JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2025

ORIGINAL RESEARCH

Disease Progression in Exercise-Induced Arrhythmogenic Cardiomyopathy Compared With Arrhythmogenic Right Ventricular Cardiomyopathy

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ABSTRACT

BACKGROUND Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inheritable heart disease, whereas exercise-induced arrhythmogenic cardiomyopathy (EiAC) is a proposed acquired similar phenotype in athletes. The differences in disease progression between these entities are not well understood.

OBJECTIVES This study aims to assess structural, functional, and arrhythmic disease progression in EiAC compared with ARVC.

METHODS This longitudinal cohort study included EiAC patients who were competitive endurance athletes (>24 MET-hours/week for >6 consecutive years) referred due to ventricular arrhythmias (VA), without inherited or genetic factors or other evident causes, and genotype-positive ARVC patients with a definite diagnosis and their genotype-positive family members for comparison. Disease progression was assessed by repeated echocardiographic examinations and incident VA during long-term follow-up.

RESULTS The authors included 125 ARVC patients (61 women, aged 38 ± 17 years) and 41 EiAC patients (6 women, aged 45 ± 13 years) and followed them for 96 months (Q1-Q3: 73-132 months) and 82 months (Q1-Q3: 50-118 months), respectively. The authors analyzed 730 echocardiographic examinations (538 ARVC, 192 EiAC). Right ventricular (RV) structure and function remained stable in EiAC patients, whereas those in ARVC patients deteriorated during follow-up. The 5-year and 10-year cumulative incidences of VA were similar between EiAC and ARVC patients.

CONCLUSIONS RV structure and function deteriorated in ARVC patients but remained stable in EiAC patients during follow-up. The incidence of VA was high in both populations. These results indicate that EiAC patients should be followed closely over time regardless of structural and functional progression. (JACC Cardiovasc Imaging. 2025;■:■–■)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 16, 2024; accepted March 13, 2025.

ISSN 1936-878X https://doi.org/10.1016/j.jcmg.2025.03.018

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

EiAC = exercise-induced arrhythmogenic cardiomyopathy

LV = left ventricular

RV = right ventricular

RVOT = right ventricular outflow tract

VA = ventricular arrhythmia

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inheritable heart disease caused by genetic variants encoding cardiac desmosomes, leading to impaired intercellular communication and loss of structural integrity. The disease is clinically characterized by life-threatening ventricular arrhythmias (VA), structural and functional ventricular impairment, and histologically by fibrofatty myocardial replacement.[1]

Several independent groups have proposed an acquired exercise-induced clinical entity resembling ARVC.[2-7] However, the reports describe slightly different populations as a result of inconsistent definitions and the absence of a clear consensus regarding the clinical condition. These patients are negative for the so-far-known genetic desmosomal variants, and the understanding is based on the hypothesis of hemodynamic forces causing disruption of the intercellular matrix and high-intensity exercise challenging the "desmosomal reserve."[8,9] The understanding has evolved, and exercise-induced arrhythmogenic cardiomyopathy (EiAC) is now described as a syndrome characterized by myocardial damage and serious VA in susceptible athletes,[6,10,11] associated with abnormalities involving the right ventricle (RV), the left ventricle (LV), and the right ventricular outflow tract (RVOT).

The resemblance and considerable overlap between these conditions may lead to similar clinical management and decision-making strategies for affected individuals with EiAC and ARVC. However, comparisons of long-term follow-up of EiAC and ARVC are lacking.

The objectives of this study were to collect, assess, and compare data on structural and functional disease progression and incident life-threatening VA in EiAC and ARVC during long-term follow-up.

METHODS

STUDY DESIGN AND POPULATION. Patients with EiAC and ARVC who were referred for evaluation at our tertiary referral hospital between 1997 and 2019 were included in a longitudinal cohort study.

To address the proposed existence of EiAC and its various manifestations, we applied broad inclusion criteria for our EiAC cohort. 1) High activity level: this cohort comprised athletes defined as individuals with current or previous exercise levels exceeding 24 MET-hours per week for >6 consecutive years, actively participating in organized and competitive sports. 2) VA: athletes were eligible for inclusion if they presented with VA, such as premature ventricular contractions, ventricular tachycardia, or ventricular fibrillation. 3) Absence of inherited or genetic factors: Inclusion required the absence of a suggestive family history of premature cardiac disease or sudden cardiac death, as well as no known pathogenic or likely pathogenic genetic variants associated with ARVC in patients undergoing genetic testing. 4) Exclusion of significant other causes: significant underlying causes were excluded through invasive coronary angiography or noninvasive ischemia testing as clinically indicated, ruling out significant coronary artery disease. Additionally, inflammatory causes were excluded using cardiac magnetic resonance and/or positron emission tomography. Patients with cardiac shunts or moderate to severe valvular disease, as identified by echocardiographic examination, were also excluded.

ARVC patients were genotype-positive probands (the first individual in the family who were identified with and received diagnoses of the disease) with definite ARVC diagnosis according to the 2010 TFC (Task Force Criteria)[12] along with their genotype-positive family members regardless of criteria at baseline.

Patients underwent genetic testing for cardiomyopathy-associated and cardiac channelopathy-associated genetic variants by next-generation sequencing analysis (TruSight Cardio Sequencing Kit, Illumina Inc) and multiplex ligation-dependent probe amplification (MLPA, SALSA MLPA Probemix P168 ARVCPKP2). The likely pathogenic variant was evaluated according to the guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology,[13] with focus on segregation analysis and, where needed, supplementing functional studies. Patients with pathogenic (P) and likely pathogenic (LP) genetic variants were considered genotype-positive. Variants of uncertain significance (VUS) were considered genotype-negative.

The distribution of patients within the various categories in the ARVC and EiAC populations was assessed according to the 2010 TFC at the time of diagnosis.

A standardized nonvalidated questionnaire was used to assess exercise habits in both ARVC and EiAC patients (Supplemental Table 1). All patients in both groups were recommended to avoid high-intensity and competitive exercise once the diagnoses were established, but follow-up care did not include systematic monitoring of individual exercise dose.

The study was approved by the Regional Committee for Medical and Health Research Ethics of

South-Eastern Norway, in accordance with the Declaration of Helsinki. Written informed consent for inclusion in a registry was obtained from all patients.

LIFE-THREATENING VENTRICULAR ARRHYTHMIAS. Arrhythmic disease manifestations were assessed by the presence or absence of life-threatening VA, defined as sustained ventricular tachycardia (>30 s), appropriate therapy (antitachycardia pacing and shock) from an implantable cardioverter-defibrillator (ICD) or aborted cardiac arrest. The presence of life-threatening VA was assessed at baseline and consecutively during long-term follow-up. The presence of documented VA during follow-up was defined as first-time life-threatening VA in patients who were without documented life-threatening VA at baseline, and recurrent life-threatening VA in patients with already documented life-threatening VA at baseline.

ECHOCARDIOGRAPHY. Structural and functional disease progression was assessed by repeated comprehensive echocardiographic examinations (GE Vivid 7, E9, or E95, Vingmed) during long-term follow-up. Key parameters of cardiac function and structure in multiple echocardiographic examinations were analyzed off-line (EchoPac 202, GE Vingmed) by observers blinded to outcome data.[14] To minimize interobserver variability, all echocardiographic examinations for each individual patient during long-term follow-up were analyzed by the same observer.

LV function was assessed by left ventricular ejection fraction (LVEF) by biplane Simpson's method, and LV global longitudinal strain (GLS) from a 16-segment LV model. Left ventricular mechanical dispersion (LVMD) was defined as the SD of the time from the Q/R wave on the surface electrocardiogram to the peak negative strain in 16 LV segments. LV structure was assessed by left ventricular end-diastolic diameter (LVEDd). RV morphology was assessed by right ventricular fractional area change (RVFAC) and right ventricular free wall longitudinal strain (RVFWSL) from a 3-segment RV model for its function, and right ventricular basal diameter (RVD), and RVOT proximal diameter in the parasternal short-axis view for its structure.

STATISTICAL ANALYSES. Values were presented as mean ± SD, median (Q1-Q3), or frequency with percentages, and compared by Student's *t* test, Fisher exact test, or Mann-Whitney *U* test as appropriate.

Disease progression during long-term follow-up was evaluated and compared using linear mixed model regression with random intercept and random slope, and unstructured covariance structure. The trajectories of parameters of myocardial structure and function were visualized using fit plots with 95% CIs.

Kaplan-Meier curves with 95% CIs were used to visualize event-free survival over time. Additionally, the cumulative number of events at 5 and 10 years is presented in tabular format to provide a detailed overview of estimated event occurrence at these time points.

Sensitivity analyses were performed comparing EiAC patients with ARVC patients who met the 2010 TFC criteria for a definite diagnosis in both cohorts. Additionally, analyses were conducted for patients in both cohorts who presented with life-threatening VA at baseline.

Two-sided values of $P < 0.05$ were considered significant. All analyzes were performed in Stata SE 17.0 (StataCorp).

RESULTS

STUDY POPULATION. One hundred twenty-five ARVC patients (34% probands) and 41 EiAC patients were followed for 96 months (Q1-Q3: 73-132 months) and 82 months (Q1-Q3: 50-118 months), respectively. EiAC patients were older, were more often male, and had considerably higher exercise doses than ARVC patients (3,686 MET hours/year vs 728 MET hours/year; $P < 0.001$) (**Table 1**).

A total of 30 (73%) EiAC patients consented to genetic testing. Of the remaining 11, 6 had no clinical indication for testing, and 4 declined to undergo testing. Of the 30 tests conducted, results were unavailable for 2 individuals. No P/LP genetic variants were identified in any of the evaluated genes associated with cardiomyopathy or channelopathy. Furthermore, no VUS were identified in the 6 previously reported genes with strong evidence of association to ARVC disease.[15]

In the ARVC population, 52% fulfilled a definite diagnosis, and 21% had a borderline diagnosis, whereas in the EiAC population, 34% fulfilled a definite diagnosis and 12% had a borderline diagnosis according to the 2010 TFC (Supplemental Table 2).

MORPHOLOGIC DISEASE PROGRESSION. Key parameters from 730 echocardiographic examinations (538 ARVC and 192 EiAC) were assessed. At baseline, both EiAC and ARVC patients had RV dilatation, which was more severe in EiAC patients (**Table 1**). RV function was preserved in both EiAC and ARVC patients, whereas LV function was distinctly impaired only in EiAC patients (**Table 1**).

Patients with EiAC showed no evidence of RV structural or functional disease progression during

TABLE 1 Baseline Characteristics and Key Echocardiographic Parameters

	EiAC (n = 41)	ARVC (n = 125)	*P* Value
Characteristics			
Age, y	45 ± 13	38 ± 17	0.023
Height, cm	183 ± 8	174 ± 11	<0.001
Weight, kg	85 ± 14	75 ± 17	<0.001
BMI, kg/m^2	25 ± 3	25 ± 4	0.490
BSA, m^2	2.1 ± 0.2	1.9 ± 0.3	0.001
Female	6 (15)	61 (49)	<0.001
Genetic variants			
PKP2		109 (87)	NA
DSP		7	NA
DSG2		8	NA
CDH2		1	NA
Probands		42 (34)	NA
Intensity, MET	9 (8.5-10)	6 (5-8)	<0.001
Exercise dose, MET-h/y (IQR)	3,686 (2,080-5,294)	728 (520-1,872)	<0.001
Life-threatening VA	10 (24)	33 (26)	1.000
Medication			
β-blockers	27	50	0.006
Other medications (flecainide, amiodarone, calcium channel blockers)	7	14	0.417
Key echocardiographic parameters			
RVFAC, %	39 ± 8	40 ± 11	0.579
RVFWSL, %	−22.6 ± 4.2	−20.8 ± 5.7	0.172
RVOT, mm	39 ± 6	35 ± 9	0.018
RVD, mm	48 ± 7	41 ± 9	<0.001
LVEF, %	55 ± 4	57 ± 8	0.128
LVGLS, %	−15.2 ± 2.7	−18.3 ± 4.9	0.010
LVMD, ms	48.7 ± 19.5	50.2 ± 20	0.758

Values are mean ± SD, median (Q1-Q3), or n (%), unless otherwise indicated. Values are compared by unpaired Student's *t* test, Mann-Whitney *U* test or Fischer exact test as appropriate.

ARVC = arrhythmogenic right ventricular cardiomyopathy; BMI = body mass index; BSA = body surface area; CDH2 = cadherin-2; DSG2 = desmoglein-2; DSP = desmoplakin; EiAC = exercise-induced arrhythmogenic cardiomyopathy; LVEF = left ventricular ejection fraction; LVGLS = left ventricular global longitudinal strain; LVMD = left ventricular mechanical dispersion; PKP2 = plakophilin-2; RVD = right ventricular diameter; RVFAC = right ventricular fractional area change; RVFWSL = right ventricular free wall longitudinal strain; RVOT = right ventricular outflow tract; VA = ventricular arrhythmia.

long-term follow-up (yearly progression rate: RVOT +0.02 mm; P = 0.892; RVD +0.14 mm; P = 0.154; RVFAC +0.03%; P = 0.863; RVFWSL 0.13%; P = 0.108) (Table 2, Figure 1). By contrast, ARVC patients had progressive RV dilatation (yearly progression rate: RVOT +0.58 mm; P < 0.001; RVD +0.88 mm; P < 0.001) and deterioration of RV function (yearly progression rate: FAC −0.89%; P < 0.001; RVFWSL 0.16%; P = 0.006). Interaction analyses suggested higher disease progression rates for RV structure and function in ARVC patients than in EiAC patients (P for interaction: RVD <0.001, RVOT <0.001, and RVFAC <0.001; RVFWSL 0.933) (Table 2, Figure 1). There were no clear differences in LV measurements between the populations.

Sensitivity analyses of patients who met the 2010 TFC criteria for a definite diagnosis in both cohorts (14 EiAC patients vs 66 ARVC patients) were consistent with the findings in the total study populations (Table 3, Figure 2), with more balanced baseline characteristics and key echocardiographic parameters (Supplemental Table 3).

Sensitivity analyses comparing genotype-positive ARVC patients and EiAC patients, all of whom presented with life-threatening VA at baseline, were largely aligned with the findings in the total study population (Supplemental Table 4).

LIFE-THREATENING VENTRICULAR ARRHYTHMIAS. At baseline, 33 (26%) patients with ARVC and 10 (24%) patients with EiAC had experienced life-threatening VA. Recurrent life-threatening VA occurred in 21 (64%) ARVC patients and 4 (40%) EiAC patients during follow-up (P = 0.325). Among patients without previous life-threatening VA, first-time VA occurred in 12 (13%) ARVC patients and 7 (23%) EiAC patients during follow-up (P = 0.256). In total, 45 (36%) ARVC patients and 17 (41%) EiAC patients had experienced life-threatening VA by the last follow-up visit (P = 0.580).

TABLE 2 Progression Rates of Key Echocardiographic Parameters in EiAC and ARVC Patients

	EiAC		ARVC		
	Progression Rate	95% CI	Progression Rate	95% CI	*P* Value for Interaction
RVFAC, %	0.03	−0.28 to 0.33	−0.89	−1.05 to −0.73	<0.001
RVFWSL, %	0.17	−0.05 to 0.28	0.16	0.05-0.28	0.933
RVOT, mm	0.02	−0.24 to 0.28	0.58	0.46-0.71	<0.001
RVD, mm	0.14	−0.05 to 0.34	0.88	0.75-1.01	<0.001
LVEF, %	−0.05	−0.21 to 0.11	0.01	−0.13 to 0.14	0.716
LVGLS, %	−0.04	−0.13 to 0.06	0.10	0.01-0.19	0.558
LVMD, ms	−0.04	−1.73 to 1.65	1.71	0.74-2.69	0.076

The populations had different disease progression patterns during follow-up. In contrast to patients with ARVC, patients with EiAC had no evidence of RV functional or structural disease progression.

Abbreviations as in Table 1.

The 5-year and 10-year cumulative incidences of events were similar between EiAC and ARVC patients (Table 4). At 5 years, ∼22% of patients in both groups had experienced an event, with only a slight increase at 10 years. No clear differences were observed between the groups over time. Kaplan-Meier curves with 95% CIs were used to visualize event-free survival over time, illustrating that there were no clear differences between patients with EiAC and ARVC throughout the follow-up period (Figure 3).

Sensitivity analysis including only patients meeting the 2010 TFC criteria for a definite diagnosis in both cohorts were consistent with the main findings, showing no clear differences in cumulative incidence between the groups at 5 and 10 years (Table 5).

DISCUSSION

The present study showed that ARVC patients had greater structural and functional disease progression during long-term follow-up than did EiAC patients, who remained structurally and functionally unchanged. However, EiAC patients had a high incidence of life-threatening VA during long-term follow-up, with rates similar to those observed in ARVC patients. These results suggest a greater RV morphologic reserve in EiAC patients, leading to less structural and functional disease progression, but this reserve did not protect against arrhythmic events. This should motivate further studies on the arrhythmogenic mechanisms and desmosomal properties of the morphologic reserve. The findings indicate that EiAC patients may need close follow-up regardless of structural and functional disease progression because of a high long-term arrhythmic risk.

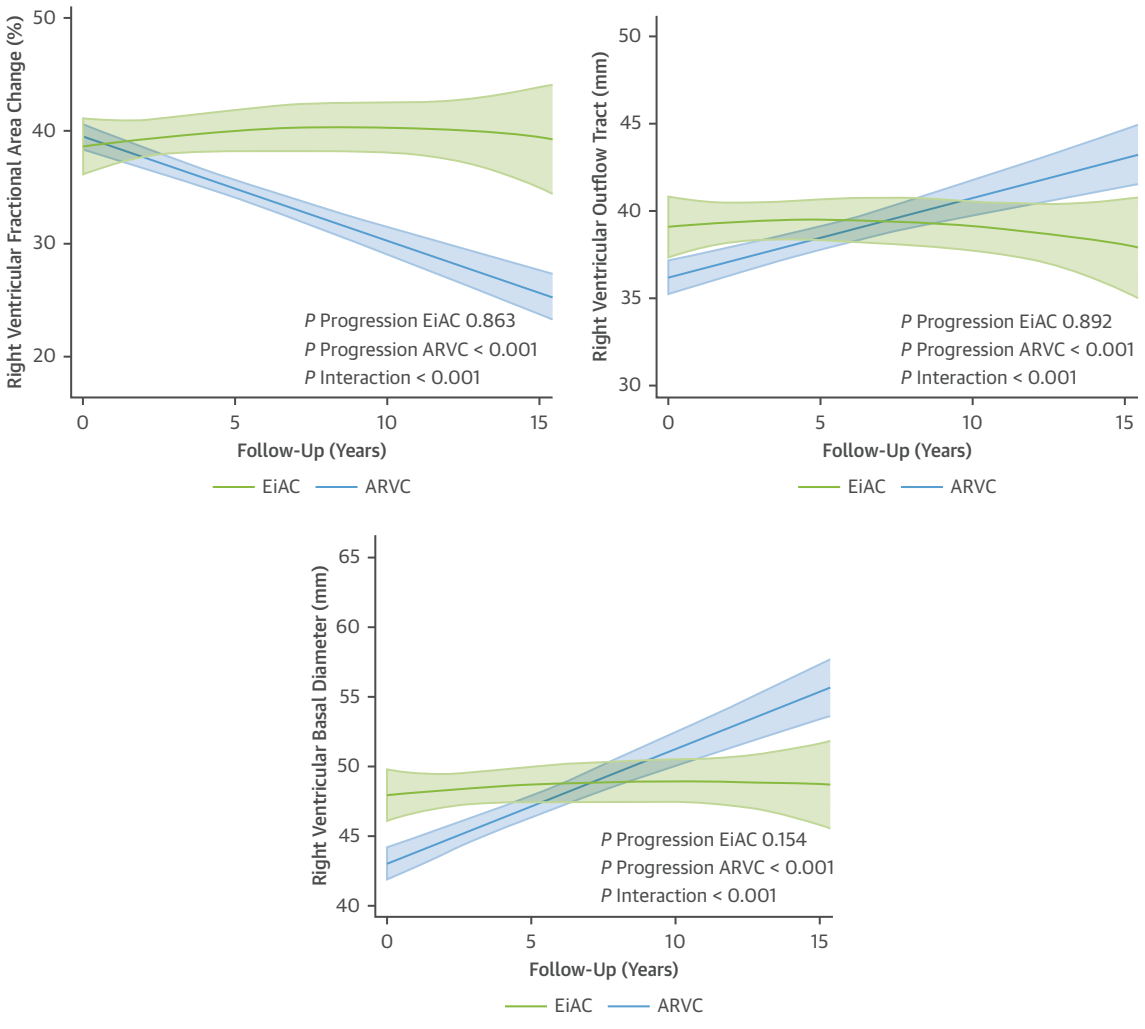
THE MORPHOLOGIC RESERVE. The findings in this study illustrate that individuals diagnosed with ARVC and EiAC show similar and overlapping clinical features at the time of initial assessment, but increasingly diverge into distinct clinical entities when followed over time.

Both EiAC and ARVC patients presented with RV dilatation, which was more profound in EiAC patients who also showed mild LV dysfunction. Interestingly, cardiac dilatation and dysfunction did not progress in EiAC patients during follow-up, whereas ARVC patients experienced RV dilatation and RV dysfunction. Our sensitivity analysis, restricted to patients with a definite diagnosis, aligned with the observations in the overall populations. This phenomenon suggests that a morphologic reserve may limit structural and functional disease progression in EiAC patients.

However, it is possible that some of the "preservation" of structure and function in the EiAC population reflects reverse remodeling attributable to detraining, which may attenuate disease progression. Nonetheless, the follow-up duration should be sufficient to account for this potential confounder.

Exercise exposure is a cornerstone in the pathophysiological mechanisms in ARVC patients, in whom the mechanical stress on defective desmosomes leads to cell disruption and consecutive fibrofatty replacement.[1] Disease progression occurs in a subset of patients independently of exercise, but particularly high-intensity exercise plays a major role in aggravating and accelerating the disease.[16-19] Similarly, exercise is proposed to be the primary causative factor in EiAC, where great doses of high-intensity exercise and persistent hemodynamic forces are suggested to induce intercellular matrix disruption.[10] However, EiAC individuals have no known desmosomal variants, but one assumes an underlying vulnerability to cardiac damage, and thereby a reduced exercise tolerability. The mechanisms are partly unknown and most likely caused by polygenetic risk factors.[9]

FIGURE 1 **Right Ventricular Disease Progression in EiAC and ARVC**



Right ventricular disease progression during long-term follow-up in EiAC (green line with 95% CI) and ARVC (blue line with 95% CI). In contrast to patients with ARVC, patients with EiAC had no evidence of RV functional or structural disease progression. ARVC = arrhythmogenic right ventricular cardiomyopathy; EiAC = exercise-induced arrhythmogenic cardiomyopathy.

This study supports the recognition of EiAC as an extension of the ARVC spectrum, but EiAC may be considered a disease variant with greater morphologic reserve compared to classical ARVC. Differences in desmosomal integrity between these entities may be a key determinant of the observed difference in the morphologic reserve.

POTENTIAL DIFFERENCES IN ARRHYTHMIA MECHANISMS. The incidence and recurrence rates of life-threatening VA in the EiAC patients were high, and were similar to those observed in ARVC patients, despite a relatively stable structural and functional condition. This points to a potential difference in the mechanisms underlying arrhythmias between EiAC and ARVC.

This finding should raise awareness about the challenges of characterizing EiAC as "exercise-induced ARVC," which may lead clinicians to apply the ARVC risk prediction calculator to these patients. Established prognostic factors central in ARVC, such as prior NSVT or PVCs, will increase the risk estimates in the model, whereas stable RV function might lead to an underestimation of the actual risk of serious arrhythmic events when patients are re-evaluated during long-term follow-up. However, the

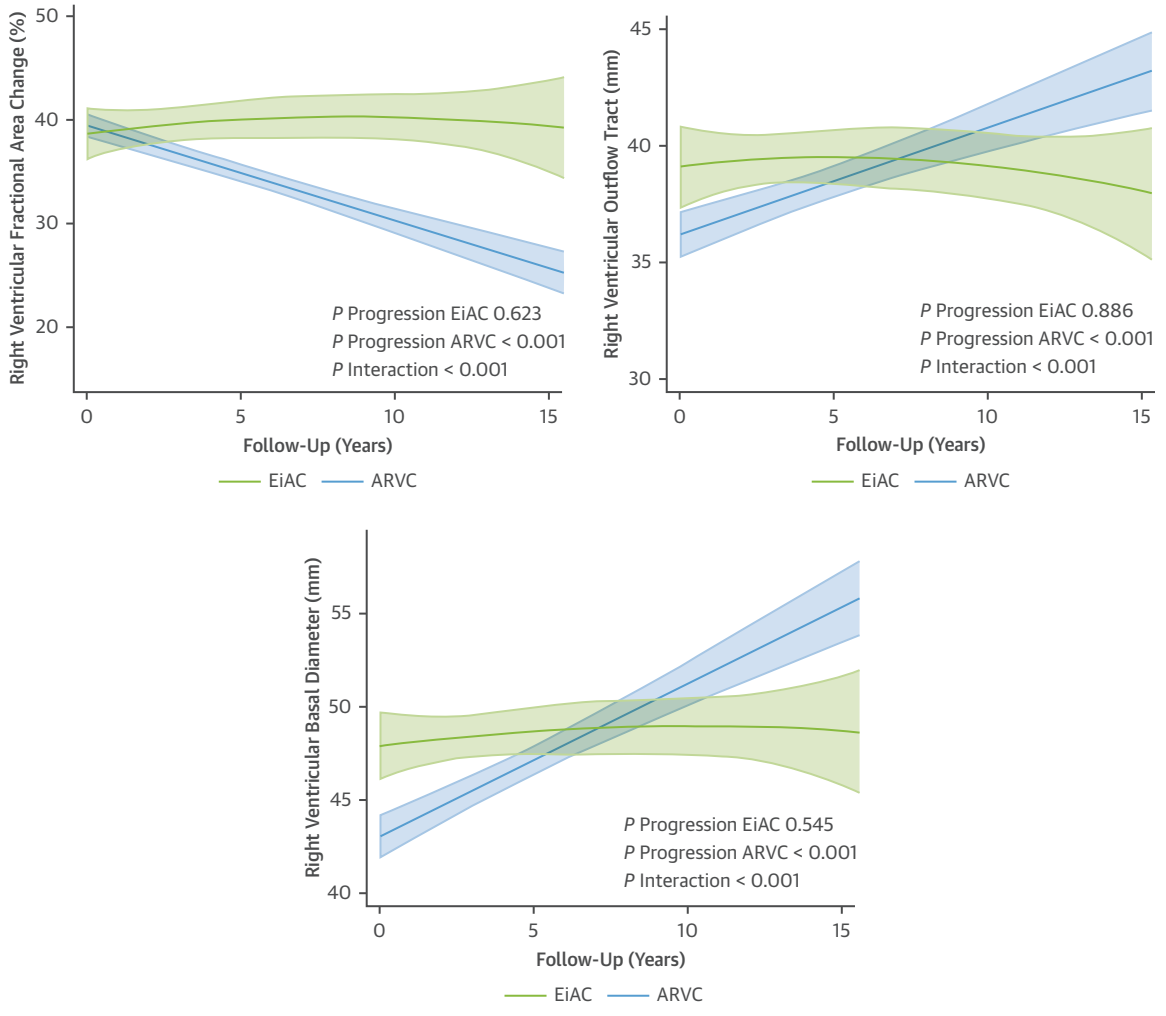
TABLE 3 Progression Rates of Key Echocardiographic Parameters in EiAC and ARVC Patients Meeting Definite 2010 TFC Criteria

	EiAC (n = 14)		ARVC (n = 66)		
	Progression Rate	95% CI	Progression Rate	95% CI	*P* Value for Interaction
RVFAC, %	−0.09	−0.46 to 0.27	−0.85	−1.08 to −0.62	<0.001
RVFWSL, %	0.08	−0.17 to 0.34	0.30	0.17-0.43	0.035
RVOT, mm	0.03	−0.33 to 0.39	0.51	0.32-0.69	<0.001
RVD, mm	0.13	−0.28 to 0.53	0.98	0.80-1.15	<0.001
LVEF, %	−0.09	−0.30 to 0.13	0.01	−0.15 to 0.18	0.767
LVGLS, %	−0.12	−0.23 to 0.001	0.07	−0.06 to 0.20	0.833
LVMD, ms	−1.25	−3.73 to 1.23	1.77	0.45-3.09	0.149

Sensitivity analyses of patients meeting the 2010 TFC criteria for a definite diagnosis in both cohorts were consistent with the total study population's findings. Unlike ARVC patients, those with EiAC showed no evidence of progression in right ventricular functional or structural disease.

TFC = Task Force Criteria; other abbreviations as in Table 1.

FIGURE 2 RV Disease Progression in EiAC and ARVC Meeting 2010 Task Force Criteria



RV disease progression during long-term follow-up in EiAC (green line with 95% CI) and ARVC (blue line with 95% CI) meeting 2010 TFC. In contrast to ARVC, patients with EiAC had no evidence of RV functional or structural disease progression. TFC = Task Force Criteria; other abbreviations as in Figure 1.

TABLE 4 Number of Events at 5 and 10 Years in All EiAC and ARVC Patients

	5-Year Cumulative Incidence (%)	10-Year Cumulative Incidence (%)
EiAC (n = 41)	9 (22.0)	10 (24.4)
ARVC (n = 125)	28 (22.4)	33 (26.4)

Cumulative incidence of events at 5 and 10 years in EiAC and ARVC patients, demonstrating comparable event rates with no clear differences over time.
Abbreviations as in Table 1.

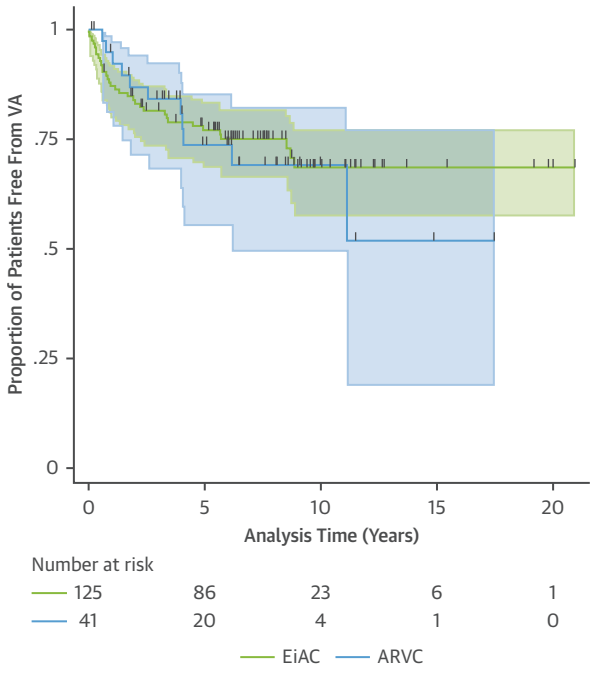
TABLE 5 Number of Events at 5 and 10 Years in EiAC and ARVC Patients Meeting Definite 2010 TFC Criteria at Baseline

	5-Year Cumulative Incidence (%)	10-Year Cumulative Incidence (%)
EiAC (n = 14)	6 (42.8)	6 (42.8)
ARVC (n = 66)	28 (42.4)	33 (50.0)

Cumulative incidence of events at 5 and 10 years in EiAC and ARVC patients who met the definite 2010 TFC criteria at baseline, demonstrating comparable event rates with no clear differences over time.
Abbreviations as in Tables 1 and 3.

calculator may not fully capture the arrhythmogenic risks in high-performance athletes, even if they meet the 2010 TFC for ARVC diagnosis, potentially leading to misclassification. It is important to note that previous validation studies on the calculator did include athletes, but these individuals all had a confirmed ARVC diagnosis, most with genetic confirmation, and exhibited a different athletic profile with significantly lower exercise levels than the high-performing athletes in the EiAC cohort.[20,21] Thus, careful consideration is needed when the ARVC risk calculator is applied in this population.

FIGURE 3 Survival Free of Life-Threatening Ventricular Arrhythmias



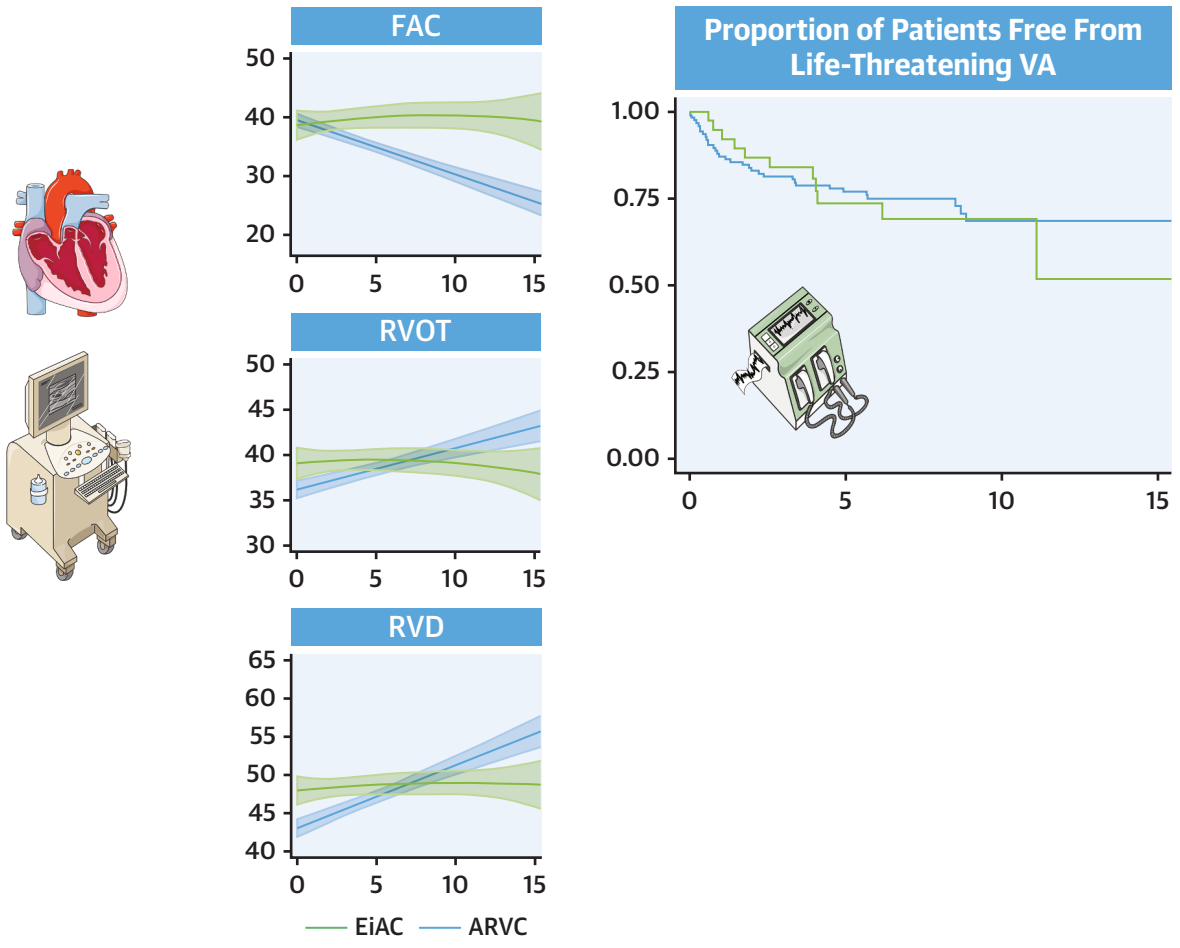
Time to first life-threatening ventricular arrhythmia during follow-up in EiAC (green line) compared with ARVC (blue line). VA = ventricular arrhythmia; other abbreviations as in Figure 1.

Our findings suggest that the morphologic reserve limiting overt disease progression may not protect against the underlying arrhythmic substrate in EiAC patients.[6,11,22] Further studies are essential to refine risk stratification in EiAC and to assess potential differences in the arrhythmia mechanisms between EiAC and ARVC.

SEX DIFFERENCES AND EXERCISE EXPOSURE. The EiAC cohort is predominantly male, consistent with previous publications, although women are not believed to be immune to the condition. The relative risk difference between the sexes cannot be fully assessed without knowing the distribution in the derivation population, which remains unknown. Previous studies have suggested that men with ARVC may experience more severe disease and higher rates of VA. However, 1 report showed that when adjusted for exercise exposure, the odds of VA did not differ between sexes, suggesting that exercise may be a significant confounder in the perceived higher risk in men.[23] This may also be relevant in EiAC, potentially explaining the male predominance in the cohort and highlighting that women should not be considered at low-risk solely based on sex, given that both sexes may have similar risk profiles.

GENETICS AND ENVIRONMENT IN EXERCISE-INDUCED CARDIAC CONDITIONS. Our evolving understanding of EiAC sheds light on the complexities of exercise-induced cardiac conditions while also underscoring the challenges in categorizing these diagnoses. The diagnostic frameworks we use are not definitive and can often lead to confusion. For example, some high-level endurance athletes may carry inherited forms of ARVC but possess an "elusive" gene, with family histories that may be obscured by variable penetrance. This complicates our understanding of the genetic contributions to these conditions. Similarly, athletes with specific pathogenic variants, such as a PKP2 variant, may exhibit phenotypes significantly influenced by their exercise dose rather than by their genetic predisposition.[24] Consequently, there is

CENTRAL ILLUSTRATION **Disease Progression in Exercise-Induced Arrhythmogenic Cardiomyopathy and Arrhythmogenic Right Ventricular Cardiomyopathy**



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ARVC and EiAC patients had similar cardiac phenotypes at presentation, but only ARVC progressed over time, suggesting a "morphologic reserve" in EiAC. Both groups had high rates of life-threatening VA, indicating that the reserve is not protective against VA in EiAC. ARVC = arrhythmogenic right ventricular cardiomyopathy; EiAC = exercise-induced arrhythmogenic cardiomyopathy; RVD = right ventricular diameter; VA = ventricular arrhythmia.

likely a substantial overlap between genetic and environmental influences that remains inadequately captured by current diagnostic frameworks. This highlights the need for a more nuanced approach to understanding and diagnosing these athletes' conditions.

STUDY LIMITATIONS. This was a longitudinal cohort study conducted at a tertiary referral single center, which inherently carries limitations that affect the generalizability of our findings. The ARVC cohort had a high prevalence of plakophilin-2 gene pathogenic variants, which resulted in a homogenous population with greater internal than external validity. The EiAC cohort was of limited size and highly selected, with the potential of several imprecisions including selection bias. The incidence of VA in both groups were high and subject to selection bias, especially in the EiAC cohort. Some patients with perceived low risk were referred to primary centers, whereas others were followed up at our center during a longer period. The small sample size limits statistical power and increases the risk of a type II error, where a true difference may exist despite lack of evidence. However, given the rarity of ARVC and EiAC, our

cohort reflects real-world data constraints. The data on exercise history and dosages were self-reported, which may have introduced reporting and recall biases. Additionally, exercise doses were not monitored during the follow-up period, and the potential for noncompliant exercise behavior could not be formally evaluated. There is a wide variety of genetic susceptibilities, and it is likely that unidentified variants not covered by genotyping could influence the EiAC phenotype and increase the risk of arrhythmia in some athletes. Echocardiographic strain parameters were analyzed post hoc on recordings that were not necessarily dedicated for that purpose, which may have had an impact on their robustness.

CONCLUSIONS

ARVC patients with desmosomal variants and genotype-negative EiAC patients had similar cardiac structural and functional phenotypes at presentation. Only ARVC patients experienced progression to RV dilatation and dysfunction during long-term follow-up, indicating a greater morphologic reserve in EiAC patients. Importantly, the incidences of life-threatening VA were high during follow-up and did not differ between the populations (**Central Illustration**). This indicates that the reserve in EiAC was not necessarily protective against arrhythmic events. Patients with EiAC may need to be followed up closely despite stable structural and functional findings.

ACKNOWLEDGMENTS The authors are grateful for the valuable contributions made by all the study participants.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by Precision Health Care Center for optimized cardiac care (ProCardio) supported by the Norwegian Research Council (grant number #309762), European Research Area Network on Cardiovascular Diseases (EMPATHY project, NFR grant number #298736). The authors have reported that they have no relationships relevant to the content of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Diagnostic categories such as EiAC may oversimplify the complex interplay between genetic and environmental influences, overlooking their significant overlap. Our findings highlight the need for proactive arrhythmia management in athletes, even when cardiac morphology appears stable. This underscores the importance of careful follow-up and individualized risk assessment.

TRANSLATIONAL OUTLOOK: Further research is needed to explore the arrhythmogenic mechanisms and desmosomal properties underlying the morphologic reserve in EiAC compared with ARVC. A deeper understanding of these mechanisms could improve risk stratification and lead to more tailored management strategies for affected athletes.

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KEY WORDS **arrhythmogenic right ventricular cardiomyopathy, athlete, echocardiography, exercise-induced arrhythmogenic cardiomyopathy, ventricular arrhythmia**

APPENDIX **For supplemental tables, please see the online version of this paper.**