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Isolated Subepicardial Right Ventricular Outflow Tract Scar in Athletes With Ventricular Tachycardia

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ABSTRACT

BACKGROUND High-level endurance training has been associated with right ventricular pathological remodeling and ventricular tachycardia (VT). Although overlap with arrhythmogenic right ventricular cardiomyopathy (ARVC) has been suggested, the arrhythmogenic substrate for VTs in athletes is unknown.

OBJECTIVES The goal of this study was to evaluate whether electroanatomic scar patterns related to sustained VT can distinguish exercise-induced arrhythmogenic remodeling from ARVC and post-inflammatory cardiomyopathies.

METHODS In 57 consecutive patients (mean age 48 ± 16 years; 83% male) undergoing catheter ablation for scar-related right ventricular VT, 2 distinct scar distributions were identified: 1) scars involving the subtricuspid right ventricle in 46 patients (group A); and 2) scars restricted to the anterior subepicardial right ventricular outflow tract in 11 patients (group B).

RESULTS Definite ARVC or post-inflammatory cardiomyopathy was diagnosed in 40 (87%) of 46 group A patients but was not diagnosed in any patients in group B. All group B patients underwent intensive endurance training for a median of 15 h/week (interquartile range [IQR]: 10 to 20 h/week) for a median of 13 years (IQR: 10 to 18 years). The cycle lengths of scar-related VTs were significantly faster in group B patients (257 ± 34 ms vs. 328 ± 72 ms in group A; $p = 0.003$). Catheter ablation resulted in complete procedural success in 10 (91%) of 11 group B patients compared with 26 (57%) of 46 group A patients ($p = 0.034$). During a median follow-up of 27 months (IQR: 6 to 62 months), 50% of group A patients but none of the group B patients had a VT recurrence.

CONCLUSIONS This study describes a novel clinical entity of an isolated subepicardial right ventricular outflow tract scar serving as a substrate for fast VT in high-level endurance athletes that can be successfully treated by ablation. This scar pattern may allow distinguishing exercise-induced arrhythmogenic remodeling from ARVC and post-inflammatory cardiomyopathy. (J Am Coll Cardiol 2017;69:497–507) © 2017 by the American College of Cardiology Foundation.

Intense endurance training has been associated with acute but reversible dysfunction of the right ventricle, while the left ventricle remains unaffected (1). Repetitive training of long duration without sufficient recovery may lead to pathological right ventricular (RV) remodeling (1). Although exercise-induced nonsustained ventricular tachycardia (VT) in athletes is usually considered benign (2), in some athletes performing exercise at high levels of dynamic and static demand, fatal arrhythmic events occur (3). Identifying the substrate for VTs in athletes and distinguishing exercise-induced

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ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

CMR = cardiac magnetic resonance

EA = electroanatomic

EIAR = exercise-induced arrhythmogenic remodeling

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

LGE = late gadolinium enhancement

LV = left ventricular

MET-h = metabolic equivalent hour

RV = right ventricular

RVOT = right ventricular outflow tract

TFC = Task Force Criteria

VA = ventricular arrhythmia

VT = ventricular tachycardia

arrhythmogenic remodeling (EIAR) from arrhythmogenic right ventricular cardiomyopathy (ARVC) has important clinical and prognostic implications. ARVC typically exhibits fibrofatty replacement affecting the subepicardial subtricuspid right ventricle extending toward the apex and right ventricular outflow tract (RVOT) with disease progression (4). No data are available on the substrate for ventricular arrhythmias (VAs) in endurance athletes.

The goal of this study was to evaluate whether RV electroanatomic (EA) scar patterns related to VTs can distinguish EIAR from ARVC and post-inflammatory cardiomyopathies.

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METHODS

Since December 2006, clinical and procedural data of consecutive patients undergoing ablation for any VA at the Leiden University Medical Center have been prospectively collected. Of 371 patients with VAs originating from the right ventricle, the following were excluded: idiopathic VA (n = 229), ischemic cardiomyopathy (n = 15), congenital heart disease (n = 65), and dominant left ventricular (LV) cardiomyopathy (normal RV and abnormal LV dimensions and function) (n = 5). In cases of multiple ablation procedures, the first was defined as the index procedure. If an endocardial ablation approach was followed by a combined endocardial/epicardial procedure, the latter was considered as the index procedure. The local ethics committee approved the study protocol and sport questionnaire and waived the need for individual written patient consent. All patients provided oral informed consent for the ablation procedure.

All records of previous admissions were reviewed for the first presentation related to cardiac disease, including symptoms and signs of perimyocarditis and sarcoidosis. First presentation was categorized as out-of-hospital cardiac arrest, pre-syncope, palpitations, or other symptoms (dyspnea, chest pain, and dizziness) occurring during exercise or at rest. Patients underwent a comprehensive evaluation, including assessment of the following: family history for sudden death, ARVC, or other cardiomyopathies; 12-lead electrocardiograms (Online Appendix); imaging studies; biopsy (if appropriate); and genetic testing. They were recategorized according to the revised Task Force criteria (TFC) for ARVC (5). Cardiac sarcoidosis was diagnosed according to the Heart Rhythm Society expert consensus (6).

All VTs before the index ablation were documented on 12-lead electrocardiogram, Holter recording, exercise test, or implantable cardioverter-defibrillator (ICD), and were evaluated for cycle length and morphology. The 12-month VT burden before the index procedure was determined and arrhythmia presentation was classified as electrical storm (≥3 ICD shocks/24 h), recurrent VT terminated by ICD therapy, or sustained VT recorded in the monitor zone or below the ICD detection rate.

SPORTS HISTORY. All patients completed a standardized sports history questionnaire (Online Appendix) to extract information on type of sport and total sport participation before the index procedure (7). Endurance athletes were defined as those performing endurance training of dynamic category B (50% to 75% of maximal oxygen) or category C (>75% of maximal oxygen) for ≥6 h/week for ≥5 years (7). Metabolic equivalent hours (MET-h) were calculated as previously described (8). Sports history was also obtained from patients with idiopathic VA, and the questionnaire was sent to those performing endurance training for ≥6 h/week for ≥2 years.

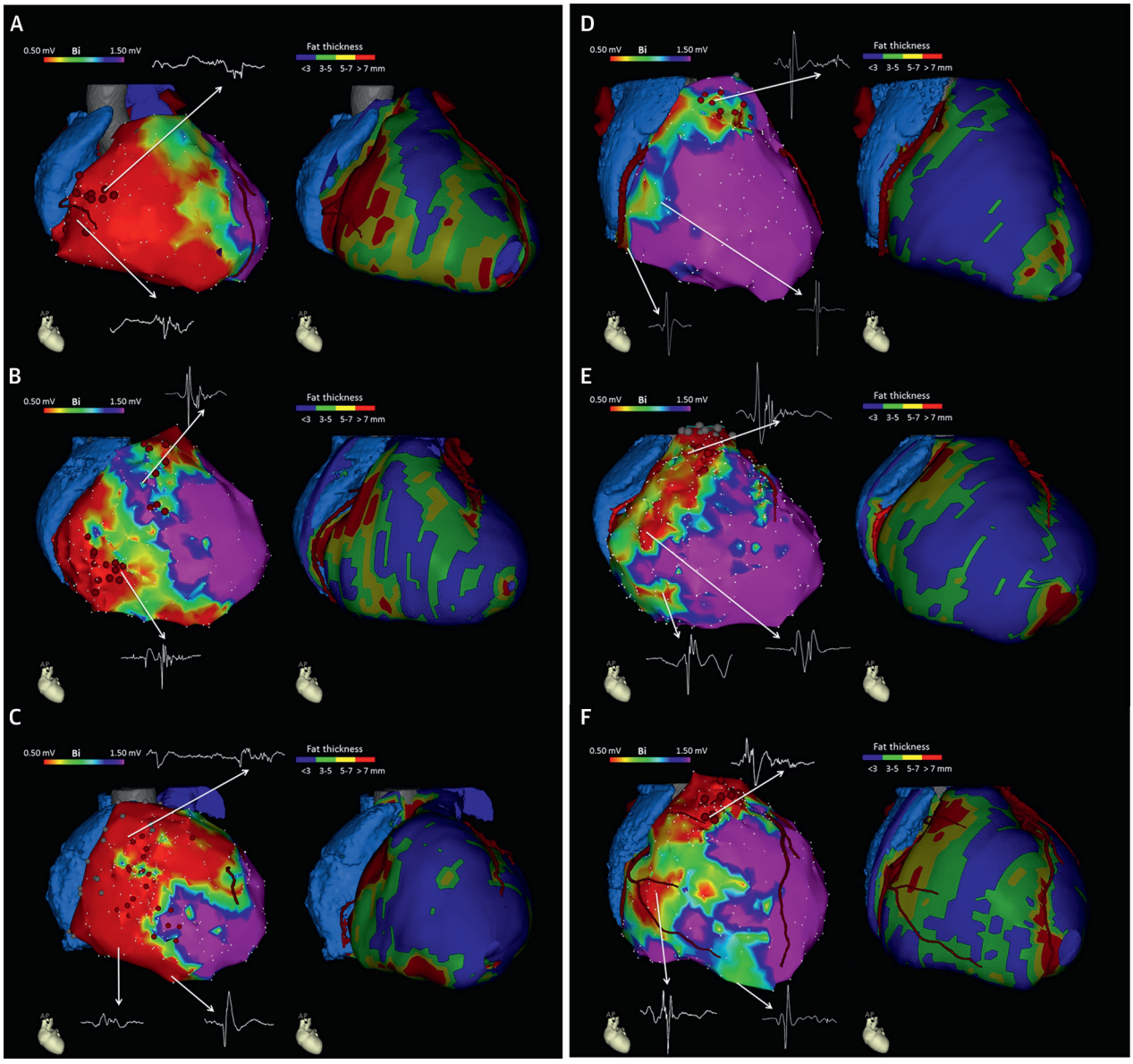
GENETIC TESTING AND IMAGING. Genetic testing by combined next-generation and Sanger sequencing of ≥55 cardiomyopathy-related genes (Online Appendix) became available in 2012 and was performed in all patients, including those ablated before 2012, unless a pathogenic mutation in a desmosomal gene had been previously identified. Detailed information about mutations is provided in the Online Appendix.

Cardiac magnetic resonance (CMR) imaging, including late gadolinium enhancement (LGE), was performed to assess LV and RV volumes and ejection fraction, regional wall motion abnormalities, and presence and location of LGE. All imaging studies performed before 2010 were reanalyzed according to the revised TFC by an independent physician blinded to all study data. Additional imaging details are given in the Online Appendix.

Programmed electrical stimulation was performed with drive cycle lengths of 600, 500, and 400 ms; 3 extra stimuli; down to 200 ms or ventricular refractory period; and burst pacing from 2 RV sites with isoproterenol (2 to 20 μg/min) if not inducible at baseline. Sustained VT was defined as lasting >30 s or requiring termination due to hemodynamic instability.

Epicardial access was obtained if previous endocardial ablation had failed or an epicardial substrate

FIGURE 1 **Scar Distribution With CT Scan–Derived Fat Images**

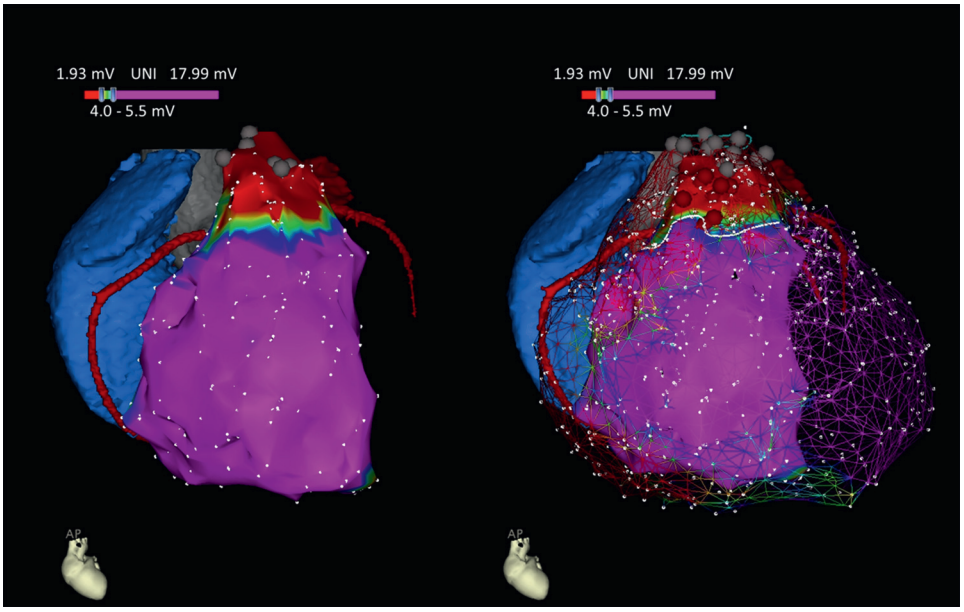


Epicardial bipolar voltage (Bi) map and computed tomography (CT) scan–derived fat mesh images are shown in an anteroposterior (AP) view. Typical scar distribution of dominant subtricuspid scar with extensions toward the apex and right ventricular outflow tract (RVOT) in arrhythmogenic right ventricular cardiomyopathy patients of group A **(A to C)** and isolated epicardial RVOT scar in endurance athletes of group B **(D to F)**. In group B, the low-voltage areas outside the RVOT were due to fat.

was suspected based on endocardial voltage and/or activation mapping. Further details about EA mapping are presented in the Online Appendix.

EA maps were reviewed for scar distribution. A scar area was defined by the presence of ≥3 adjacent mapping points with a bipolar voltage <1.5 mV (at the epicardium in the absence of ≥3 mm fat), and/or fragmented electrograms/late potentials (9). In cases of overlap of epicardial low bipolar voltage areas and epicardial fat ≥3 mm, corresponding endocardial unipolar voltages <5.5 mV (10) or epicardial abnormal electrograms were used to distinguish between scar and fat. Scar distribution was described according to a 3-plus 1-segment model: subtricuspid inflow tract (consisting of RV inferior wall, anterior wall, and acute angle); RV apex; RVOT; and septum (Online Figure 1).

FIGURE 2 Endocardial Unipolar Voltage Mapping



Typical endocardial unipolar voltage (UNI) map in anteroposterior (AP) view in group B demonstrated low UNIs in the right ventricular outflow tract **(left)**. The endocardial UNI map and the epicardial UNI map (mesh) combined show that the epicardial ablation sites **(red dots)** overlap with the low endocardial UNI area **(right)**. **Red** <4.0 mV; **purple** >5.5 mV. AP= anteroposterior view.

Critical re-entry circuit sites were identified by activation and entrainment mapping for hemodynamically tolerated VTs. For hemodynamically unstable VTs, the region of interest was identified by using substrate and pace mapping. VT-related sites and fragmented and late potentials were targeted by ablation.

At the end of the procedure, the entire stimulation protocol was repeated. Complete success was defined as noninducibility of any sustained monomorphic VT, partial success as elimination of the clinical VT but inducibility of any nonclinical VT, and failure as persistent inducibility of the clinical VT. If clinically indicated, EA-guided (endocardial low bipolar voltage) biopsy specimens were obtained but not from the RVOT free wall (11).

Patients were routinely followed up 2 and 6 months after ablation and every 6 months (ICD recipients) to 12 months, thereafter. Follow-up visits included clinical history, 12-lead electrocardiogram, echocardiography, ICD interrogation, or 24-h Holter recording for non-ICD patients. VT recurrence was defined as occurrence of any documented sustained VT.

STATISTICAL ANALYSIS. Categorical variables are displayed as numbers (percentages), and continuous variables are expressed as mean ± SD or median (interquartile range [IQR]). Categorical variables were compared by using the chi-square test or Fisher exact test. Continuous variables were compared by using the Student *t* test or Mann-Whitney *U* test. All tests were 2-sided, and p values <0.05 were considered statistically significant. All analyses were performed with SPSS version 23.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

A total of 57 patients (mean age 48 ± 16 years; 83% male) underwent ablation for scar-related VT of RV origin. Patients presented with symptomatic VT (VT cycle length 278 ± 37 ms) recorded on 12-lead electrocardiogram (n = 21), Holter monitoring (n = 5), or ICD (n = 31). Of the 31 (54%) patients with previous ICD implantation, 6 (11%) presented with an electrical storm, 17 (30%) with monomorphic VT requiring ICD shocks, 4 (7%) with antitachycardia pacing-terminated VT, and 2 (4%) with symptomatic slow VT in the monitor zone.

PRESENTATION AND SCAR PATTERN. Antiarrhythmic drugs were discontinued, except for amiodarone in 11 patients and sotalol in 2 patients requiring ablation for incessant VT. An endocardial/epicardial

approach was used in 39 patients (68%) with computed tomography image integration in 38 patients. The mean number of mapping points was 211 ± 84 at the RV endocardium and 282 ± 136 at the epicardium. All patients had an EA scar in ≥1 predefined segment (detailed scar distribution provided in Online Table 1). Two distinct scar patterns were identified. The majority of patients had a dominant scar located at the subtricuspid RV inflow tract (group A, 46 patients [81%]) with additional involvement of the RVOT in 15 (33%), apex in 2 (4%), and both the RVOT and apex in 14 (30%). In 7 of 46 patients, the scar also extended toward the septum. The second pattern was a scar restricted to the subepicardial anterior RVOT below the pulmonary valve (scar size 8.4 cm^2; IQR: 7.9 to 9.4 cm^2); the location was confirmed by using integrated computed tomography data, with normal local endocardial bipolar voltages but abnormal endocardial unipolar voltages. This scar pattern was observed in 11 patients (19%) (group B) (**Figures 1 and 2**, Online Table 1).

The first presentation was out-of-hospital cardiac arrest with documented ventricular fibrillation in 6 (13%) group A patients but no group B patients (**Table 1**). However, 6 (55%) group B patients presented with syncopal fast VT (cycle length 257 ± 22 ms). Symptoms at first presentation were exercise related in all group B patients but in only 17 (37%) group A patients.

In group A, 38 (83%) patients had ≥1 documented VT with left bundle branch block and superior axis, whereas all documented VTs in the group B patients had a left bundle branch block and inferior axis ($p < 0.001$). Of interest, 10 group B patients had 2 different RVOT VT morphologies with either a dominant negative or isoelectric/positive deflection in lead I; 7 also had premature ventricular contractions with these 2 morphologies (**Figure 3**, Online Figure 2).

The VT burden during the 12 months before ablation in the 31 patients with ICDs was similar for both groups: 5 (IQR: 2 to 22) VTs in group A versus 3 (IQR: 1 to 20) VTs in group B ($p = 0.441$). One or more electrical storms occurred in 5 (19%) patients of group A and 1 (25%) patient of group B ($p = 1.000$).

EXERCISE HISTORY. Importantly, all patients in group B were high-level endurance athletes of dynamic class C and performed training for 15 h/week (IQR: 10 to 20 h/week) for 13 years (IQR: 10 to 18 years) until presentation. All endurance athletes denied the structural use of doping. Five were professional athletes, and 6 were competitive athletes; of these, 6 (55%) were cyclists, 4 were runners (2 ultramarathon), and 1 was a professional soccer player. In contrast, patients in group A performed training for 4 h/week (IQR: 2 to 8 h/week). Although 16 (35%) patients in group A fulfilled the predefined criteria for endurance athletes, athletes in group A performed significantly less exercise compared with athletes in group B: median of 4,859 MET-h/year (IQR: 3,684 to 5,539 MET-h/year) versus 9,405 MET-h/year (IQR: 6,270 to 12,540 MET-h/year) ($p = 0.001$). Similarly, the 22 patients with idiopathic VA who were categorized as endurance athletes performed significantly less exercise compared with group B athletes (median: 3,744 MET-h/year [IQR: 3,260 to 4,224 MET-h/year] vs. 9,405 MET-h/year [IQR: 6,270 to 12,540 MET-h/year]; $p < 0.001$).

TABLE 1 Baseline Characteristics

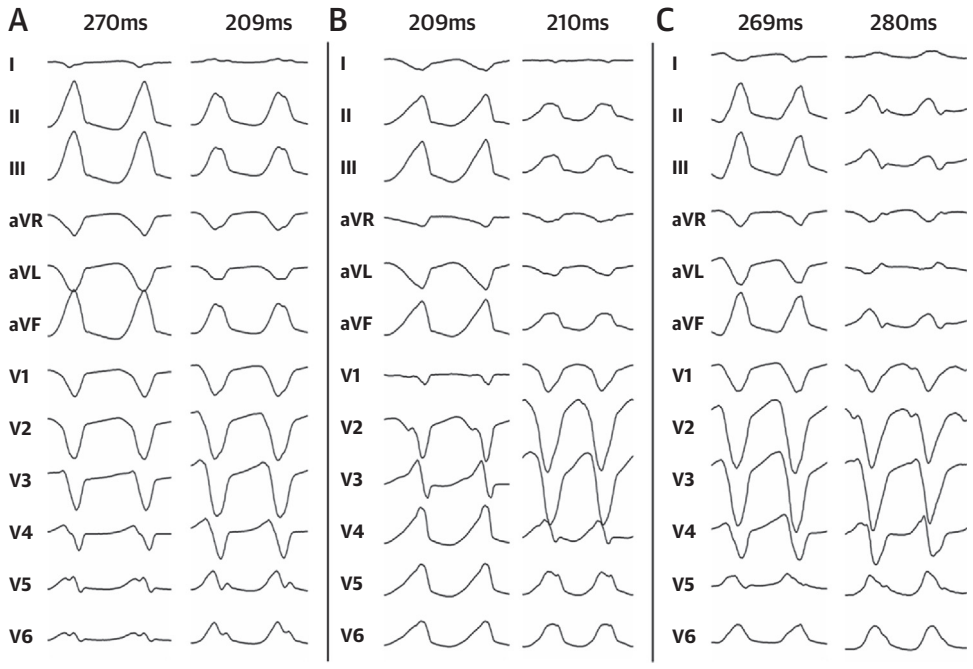
	All Patients (N = 57)	Group A (Subtricuspid) (n = 46)	Group B (Isolated RVOT) (n = 11)	p Value*
Age, yrs	48 ± 16	49 ± 16	42 ± 15	0.152
Male	47 (83)	38 (83)	9 (82)	0.951
ICD (before ablation)	31 (54)	27 (59)	4 (36)	0.182
White/black/Asian	54/2/1	43/2/1	11/0/0	0.685
NT-proBNP, pg/ml	146 (75–286)	180 (84–366)	46 (25–116)	0.001
First presentation				
OHCA	6 (11)	6 (13)	0	0.205
Pre-syncope	18 (32)	12 (26)	6 (55)	0.068
Palpitations	26 (46)	23 (50)	3 (27)	0.174
Other	7 (12)	5 (11)	2 (18)	0.507
Exercise-related	28 (49)	17 (37)	11 (100)	0.001
First documented VA				
VT	52 (92)	41 (89)	11 (100)	0.252
VF	5 (9)	5 (11)	0	
VT cycle length, ms	278 ± 37	283 ± 39	257 ± 22	0.043
Ventricular tachycardia				
Superior axis	12 (21)	12 (26)	0	
Inferior axis	19 (33)	8 (17)	11 (100)	<0.001
Both axes	26 (46)	26 (57)	0	
Endurance athlete	27 (47)	16 (35)	11 (100)	<0.001
Training, h/week	5 (2–10)	4 (2–8)	15 (10–20)	<0.001
Training, yrs	15 (8–25)	18 (6–26)	13 (10–18)	0.029
MET-h/yrs	2,613 (888–5,121)	2,142 (607–3,867)	9,405 (6,270–12,540)	<0.001
Family history of ARVC	14 (25)	14 (30)	0	0.025
Genetic testing	n = 56†	n = 45†	n = 11	
Desmosomal	23 (41)	23 (51)	0	0.002
ARVC associated	25 (45)	25 (56)	0	0.001
Any pathogenic	29 (52)	29 (64)	0	<0.001

Values are mean ± SD, n (%), n, or median (interquartile range). *Isolated right ventricular outflow tract (RVOT) (Group A) versus the subtricuspid group (group B). †No genetic testing performed in a patient with cardiac sarcoidosis.

ARVC = arrhythmogenic right ventricular cardiomyopathy; ICD = implantable cardioverter-defibrillator; MET-h = metabolic equivalent hours; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OHCA = out-of-hospital cardiac arrest; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

GENETIC TESTING AND IMAGING RESULTS. In group A, 14 patients (30%) had a family history of ARVC, and 29 (64%) of 45 patients had a pathogenic or likely pathogenic mutation in 11 genes (25 [56%] patients

FIGURE 3 Group B VT Morphologies



Typical examples of 12-lead ventricular tachycardia (VT) electrocardiograms of 3 endurance athletes of group B, in whom 2 distinct fast VT morphologies could be recorded in the same athlete: both left bundle branch block type and inferior axis with either a dominant negative or isoelectric/positive deflection in limb lead I.

with ARVC-associated genes) (**Table 2**, Online Table 2). In group B, no patients had a family history of ARVC or pathogenic or likely pathogenic mutation.

T-wave inversion was more frequent in group A than in group B; only 2 patients in group B had T-wave inversion, and it was confined to V_1-V_2. Terminal activation duration was 60 ms (IQR: 50 to 70 ms) in group A compared with 50 ms (IQR: 44 to 51 ms) in group B, exceeding the suggested cutoff of 55 ms in 69% of group A compared with 10% of group B ($p = 0.001$). Epsilon waves were only observed in group A. Precordial voltages <1.8 mV were found in 63% of group A but not in group B ($p < 0.001$). Data regarding electrocardiogram parameters are provided in **Table 3** and Online Table 3.

CMR imaging was performed in 40 (70%) patients; echocardiography was performed in the remaining 17 (30%) (**Table 4**, Online Table 4). LV dimensions were larger in group B compared with group A, with normal LV function in both groups. Global RV dimensions and function were similar between groups; however, regional RV wall motion abnormalities, according to TFC, were only present in group A. LGE-CMR images were acquired in 30 patients (53%). RV LGE was observed in both groups (10 of 22 in group A and 2 of 8 in group B) but was subtle and restricted to the ablation site after failed endocardial procedures in both group B patients. LV LGE was only present in group A (11 of 22 patients). Endocardial biopsy specimens were obtained in 14 (30%) patients in group A, which showed tissue characteristics consistent with ARVC, per TFC, in 9 patients. In group B, a biopsy was performed in 1 of 11 patients with normal histology findings.

DIAGNOSIS PER SCAR PATTERNS. According to revised TFC, 34 patients (74%) of group A had definite ARVC, of whom 25 (74%) were ARVC-associated gene mutation carriers (**Table 2**) and 3 (7%) had borderline ARVC. Cardiac sarcoidosis was diagnosed in 5 (11%) patients (3 of 5 with septal involvement) and perimyocarditis in 1. In 3 patients, the subtricuspid scar remained of unknown origin. None of these patients had a history of endurance training. In group B, no patient was diagnosed with definite or borderline ARVC, cardiac sarcoidosis, or myocarditis, but all were high-level endurance athletes, strongly suggesting exercise-induced RVOT scar. The presence of TFC for each diagnosis is listed in Online Table 5.

ACUTE AND LONG-TERM OUTCOMES. A median of 2 (IQR: 1 to 4) VTs with a cycle length of 328 ± 72 ms was induced in group A, compared with a median of 2 (IQR: 1 to 3) VTs in group B with a cycle length of 257 ± 34 ms (p = 0.003). In group A, 15% were inducible only after isoproterenol administration compared with 27% in group B (p = 0.387). Complete or partial procedural success was achieved in 26 (57%) and 11 (24%) group A patients, respectively, and the procedure failed in 9 (20%). Independent from the acute results, all 19 patients without an ICD pre-ablation underwent implantation before discharge. At last follow-up, 37 (80%) group A patients were taking antiarrhythmic drugs.

In group B patients, all VTs could be mapped to the epicardial RVOT scar. Complete success was achieved in 10 (91%) patients and partial success in 1 (p = 0.034 for complete success). Nine patients were rendered noninducible after limited epicardial ablation and 1 after extensive endocardial ablation of a low unipolar voltage RVOT area. In the remaining patient, a nonclinical VT remained inducible and was mapped to the subepicardial RVOT scar, which was partly covered by the large right atrial appendage and epicardial fat, preventing complete substrate elimination. This patient was discharged on sotalol after ICD implantation. Overall, 9 of 11 patients were discharged off antiarrhythmic drugs. All patients were advised to avoid intense endurance training. Two (18%) athletes continued training at the same level, 2 (18%) decreased the amount but kept training at a competitive level, and the remaining 7 (64%) athletes continued training at a recreational level. During a median follow-up of 27 months (IQR: 6 to 62 months), 50% of the patients in group A had a VT recurrence, but none of the group B patients experienced recurrence.

TABLE 2 Group A: Presence of Pathogenic/Likely Pathogenic Mutations

	All Patients (n = 46)	Definite ARVC (n = 34)	Borderline ARVC (n = 3)	Inflammatory (n = 6)	SuO (n = 3)
Genetic testing	45	34	3	5	3
Patients with mutation	29* (64)	25 (74)	1 (33)	1* (20)	2 (67)
Pathogenic mutations	31†	27†	1	1	2
Type of pathogenic mutation					
Plakophilin 2	20	20	0	0	0
Desmoglein 2	1	1	0	0	0
Desmocollin 2	1	1	0	0	0
Plakoglobin	0	0	0	0	0
Desmoplakin	1	1	0	0	0
Other	8	4	1	1	2

Values are n or n (%). *One patient in the inflammatory group did not undergo genetic testing; the percentages reflect the lower total patient number. †Two patients with a double mutation (PKP2 and other, PLN and other mutation).

ARVC = arrhythmogenic right ventricular cardiomyopathy; SuO = scar of unknown origin.

DISCUSSION

In the present study, we described 2 EA scar patterns associated with VT of RV origin: 1) a novel entity of an isolated subepicardial RVOT scar, exclusively observed in endurance athletes; and 2) a dominant subtricuspid scar pattern typically related to ARVC and inflammatory cardiomyopathies. None of the endurance athletes with isolated RVOT scars fulfilled criteria for ARVC or sarcoidosis, and none had pathogenic or likely pathogenic mutations in ≥55 cardiomyopathy-related genes; however, all were longstanding high-level endurance athletes. The isolated RVOT scar served as a substrate for fast, reentry VT with 2 distinct morphologies. The substrate could be successfully abolished by epicardial ablation in most patients with freedom of VT recurrence. This specific scar pattern, detectable by using endocardial unipolar voltage mapping but not by imaging, likely results from exercise-induced pathological remodeling. It may allow distinguishing EIAR from ARVC with important implications for prognosis and treatment.

A CONTINUUM FROM PURELY EXERCISE-INDUCED RV CARDIOMYOPATHY TO INHERITED ARVC? It has been suggested that a continuum exists between an entirely acquired exercise-induced form of ARVC, an intermediate form of desmosomal gene-elusive, nonfamilial ARVC with exercise as an important factor, and classic ARVC with causal desmosomal mutations, which can be aggravated by endurance training (12,13). This assumption was based on the observed association between complex VAs of RV origin and the presence of ARVC TFC among 46 high-level endurance athletes referred for evaluation of arrhythmia-related symptoms (3). Further support for the concept came from the lower-than-expected prevalence of desmosomal mutations in these endurance athletes (8,14). Although 59% had definite ARVC if original TFC were applied and/or some pathological involvement of the right ventricle, none had regional RV akinesia, dyskinesia, or aneurysm formation (3). Despite only minor structural alterations and only minor or no revised TFC in the majority, 18 (39%) athletes developed major arrhythmic events, including sudden death in 9 athletes. Although endurance training likely played a role, the underlying substrate and the mechanism to explain the majority of these VAs remained unclear.

In a recent series of 82 TFC-positive patients with ARVC, those without desmosomal mutations presented at older age and had performed significantly more intense exercise (based on MET-h/year)

TABLE 3 Electrocardiogram Parameters

	All Patients (n = 57)	Group A (Subtricuspid) (n = 46)	Group B (Isolated RVOT) (n = 11)	p Value*
TWI, >0.1 mV	33 (58)	30 (65)	3 (27)	0.022
TWI, >0.2 mV	23 (40)	22 (48)	1 (9)	0.019
TWI in V_1–V_3 (major)	17 (30)	17 (37)	0	0.016
TWI in V_1–V_2 (minor)†	5 (9)	3 (7)	2 (18)	0.219
TWI in V_1–V_4 with cRBBB	7 (12)	7 (15)	0	0.167
TWI in V_4–V_6 (minor)	11 (19)	11 (24)	0	0.071
TWI inferior leads	16 (28)	16 (35)	0	0.021
Epsilon wave	10 (18)	10 (22)	0	0.089
TAD duration	55 (50–65)	60 (50–70)	50 (44–51)	<0.001
TAD >55 ms (minor)‡	25/45 (56)	24/35 (69)	1/10 (10)	0.001
QRS-Amp_{max}, limb, mV	0.9 ± 0.4	0.8 ± 0.3	1.2 ± 0.4	0.002
QRS-Amp_{max}, precordials, mV	1.7 ± 0.6	1.5 ± 0.6	2.4 ± 0.4	<0.001
QRS-Amp_{max}, precordials <1.8 mV	29 (51)	29 (63)	0	<0.001

Values are n (%), median (interquartile range), or mean ± SD. *Isolated right ventricular outflow tract (RVOT) (Group B) versus. subtricuspid (Group A) group. †Isolated T-wave inversion (TWI) in V_1–V_2. ‡Only in patients without complete right bundle branch block (cRBBB).

TAD = terminal activation duration.

compared with desmosomal mutation-positive patients (8). In contrast to the aforementioned high-level endurance athletes, the majority of both gene-elusive and desmosomal mutation-positive ARVC patients had major structural alterations, and 80% of their presenting VTs had a superior axis VT, suggesting a non-RVOT substrate. Indeed, ARVC has a typical scar pattern with early involvement of the subtricuspid right ventricle and progression toward the apex and RVOT (4). Gene-elusive ARVC had a similar phenotype (8).

Assuming a continuum with EIAR, areas more exposed and more vulnerable to mechanic load may be affected first, resulting in the same scar pattern with increasing scar size either as disease progressed or with "higher exercise dose."

An isolated or dominant subepicardial RVOT scar, as identified in the high-level endurance athletes in the present study, has not been observed in any stage of ARVC or inflammatory cardiomyopathy in our cohort and has not been reported in previous studies (4). All patients with ARVC and an identified (likely) pathogenic mutation had a dominant subtricuspid scar. Likewise, in line with our findings, cardiac sarcoidosis often involves the peri-tricuspid region with additional involvement of the RVOT and septum (15).

None of the group B athletes in our study fulfilled revised TFC for ARVC and, importantly, none had a positive family history or pathogenic mutation related to any cardiomyopathy. Athletes with an isolated subepicardial scar presented at similar age but with even higher intensity of endurance training (median 9,405 MET-h/year) compared with patients in group A but also compared with the previously described gene-elusive ARVC patients (8).

These findings suggest that the isolated RVOT scar, identified in our cohort of high-level endurance athletes, is a distinct clinical entity and not part of a continuum.

VAs IN ATHLETES. Exercise-induced VAs in asymptomatic athletes without apparent structural heart disease are considered benign and often resolve with deconditioning (2). However, some symptomatic endurance athletes are at risk for fatal arrhythmic events (3). In our cohort, re-entry was the underlying mechanism of all spontaneous and induced VTs in patients with isolated RVOT scars. Interestingly, 2 distinct morphologies were observed in 10 of 11 patients, consistent with 2 different exit sites from the subepicardial scar (**Figure 3 and Central Illustration**). Of concern, VTs were fast, with a mean VT cycle length of 257 ± 22 ms, leading to pre-syncope in 6 patients. If untreated, these VTs may accelerate and be fatal (Online Figure 2). A dominant RVOT site of origin and multiple inducible morphologies have also been described in a previous cohort of athletes, with VT inducibility as the only, albeit weak, predictor of fatal arrhythmic events.

In a recent study, 33 asymptomatic elite master athletes with a training history of 29 ± 8 years showed no signs of a chronic exercise-induced maladaptation (16), and life expectancy of former professional cyclists participating in the Tour de Suisse was similar to a matched control group (17). However, in symptomatic athletes, subepicardial RVOT scar may be underestimated. In our cohort of consecutive patients referred for ablation of scar-related RV VT, the novel entity of an arrhythmogenic RVOT scar in athletes accounted for 19% of all patients. Of interest, exercise-related premature ventricular contractions and nonsustained VTs have been observed in 7.3% of asymptomatic athletes, with 68% of RVOT origin (2). Although the mechanism and substrate of these arrhythmias are poorly understood, the common site of origin is striking.

POTENTIAL UNDERLYING MECHANISMS. Physiological cardiac adaptation related to regular exercise includes biventricular dilation, T-wave inversion, and prolonged QRS terminal activation, and might result in a phenotypic overlap with gene-elusive ARVC and inherited ARVC (18). However, global physiological remodeling does not necessarily imply the presence of a distinct scar.

Long-lasting endurance training leads to transient RV dysfunction and increases in brain natriuretic

peptide and troponin levels after a race that are even more pronounced after the longest events (e.g., alpine cycling, ultra-triathlon) (1). Repetitive training of long duration without recovery may lead to repetitive and cumulative injury, pathological ventricular remodeling and, ultimately, arrhythmogenic scar (12). Imaging studies in athletes have identified LGE only in a small number, usually confined to the interventricular septum in the vicinity of the hinge points (1,19), which has been described under several conditions (including pulmonary hypertension) without prognostic implications (20). However, the applied LGE-CMR image acquisition may be insufficient to detect subepicardial RVOT scar.

What causes the predilection of EIAR for the subepicardial RVOT is unclear. Shear stress occurring at the transition between the anterior RVOT myocardium and the fibrous ring of the pulmonary valve may play an important role, and the subepicardium may be more prone to wall stress due to its larger radius according to Laplace's equation. However, additional predisposing factors are likely to be operative to develop the substrate for sustained VT.

IDENTIFICATION OF THE SUBSTRATE. A small scar confined to the RVOT is unlikely to result in electrocardiogram abnormalities as observed in advanced ARVC. Accordingly, voltages in the precordial and limb leads were high, and isolated T-wave inversion in V_1-V_2 was only observed in 2 of 11 group B patients, and only 1 had prolonged terminal activation duration.

The subepicardial VT substrate could not be diagnosed by using detailed imaging, including LGE-CMR. Endocardial bipolar voltage mapping has been described as superior to LGE-CMR for detection of RV scar (21). In the present study, endocardial bipolar voltages at the location of the opposing subepicardial RVOT scar were normal, which may lead to a misdiagnosis of "idiopathic, benign RVOT VT," particularly if other noninvasive findings are inconspicuous. Of importance, endocardial unipolar voltages of ≤5.5 mV, a previously suggested cutoff value based on structural normal right ventricles, already suggested the presence of epicardial scar in all athletes (10). These scar areas could be correctly identified if the more specific cutoff value of 4.4 mV was applied (22).

A limited epicardial substrate for potentially fatal VTs may even be missed at routine autopsy. Identification of this specific substrate has important implications for risk stratification, family advice, and treatment. Limited epicardial catheter ablation was successful in the majority, with an excellent prognosis during long-term follow-up.

TABLE 4 Imaging and Biopsies

	All Patients (N = 57)	Group A (Subtricuspid) (n = 46)	Group B (Isolated RVOT) (n = 11)	p Value*
CMR, cine images	40	31	9	
LVEDV, ml	191 ± 42	181 ± 42	225 ± 22	0.005
LVEDV index, ml/m^2	95 ± 22	90 ± 22	113 ± 15	0.005
LVEF, %	56 ± 11	56 ± 13	56 ± 6	0.985
RVEDV, ml	252 ± 79	251 ± 86	254 ± 53	0.914
RVEDV index, ml/m^2	125 ± 40	124 ± 44	127 ± 26	0.88
RVEF, %	44 ± 10	43 ± 11	48 ± 7	0.171
RVEDV/LVEDV	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.2 (0.97–1.3)	0.177
RV WMA	18/40 (45)	18/31 (58)	0/9 (0)	0.002
CMR, LGE images	30	22	8	
LGE presence	16/30 (53)	14/22 (64)	2/8 (25)†	0.061
LGE presence in right ventricle	12/30 (40)	10/22 (46)	2/8 (25)†	0.312
LGE presence in left ventricle	11/30 (37)	11/22 (50)	0/8 (0)	0.012
Echocardiography	17‡	15‡	2‡	
PLAX RVOT, mm	43 ± 6	43 ± 6	38 ± 6	0.281
PLAX RVOT index, mm/m^2	22 ± 4	22 ± 4	22 ± 6	0.929
PSAX RVOT, mm	41 ± 6	41 ± 6	38 ± 5	0.454
PSAX RVOT index, mm/m^2	21 ± 3	21 ± 3	22 ± 6	0.646
RV FAC, %	30 ± 11	29 ± 11	33 ± 11	0.658
RV WMA and/or aneurysms	9/17 (53)	9/15 (60)	0/2 (0)	0.11
Endomyocardial biopsy	15	14	1	
Biopsy, major	7/15 (47)	7/14 (47)	0/1 (0)	0.167
Biopsy, minor	2/15 (13)	2/14 (4)	0/1 (0)	0.481

Values are n, mean ± SD, n/N (%), or median (interquartile range). *Isolated right ventricular outflow tract (RVOT) (Group B) versus subtricuspid (Group A) group. †Late gadolinium enhancement (LGE) in the right ventricle confined to site of previous ablation. ‡Revised Task Force criteria measured on echocardiogram in patients without contraindication for cardiac magnetic resonance (CMR) imaging.

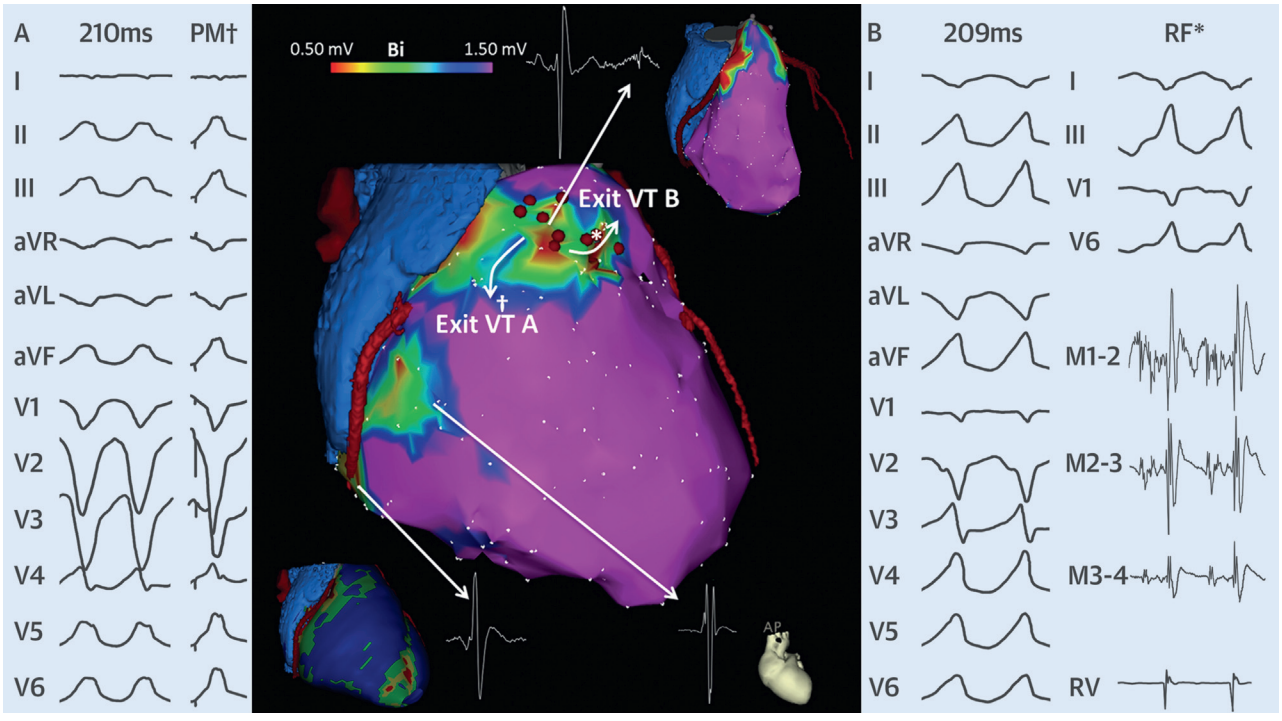
LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; PLAX = parasternal long-axis view; PSAX = parasternal short-axis view; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RV FAC = right ventricular fractional area change; RV WMA = right ventricular wall motion abnormalities.

CLINICAL IMPLICATIONS. The described novel clinical entity of an isolated subepicardial RVOT scar, serving as substrate for fast VT in athletes, should be considered in high-level endurance athletes presenting with symptomatic VAs. Suspicion may be particularly high if 2 different RVOT VT morphologies are observed. Of importance, major TFC and cardiac imaging results were negative, but endocardial unipolar voltage mapping was diagnostic in all athletes. This scar pattern might be used to distinguish exercise-induced arrhythmogenic remodeling from ARVC and post-inflammatory cardiomyopathy.

The recognition of the clinical entity (**Central Illustration**) may have important therapeutic consequences because limited epicardial ablation is potentially curative and associated with an excellent prognosis.

STUDY LIMITATIONS. The study sample was small, and the Leiden University Medical Center is a

CENTRAL ILLUSTRATION **Isolated Subepicardial RVOT Scar**



Venlet, J. et al. J Am Coll Cardiol. 2017;69(5):497–507.

The epicardial bipolar voltage map shows a typical isolated subepicardial right ventricular outflow tract (RVOT) scar, serving as substrate for fast re-entry ventricular tachycardia (VT) with 2 morphologies. The map includes the best pace-match (PM) site for VT A (†) and the radiofrequency (RF) termination site of VT B with recording of mid-diastolic activity (*). The computed tomography scan–derived fat mesh (fat thickness, **blue** <3 mm; **red** >7 mm) **(lower left)** and the endocardial unipolar voltage map (**red** <4.0 mV; **purple** >5.5 mV) **(upper right)** are shown.

tertiary referral center for VT ablation, which may have resulted in referral bias. In the Netherlands, signal-averaged electrocardiograms are not part of routine clinical practice and were therefore not acquired in the present study. Biopsies were only performed if the diagnosis was unclear and endocardial low bipolar voltage areas were present. Although no genetic mutation was found in the athletes by using combined next-generation and Sanger sequencing tests, whole exome sequencing and whole genome sequencing were not performed.

Subepicardial RVOT scar has been described in patients with Brugada syndrome and Brugada-type electrocardiograms. Although Brugada syndrome cannot be completely excluded, none of the group B patients had a Brugada type 1 or 2 electrocardiogram, a family history suggestive of Brugada syndrome, or a pathogenic mutation in the SCN5A gene.

We cannot exclude the possibility that some patients with small epicardial RVOT scar may have been misclassified as having idiopathic VT. Results of unipolar voltage mapping and programmed electrical stimulation, which have been systematically performed in recent years, were in line with the diagnosis of idiopathic VA. In addition, only 3 athletes with idiopathic VA performed exercise above the 25th percentile of MET-h/year of group B patients. Although we could identify the subepicardial scars in all athletes by unipolar voltage mapping, this method may still not be sensitive enough to detect subtle structural changes that can occur in those exercising at lower levels.

This study could not prove any causal relationship between endurance training and an epicardial RVOT scar. However, the uniform scar pattern found only in high-endurance athletes supported a strong association.

The only modest outcome in group A might be due to our more conservative approach offering epicardial ablation only to patients with symptomatic recurrent

antitachycardia pacing or ICD shocks. Finally, larger studies with long follow-up after epicardial substrate ablation are warranted to confirm the favorable prognosis and exclude disease progression.

CONCLUSIONS

This study describes a novel clinical entity of an isolated subepicardial RVOT scar as substrate for fast VT in high-level endurance athletes that can be successfully treated by ablation. The specific scar pattern identified by using EA voltage mapping but not by imaging might distinguish EIAR from ARVC and post-inflammatory cardiomyopathy. The underlying mechanism for scar formation remains unclear, but the anterior subepicardial RVOT may be more vulnerable to exercise-induced wall stress, being the Achilles' heel of endurance athletes.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: High-level endurance athletes with RVOT tachycardia may have localized subepicardial scarring that can be successfully treated with limited epicardial radiofrequency ablation.

TRANSLATIONAL OUTLOOK: Further studies are needed to identify athletes at risk of EIAR and expose the mechanisms responsible for this anatomically specific arrhythmia substrate.

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KEY WORDS arrhythmia, arrhythmogenic right ventricular cardiomyopathy, clinical electrophysiology, endurance athletes

APPENDIX For additional methods and results, including supplemental figures and tables, please see the online version of this article.