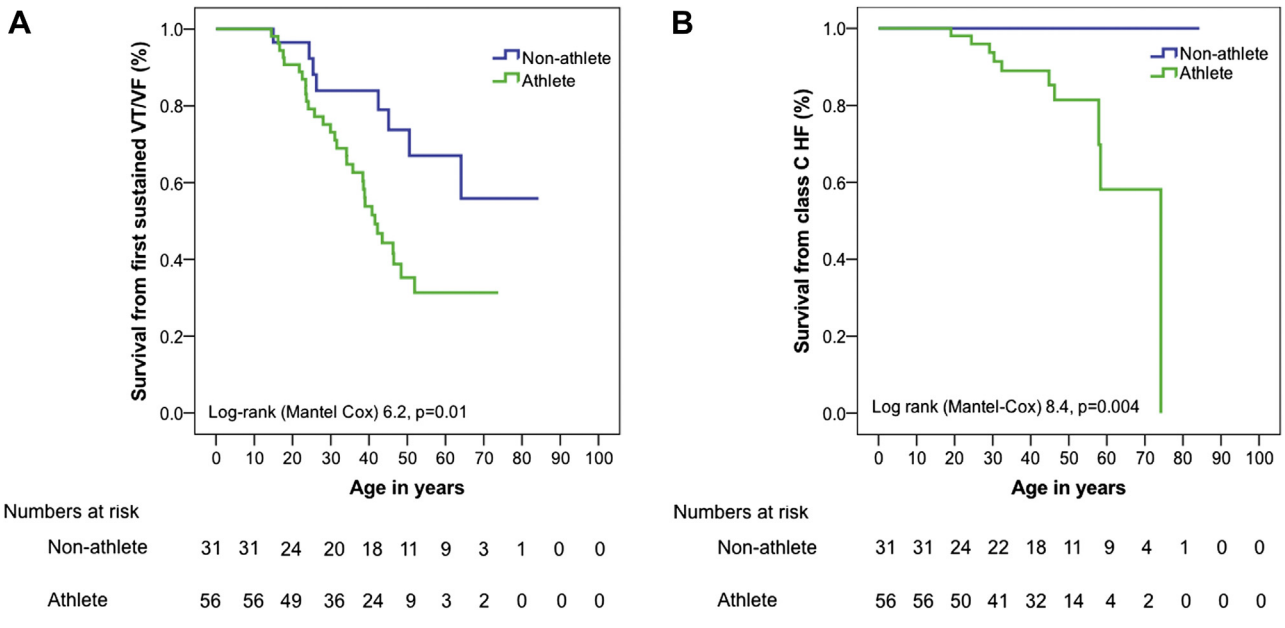

Figure 1 **Cumulative Lifetime Survival Free from Sustained Ventricular Arrhythmia and Class C Heart Failure**

Cumulative lifetime survival free of sustained ventricular arrhythmias **(A)** and stage C heart failure **(B)** stratified by participation in endurance athletics. Event-free survival from sustained arrhythmias and stage C heart failure is significantly lower among endurance athletes. HF = heart failure; VT/VF = ventricular tachycardia/ventricular fibrillation (sustained ventricular arrhythmia).

Duration of annual exercise (all types of regular exercise) both before and after clinical presentation was also associated with a first VT/VF. In those who did the most (top quartile) hours of exercise annually before presentation (>516 h/year), VT/VF was disproportionately likely to develop (7 of 16 [43%] top quartile vs. 6 of 45 [13%] bottom 3 quartiles, p = 0.01). VT/VF was also more likely to develop in patients who did the most exercise (>425 h/year) after clinical presentation during follow-up (8 of 15, 53% top quartile vs. 5 of 46, 11% in bottom 3 quartiles, p < 0.001). Overall, event-free survival free from a first VT/VF during follow-up was significantly lower among endurance athletes (Fig. 3A) (p = 0.012) and among those who exercised most before (Fig. 3B) (p = 0.036) and after (Fig. 3C) (p = 0.005) clinical presentation.

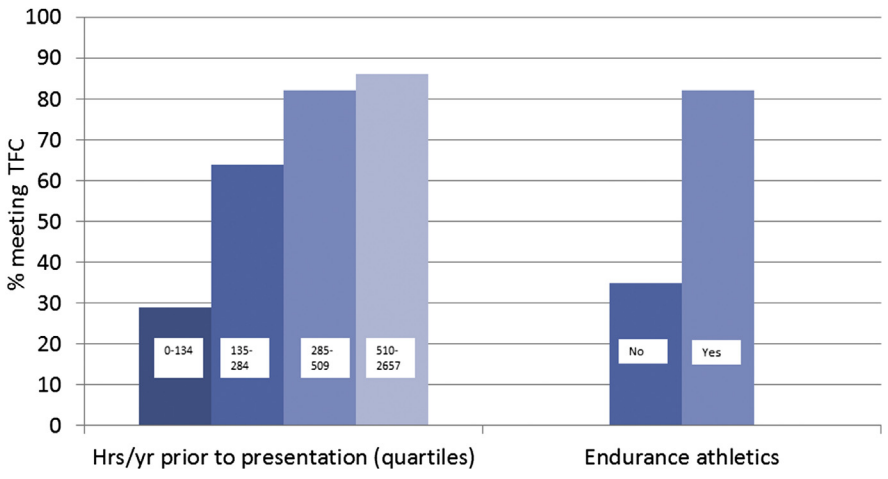

Figure 2 **Likelihood of ARVD/C Diagnosis Is Associated With Exercise History**

Likelihood of meeting arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) diagnostic criteria at last follow-up is associated with increasing hours per year of exercise (p < 0.001) and participation in endurance athletics (p < 0.001). TFC = 2010 Task Force Criteria.

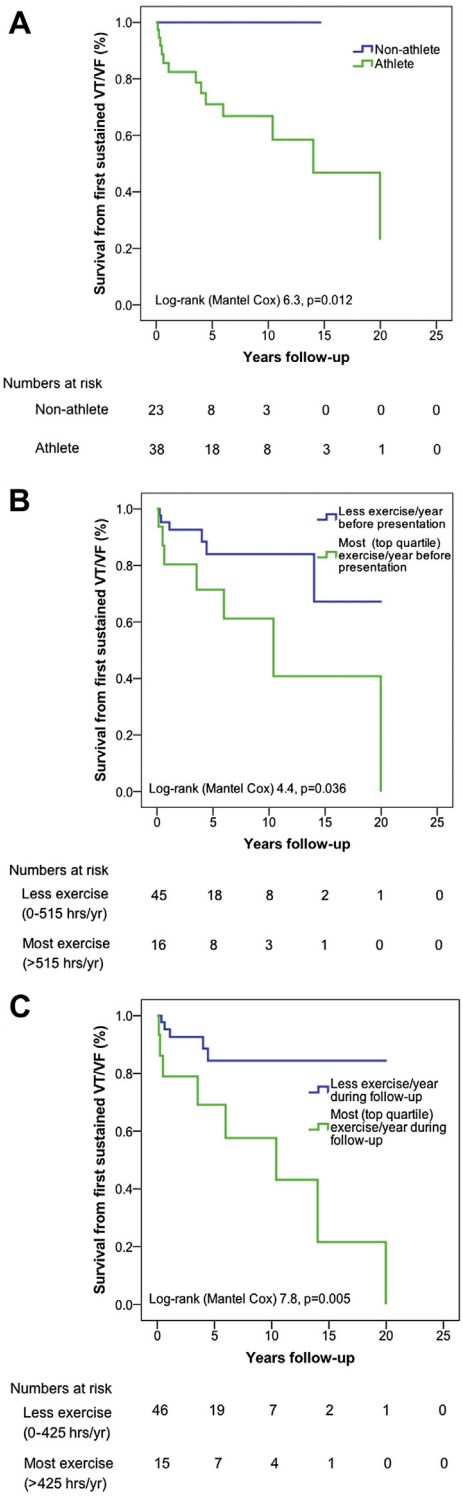

Figure 3 **Cumulative Survival Free from a First Sustained Ventricular Arrhythmia During Follow-up**

Among 61 subjects who did not present clinically with a sustained ventricular arrhythmia, survival free from a first sustained ventricular arrhythmia during follow-up was significantly lower among endurance athletes **(A)** and those doing the most (top quartile hours per year) exercise before **(B)** and after **(C)** clinical presentation. VT/VF = ventricular tachycardia/ventricular fibrillation (sustained ventricular arrhythmia).

Influence of change in exercise duration on arrhythmic outcome. The impact of changing duration of annual exercise on the likelihood of developing a first VT/VF was also evaluated in these 61 participants. We examined whether patients were in the top quartile for hours of annual exercise (all types/intensity levels) before and after presentation. As shown in Figure 4, first VT/VF events occurred disproportionately more frequently in individuals who did the most (top quartile) exercise both before and after clinical presentation ($p = 0.007$). Among 16 individuals who did the most (top quartile) exercise before presentation, 6 of 8 (75%) who continued do top quartile exercise after presentation had a first VT/VF in follow-up compared with only 1 of 8 (12%) who decreased exercise after presentation ($p = 0.04$) (Fig. 4). Among 45 individuals who were in the lowest 3 quartiles of hours of exercise before clinical presentation, in 4 of 38 (10%) who continued lower levels of exercise, a first arrhythmia developed compared with 2 of 7 (29%) who increased exercise to the top quartile level (p = NS).

Discussion

Main findings. The results of this study reveal for the first time in humans that the amount and intensity of exercise increases the likelihood of diagnosis, ventricular arrhythmias, and the development of HF among ARVD/C desmosomal mutation carriers. Furthermore, the results suggest that reducing exercise duration may alter the clinical course of ARVD/C.

Relationship between exercise and ARVD/C. During the 30 years since publication of the first major reports describing ARVD/C (1,27), threads of evidence have emerged suggesting that exercise influences both the development of ARVD/C and its associated arrhythmic risk. One of the first to highlight this important link was a study of sudden cardiac death in the Veneto region of Italy, which found that young athletes had a 5-fold higher risk of dying of ARVD/C compared with nonathletes (6). Consistent with this observation, implementation of a pre-participation screening program resulted in a sharp decline in such deaths (28). The next major line of evidence supporting a link between ARVD/C and exercise was the landmark discovery that a mutation in the desmosomal protein plakoglobin (*JUP*) caused an unusual variant of ARVD/C (12) and subsequent discovery of ARVD/C-associated mutations in other desmosomal genes (9–11,13). The cardiac desmosome provides a mechanical connection between myocytes. A third line of evidence concerns the body of research on the differential response of the right ventricle and left ventricle to exercise (29,30). Compared with rest, RV wall stress at peak exercise in athletes increases by 170% compared with only a 23% increase in left ventricular wall stress. Intense endurance exercise causes acute dysfunction of the right ventricle, but not the left ventricle (30). The right ventricle of individuals with desmosomal mutations may be particularly vulnerable to pathological remodeling in response to

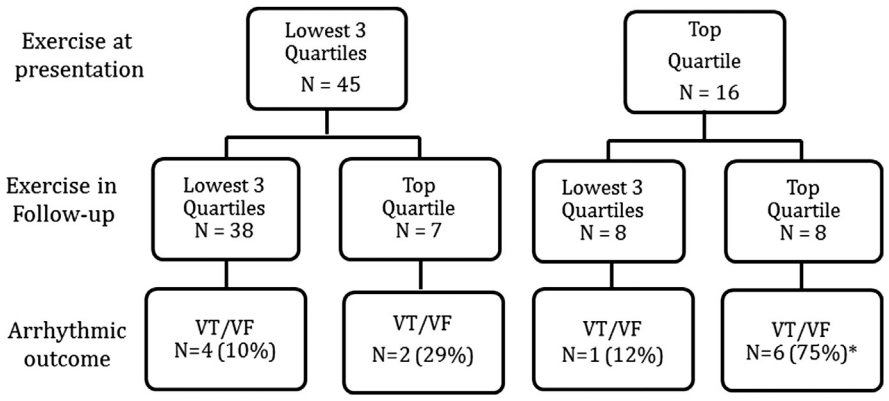

Figure 4 **Change in Exercise After Clinical Presentation Influences Likelihood of the Development of a First Sustained Ventricular Arrhythmia**

Among 61 subjects who did not present clinically with a sustained ventricular arrhythmia, in those who did the most (top quartile) exercise both before and after clinical presentation, a sustained ventricular arrhythmia during follow-up ($p = 0.007$) was most likely to develop. Among those doing the most (top quartile) exercise before presentation, in those who continued to do top quartile exercise a first sustained ventricular arrhythmia was more likely to develop than in those who reduced exercise ($p = 0.04$). VT/VF = ventricular tachycardia/ventricular fibrillation (sustained ventricular arrhythmia).

exercise. In these patients, endurance exercise may facilitate myocyte uncoupling at defective desmosomes leading to inflammation, fibrosis, adipocytosis, and direct impairment of electrical coupling (16). This sets the stage for arrhythmias, worsening structural involvement, and HF. A final thread of evidence supporting a causative link between exercise and ARVD/C was established by Kirchof et al. (18) using a plakoglobin-deficient mouse model. In this model, endurance exercise accelerated the development of RV dysfunction and ventricular arrhythmias.

Impact of exercise on the clinical course of ARVD/C-associated mutation carriers. This study tested the hypothesis that exercise is an important environmental factor in the development of ARVD/C among mutation carriers and influences outcomes of ARVD/C patients. The foundational work described earlier provided circumstantial evidence that exercise influences penetrance, arrhythmic risk, and progression to HF, but there have been no systematic studies in humans. Furthermore, the seminal work by Corrado et al. (6) assumed that "sports per se is not a cause of the increased mortality, rather, it acts as a trigger for cardiac arrest in the presence of underlying cardiovascular disease…" and therefore that the incidence of ARVD/C is the same in the athletic and nonathletic populations. With new appreciation of the pathogenesis of ARVD/C and the incomplete penetrance of disease, it is likely instead that the underlying proportion of athletes with disease may be substantially greater. Furthermore, the Corrado et al. study relied on autopsy cases, providing limited guidance to physicians treating mildly affected patients and unaffected mutation carriers. A strength of our study is the inclusion of not just ARVD/C patients, but also their at-risk relatives with desmosomal mutations. Furthermore, we found endurance athletes with desmosomal mutations not only were more likely be at risk of life-threatening arrhythmias, but also at increased risk of the development of the full ARVD/C phenotype and HF. We also examined for the first time the relationship between quantity of total exercise and outcomes of patients. We found that the duration of annual exercise is positively associated with increasing risk of meeting diagnostic criteria, of a first sustained arrhythmia, and of HF. Furthermore, among individuals doing the most average annual exercise at presentation, reducing exercise duration appeared to reduce arrhythmic risk. Our findings support the conclusion that exercise negatively influences cardiac structure and function in at least a proportion of ARVD/C-associated mutation carriers.

Study limitations. Our retrospective interview–based exercise history collection may limit interpretation of study findings. Recall of athletic participation may have been inaccurate in a way that varied across subpopulations (recall bias). Additionally, participants may have deliberately altered their responses in a way that they considered desirable (social desirability). We limited the influence of both by defining athletic history in broad categories (e.g., endurance athletics participation vs. not, quartiles of average exercise per year). Additionally, a portion of our study assessed the risk of the development of events after clinical presentation (Fig. 3), requiring a shorter period of recall.

Our study population also may limit findings. First, although one third of ARVD/C patients present with sudden death, these individuals were not included in the study. The influence of exercise in this subpopulation may differ. Additionally, this study only included desmosomal mutation carriers; thus, the results may have limited implications for ARVD/C patients who do not have a desmosomal mutation. Likewise, we anticipate that carriers of >1 copy of a desmosomal mutation may have a worse response

to exercise, but our study cannot address that question. Third, those interviewed were all participants in a research registry run by a tertiary care center, creating a potential selection bias. Additionally, because our 87 interviewees were members of 51 families, there was nonindependence of observations within families. Finally, our sample size was limited with regard to our investigation of the influence of risk reduction after exercise reduction.

Conclusions and Clinical Recommendations

The results of this study, interpreted within the context of previous studies, provide strong evidence demonstrating an important link between exercise and the development and outcomes of ARVD/C. We demonstrated for the first time in humans that both participation in vigorous endurance (aerobic) athletics and greater duration of annual exercise of all types are associated with an increased likelihood of an ARVD/C diagnosis, ventricular arrhythmias, and HF among a large cohort of patients with desmosomal mutations. These data, combined with our 15-year experience as a referral center for patients with ARVD/C, lead us to conclude that restriction of frequent and endurance exercise is important for these patients and modification of exercise at clinical presentation may change outcomes.

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Key Words: arrhythmogenic right ventricular dysplasia ■ cardiomyopathy ■ exercise ■ heart failure ■ penetrance ■ ventricular arrhythmias.

APPENDIX

For a supplemental table, please see the online version of this article.