Substrate identification and treatment of right ventricular tachycardia: scar patterns and novel mapping tools

Venlet, J.

CHAPTER 2

2

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 (RV) 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.

Objective

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

Introduction

Intense endurance training has been associated with acute but reversible dysfunction of the right ventricle (RV), while the left ventricle (LV) remains unaffected.[1] Repetitive training of long duration without sufficient recovery may lead to pathological RV remodeling.[1] Although exercise-induced non-sustained ventricular tachycardia (VT) in athletes are usually considered benign,[2] in some athletes performing exercise at high levels of dynamic and static demand, fatal arrhythmic events do occur.[3] Identifying the substrate for VTs in athletes and distinguishing exercise-induced arrhythmogenic remodeling (EIAR) from arrhythmogenic RV cardiomyopathy (ARVC) has important clinical and prognostic implications.[3] ARVC typically shows fibrofatty replacement affecting the subepicardial subtricuspid RV extending towards apex and RV outflow tract (RVOT) with disease progression.[4] No data are available on the substrate for ventricular arrhythmias in endurance athletes.

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

Methods

Patients

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

All records of previous admissions were reviewed for the first presentation related to cardiac disease, including symptoms and signs of (peri)myocarditis and sarcoidosis. First presentation was categorized as out-of-hospital cardiac arrest, pre-syncope, palpitations or other symptoms (dyspnea, chest pain, dizziness), occurring during exercise or at rest. Patients underwent a comprehensive evaluation including family history for sudden death, ARVC or other cardiomyopathies, 12-lead ECGs (Supplemental

Methods), imaging studies, biopsy, if considered appropriate, and genetic testing, and were (re-)categorized according to the revised Task Force (TF) criteria for ARVC.[5] Cardiac sarcoidosis was diagnosed according to the HRS expert consensus.[6]

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

Sport history

A standardized and detailed sport history questionnaire was filled out by all patients (Supplemental Methods) 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 (40-70% of max O_2) and C (>70% of max O_2) for ≥6 hours/week for ≥5 years.[7] Metabolic Equivalent hours (MET-Hrs) were calculated as previously described.[8] The sport history was also obtained from patients with idiopathic VA and the questionnaire was send to those performing endurance training for ≥6 hours/week for ≥2 years.

Genetic testing and imaging

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

Cardiac magnetic resonance imaging (MRI), 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 2010 TFC by an independent physician blinded to all study data. Additional imaging details are given in the supplemental material.

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

Epicardial access was obtained through a subxiphoid puncture if prior endocardial ablation had failed or an epicardial substrate was suspected based on endocardial voltage and/or activation mapping. Further details about EA mapping are presented in the supplemental material.

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 case of overlap of epicardial low bipolar voltage areas and epicardial fat ≥3 mm, corresponding endocardial unipolar voltages of <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, acute angle), RV apex, RVOT, and septum (Supplemental Figure 1).

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 substrate and pace-mapping. VT-related sites, fragmented and late potentials were targeted by ablation. At the epicardium RF-application was applied at safe distance from the coronary arteries.

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

Patients were routinely followed 2 and 6 months after ablation and every 6 (ICD recipients) to 12 thereafter. Follow-up visit included clinical history, 12-lead ECG, echocardiography, ICD interrogation or 24-hours Holter recording for patients without ICD. 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 ± standard deviation or median (interquartile range [IQR]). Categorical variables were compared using the χ^2 test or Fisher's exact test. Continuous variables were compared using the Student's 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, Armonk, NY).

Results

Patients

A total of 57 patients (age 48±16 years, male 83%) underwent ablation for scar-related VT of RV origin. Patients presented with symptomatic VT (VTCL 278±37ms) recorded on 12-lead ECG (n=21), Holter monitoring (n=5) or ICD (n=31). Of the 31 (54%) patients with prior 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

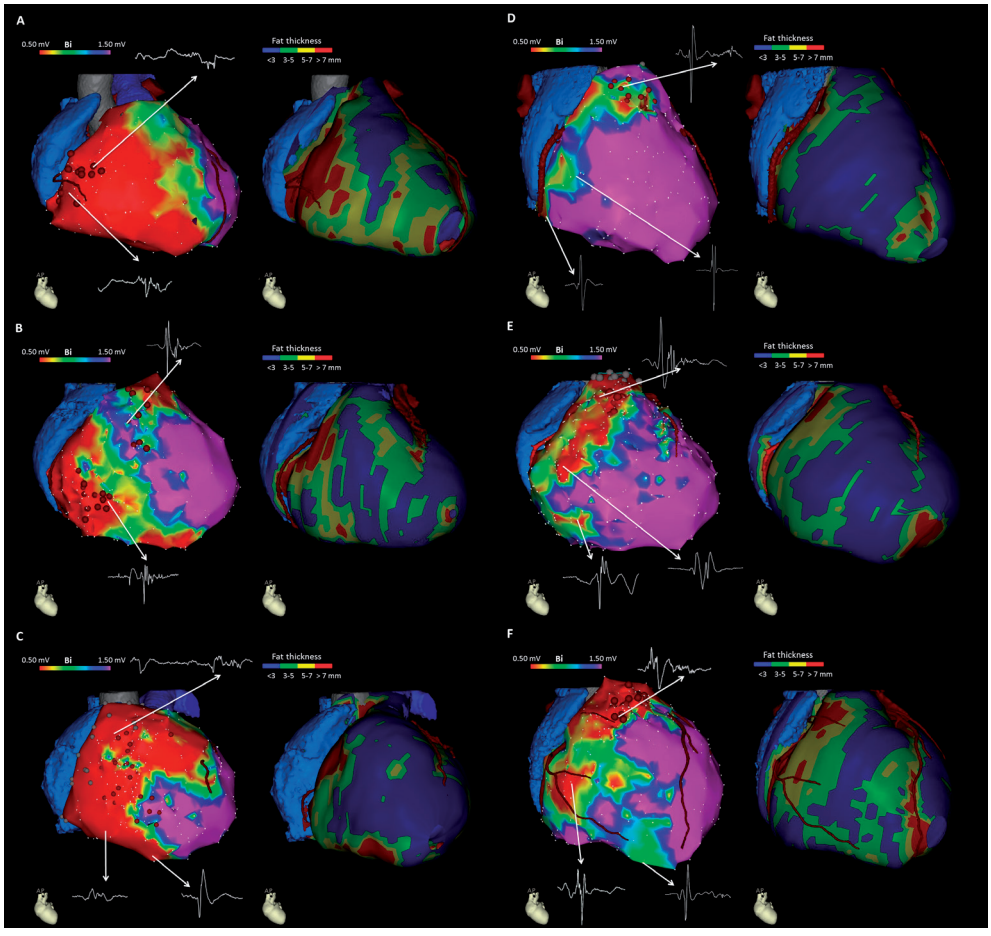
Antiarrhythmic drugs were discontinued with the exception of amiodarone in 11 patients and sotalol in 2 patients requiring ablation for incessant VT. An endocardial-epicardial approach was performed in 39 patients (68%) with CT image integration in 38 patients. The average number of mapping points was 211 ± 84 at the RV endocardium and 282 ± 136 at the epicardium. All patients had EA scar in ≥1 predefined segment (detailed scar distribution provided in Supplemental 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%), both RVOT and apex in 14 (30%). In 7/46 patients the scar also extended towards 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, 7.9-9.4), the location confirmed by integrated CT data, with normal local endocardial bipolar voltages but abnormal endocardial unipolar voltages. This scar pattern was observed in 11 patients (19%) (group B [Figure 1, 2 and Supplemental Table 1]).

Presentation and clinical evaluation according to scar pattern

The first presentation was out-of-hospital cardiac arrest with documented ventricular fibrillation in 6/46 (13%) group A patients but in none of group B (Table 1). However, 6/11 (55%) group B patients presented with syncopal fast VT (CL 257±22ms). 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 LBBB and superior axis, whereas all documented VTs in patients of group B had a LBBB and inferior axis ($P<0.001$). Of interest, 10/11 group B patients had 2 different RVOT VT morphologies with either a dominant negative or isoelectric/positive deflection in lead I, 7/11 had also PVCs with these two morphologies (Figure 3 and Supplemental Figure 2).

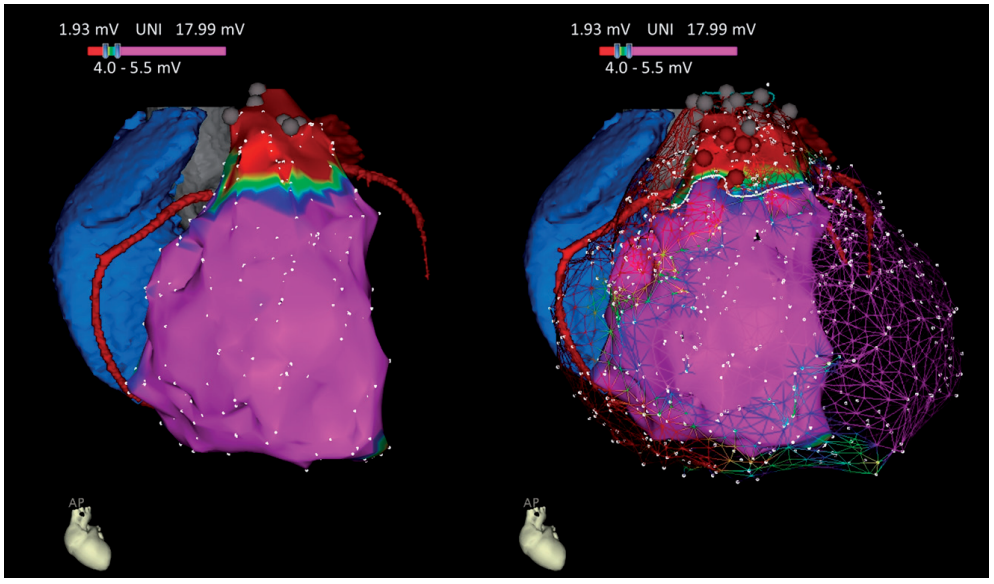
Figure 1. Scar distribution with CT scan-derived fat images



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.

The VT burden during the 12 months prior to ablation in the 31 patients with ICD was similar for both groups, 5 (IQR, 2-22) VTs in group A vs. 3 (IQR, 1-20) VTs in group B (P=0.441). An electrical storms occurred in 5 (19%) patients of group A and 1 (25%) patient of group B (P=1.000).

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.

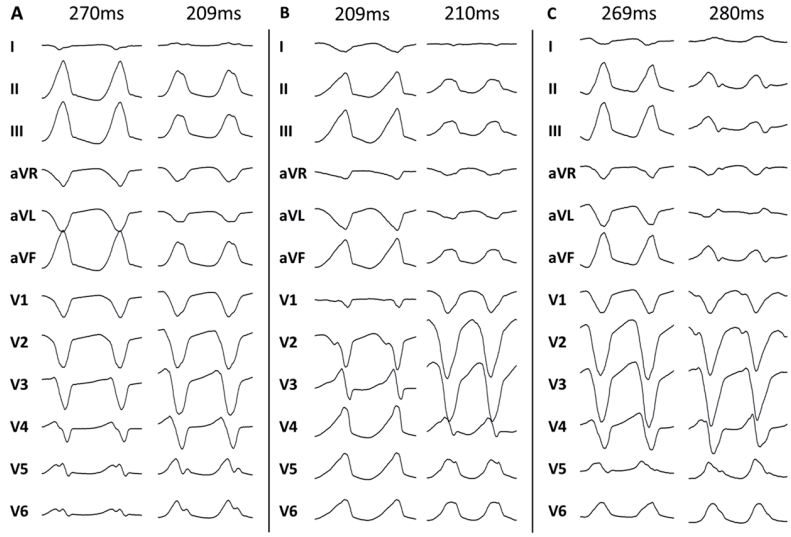
Table 1. Baseline characteristics of the patients according to dominant scar patterns

	All patients (n=57)	Group A (Subtricuspid) (n=46)	Group B (Isolated RVOT) (n=11)	P-value*
Age, years	48±16	49±16	42±15	0.152
Sex (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%)	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 (0%)	
VT cycle length (ms)	278±37	283±39	257±22	0.043
Ventricular tachycardia		283±39		
Superior axis	12 (21%)	12 (26%)	0 (0%)	
Inferior axis	19 (33%)	8 (17%)	11 (100%)	<0.001
Both axis	26 (46%)	26 (57%)	0 (0%)	
Genetic testing	56†	45†	11	
Desmosomal	23/56 (41%)	23/45 (51%)	0/11 (0%)	0.002
ARVC associated	25/56 (45%)	25/45 (56%)	0/11 (0%)	0.001
Any pathogenic	29/56 (52%)	29/45 (64%)	0/11 (0%)	<0.001
Family history of ARVC	14 (25%)	14 (30%)	0 (0%)	0.025
Endurance athlete	27 (47%)	16 (35%)	11 (100%)	<0.001
Training, hours /week	5 (2-10)	4 (2-8)	15 (10-20)	<0.001
Training, years	15 (8-25)	18 (6-26)	13 (10-18)	0.029
MET-Hrs/ year	2613 (888-5121)	2142 (607-3867)	9405 (6270-12540)	<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.

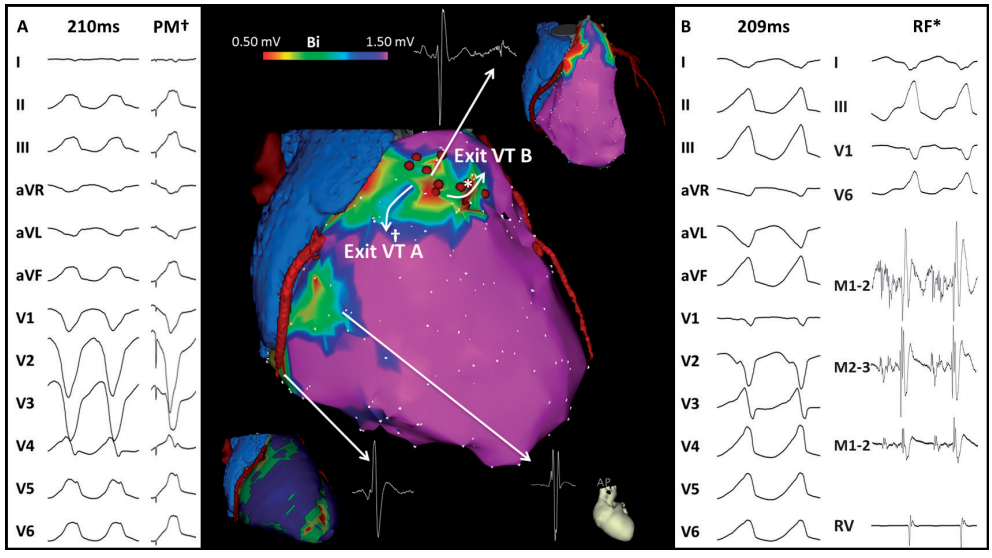
ARVC = arrhythmogenic right ventricular cardiomyopathy; ICD = implantable cardioverter-defibrillator; MET-h = metabolic equivalent hours; NT-proBNP = N-terminal pro–B-type natriuretic peptide; OHCA = out-of-hospital cardiac arrest; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular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

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.

Central Illustration. Isolated subepicardial RVOT scar



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.

Exercise history

Importantly, all patients in group B were high-level endurance athletes of dynamic class C and performed training for 15 (IQR, 10-20) hours per week, for 13 (IQR, 10-18) years until presentation. All endurance athletes denied the (structural) use of doping. Five were professional and 6 competitive athletes. Six (55%) were cyclists, 4 runners (2 ultramarathon) and 1 professional soccer player. In contrast, patients in group A performed training for 4 (IQR, 2-8) hours per week. Although 16/46 (35%) patients in group A fulfilled the predefined criteria for endurance athletes, athletes in group A performed significantly less exercise compared to athletes in group B (group A, median 4859 [IQR, 3684-5539] MET-hrs/year vs. group B, median 9405 [6270-12540] MET-hrs/year, P=0.001). Similar, the 22 patients with idiopathic VA who were categorized as endurance athletes performed significantly less exercise compared to group B athletes (median 3744 [IQR, 3260-4224] MET-hrs/year, P<0.001).

Table 2. Group A: Presence of pathogenic/ likely pathogenic mutations

	All (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	29/45 (63%)	25/34 (74%)	1 (33%)	1 (17%)	2 (67%)
Pathogenic mutations (n)	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.

Genetics

In group A, 14 patients (30%) had a family history of ARVC, and 29/45 (64%) had a pathogenic or likely pathogenic mutation in 11 genes (25/45 [56%] patients in ARVC-associated genes) (Table 2 and Supplemental Table 2). In group B, none had a family history of ARVC or pathogenic or likely pathogenic mutation.

12-lead ECG

T-wave-inversion (TWI) was more frequently found in group A compared to group B. Only 2 patients of group B had TWI confined to V1-V2. Terminal activation duration was 60ms (IQR, 50-70ms) in group A compared to 50ms (IQR, 44-51ms) in group B, exceeding the suggested cutoff of 55ms in 69% of group A and 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). ECG parameters are provided in Table 3 and in Supplemental Table 3.

Table 3. Electrocardiogram parameters

	All patients (n=57)	Group A Subtricuspid (n=46)	Group B Isolated RVOT (n=11)	P-value*
TWI (>0.1mV)	33 (58%)	30 (65%)	3 (27%)	0.022
TWI (>0.2mV)	23 (40%)	22 (48%)	1 (9%)	0.019
TWI in V1-V3 (major)	17 (30%)	17 (37%)	0 (0%)	0.016
TWI in V1-V2 (minor)†	5 (9%)	3 (7%)	2 (18%)	0.219
TWI in V1-V4 with cRBBB	7 (12%)	7 (15%)	0 (0%)	0.167
TWI in V4-V6 (minor)	11 (19%)	11 (24)	0 (0%)	0.071
TWI inferior leads	16 (28%)	16 (35%)	0 (0%)	0.021
Epsilon wave	10 (18%)	10 (22%)	0 (0%)	0.089
TAD duration	55 (50-65)	60 (50-70)	50 (44-51)	<0.001
TAD >55ms (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-$Amp_{max,}$ pre, mV	1.7±0.6	1.5±0.6	2.4±0.4	<0.001
QRS-$Amp_{max,}$ pre <1.8 mV	29 (51%)	29 (63%)	0 (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 V1–V2. ‡Only in patients without complete right bundle branch block (cRBBB).

TAD = terminal activation duration.

Imaging and histology

Cardiac MRI was performed in 40 (70%) patients with echocardiography in the remaining 17 (30%) (Table 4 and Supplemental Table 4). LV dimensions were larger in group B compared to 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 TF criteria were only present in group A. LGE-MRI images were acquired in 30 patients (53%). RV LGE was observed in both groups (10/22

in group A and 2/8 in group B), but subtle and restricted to the ablation site after failed endocardial procedure in both group B patients. LV LGE was only present in group A (11/22 patients). Endocardial biopsies were obtained in 14 (30%) patients in group A, which showed tissue characteristics consistent with ARVC according to TF criteria in 9 patients. In group B biopsy was performed in 1/11 patients with normal histology.

Table 4. Imaging and biopsies

	All patients (n=57)	Group A Subtricuspid (n=46)	Group B Isolated RVOT (n=11)	P-value*
MRI –cine images	40	31	9	
LVEDV, mL	191±42	181±42	225±22	0.005
LVEDV index, mL/m2	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/m2	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
MRI – LGE images	30	22	8	
LGE presence	16/30 (53%)	14/22 (64%)	2/8 (25%)†	0.061
LGE presence RV	12/30 (40%)	10/22 (46%)	2/8 (25%)†	0.312
LGE presence LV	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
RVFAC, %	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 diagnosis according to scar patterns

According to 2010 revised TF criteria, 34 patients (74%) of group A had definite ARVC, of whom 74% were ARVC-associated gene mutations carriers (Table 2), and 3 (7%) borderline ARVC. Cardiac sarcoidosis was diagnosed in 5 (11%) patients (3/5 with septal involvement) and (peri)myocarditis in one. In 3/46 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 TF criteria for each diagnosis is listed in Supplemental Table 5.

Acute and long-term outcome

A median of 2 (IQR, 1-4) VTs with a CL of 328±72ms was induced in group A, compared to a median of 2 (IQR, 1-3) VTs in group B with a CL of 257±34ms (P=0.003). In group A, 15% were inducible only after isoprenaline compared to 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 were implanted before discharge. At last follow-up, 37 (80%) group A patients were on antiarrhythmic drugs (amiodarone 8, sotalol 28, mexiletine 1).

In patients of group B, all VTs could be mapped to the epicardial RVOT scar. Complete success was achieved in 10/11 (91%) patients and partial success in 1/11 (P=0.034 for complete success). Nine patients were rendered non-inducible after limited epicardial ablation and one after extensive endocardial ablation of a low unipolar voltage RVOT area. In the remaining patient a non-clinical 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, 9/11 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 competitive level, the remaining 7 (64%) athletes continued training at recreational level. During a median follow-up of 27 (IQR, 6-62) months, 50% of the patients in group A had VT recurrence, but none of the patients in group B.

Discussion

In the present study we describe two electroanatomical 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, but all were longstanding high-level endurance athletes. The isolated RVOT scar served as substrate for fast, re-entry VT with two distinct morphologies. The substrate could be successfully abolished by epicardial ablation in the majority of patients with freedom of VT recurrence. This specific scar pattern, detectable by endocardial unipolar voltage mapping, but not by imaging, is likely the result of exercise-induced pathological remodeling. It may allow distinguishing exercise-induced arrhythmogenic remodeling 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, non-familial 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 ventricular arrhythmias of RV origin, and the presence of ARVC TF criteria 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% of these athletes had definite ARVC if original TF criteria were applied and/or some pathological involvement of the RV, none had regional RV akinesia, dyskinesia, or aneurysm formation.[3] Despite only minor structural alterations and only minor or no revised TF criteria in the majority, 18 (39%) athletes developed major arrhythmic events, including sudden death in 9. Although endurance training was likely to play a role, the underlying substrate and the mechanism of the majority of these ventricular arrhythmias remained unclear.

In a recent series of 82 TF criteria positive ARVC patients, those without desmosomal mutations presented at older age and had performed significantly more intense exercise (MET-Hrs/year) compared to desmosomal mutation positive patients.[8] In contrast to the above mentioned 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.[8] Indeed, ARVC has a typical scar pattern with early involvement of the subtricuspid RV and progression towards 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".

Isolated subepicardial scar in athletes

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 prior studies.[4] All patients with ARVC and an identified (likely) pathogenic mutation had a dominant subtricuspid scar. Likewise and in line with our findings, cardiac sarcoidosis is often involving the peritricuspid region with additional involvement of the RVOT and septum.[15]

None of the group B athletes in our study fulfilled revised TF criteria 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 9405 MET-hrs/year) compared to patients in group A but also compared to 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 the above-mentioned continuum.

Ventricular arrhythmias in athletes

Exercise-induced ventricular arrhythmias 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, we observed two distinct morphologies in 10/11 patients consistent with two different exit sites from the subepicardial scar (Figure 3-4). Of concern, VTs were fast with a mean VTCL of 257±22ms leading to (pre)syncope in 6/11. If untreated, these VTs may accelerate and may be fatal (Supplemental Figure 2). A dominant RVOT site of origin and multiple inducible morphologies have also been described in a prior cohort of athletes, with VT inducibility as only, albeit weak, predictor of fatal arrhythmic events.[3]

In a recent study, 33 asymptomatic elite master athletes with a training history of 29±8 years did not show any 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 PVCs and non-sustained VTs are observed in 7.3% of asymptomatic athletes and 68% are of RVOT origin.[2] Although mechanism and substrate of these arrhythmias are poorly understood, the common site of origin is striking.

Potential underlying mechanisms: disproportional RV stress in endurance athletes

Physiological cardiac adaptation related to regular exercise includes biventricular dilatation, TWI and prolonged QRS terminal activation and may 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 increase in BNP and troponin levels after a race more pronounced after the longest events (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-MRI image acquisition may not be sufficient to detect subepicardial RVOT scar.

The cause of the predilection of EIAR for the subepicardial RVOT is not clear. 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 the larger radius according to the equation of Laplace. However, additional predisposing factors are likely to be operative to develop the substrate for sustained VT.

Identification of the substrate: ECG, imaging and electroanatomical mapping

A small scar confined to the RVOT is unlikely to result in ECG abnormalities as observed in advanced ARVC. Accordingly, voltages in the precordial and limb leads were high and isolated TWI in V1-V2 was only observed in 2/11 patients in group B, and only 1 had prolonged terminal activation duration.

The subepicardial VT substrate could not be diagnosed by detailed imaging including LGE-MRI. Endocardial bipolar voltage mapping has been described to be superior to LGE-MRI 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 the misdiagnoses "idiopathic, benign RVOT VT" in particular if other non-invasive findings are inconspicuous. Of importance, endocardial unipolar voltages of ≤5.5 mV, a previously suggested cutoff value based on structural normal RV, already suggested the presence of the epicardial scar in all athletes.[10] These scar areas could also 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 perhaps 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.

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 ventricular arrhythmias. Suspicion may be particularly high if two different RVOT VT morphologies are observed. Of importance, major TF criteria and cardiac imaging were negative but endocardial unipolar voltage mapping was diagnostic in all athletes. This scar pattern may 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 as limited epicardial ablation is potentially curative and associated with an excellent prognosis.

Limitations

The study sample was small and the LUMC is a tertiary referral center for VT ablation, which may have resulted in referral bias. In the Netherlands, signal-averaged ECGs 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 voltages areas were present. Although no genetic mutation was found in the athletes by combined next-generation and Sanger-sequencing tests, whole exome sequencing and whole genome sequencing was not performed

Subepicardial RVOT scar has been described in patients with Brugada Syndrome and Brugada type ECGs. Although Brugada syndrome cannot be completely excluded, none

of the group B patients had Brugada type 1 or 2 ECG, a suggestive family history for Brugada Syndrome or a pathogenic mutation in the SCN5A gene.

We cannot exclude 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 idiopathic VA. In addition, only 3 athletes with idiopathic VA performed exercise above the 25th percentile of MET-hrs/year of group B patients. Although we could identify the subepicardial scars in all athletes by unipolar voltage mapping, these method may still not be sensitive enough for detection of subtle structural changes that may occur in those performing exercise at lower levels.

This study cannot prove any causal relationship between endurance training and an epicardial RVOT scar. However the uniform scar pattern found only in high endurance athletes' supports a strong association.

The only modest outcome in group A may be due to our more conservative approach offering epicardial ablation only to patients with symptomatic recurrent ATP or ICD shocks. Finally, larger studies with long follow-up after epicardial substrate ablation are warranted to confirm the favorable prognosis and to exclude disease progression.

Conclusion

This study describes a novel clinical entity of an isolated subepicardial RVOT scar as substrate for fast VT in high-level endurance athletes which can be successfully treated by ablation. The specific scar pattern identified by EA voltage mapping but not by imaging may allow distinguishing exercise induced arrhythmogenic remodeling 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.

Perspectives

Core Clinical Competencies: Symptomatic high-level endurance athletes presenting with RVOT VT, are at risk for an isolated subepicardial RVOT scar. Treatment with limited epicardial RF-ablation is potential curative and associated with an excellent prognosis.

Translational Outlook implications: Further studies are needed to evaluate which athlete is at risk for exercised induced arrhythmogenic remodeling and why the epicardial RVOT is the Achilles' heel in high-level endurance athletes.

Translation Outlook implications 2: Genetic testing with whole exome and whole genome testing is warranted to exclude a genetic underlying course.

Reference list

1. La Gerche, A., et al., *Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes.* Eur Heart J, 2012. **33**(8): p. 998-1006.
2. Verdile, L., et al., *Clinical significance of exercise-induced ventricular tachyarrhythmias in trained athletes without cardiovascular abnormalities.* Heart Rhythm, 2015. **12**(1): p. 78-85.
3. Heidbuchel, H., et al., *High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification.* Eur Heart J, 2003. **24**(16): p. 1473-80.
4. Te Riele, A.S., et al., *Mutation-positive arrhythmogenic right ventricular dysplasia/ cardiomyopathy: the triangle of dysplasia displaced.* J Cardiovasc Electrophysiol, 2013. **24**(12): p. 1311-20.
5. Marcus, F.I., et al., *Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria.* Eur Heart J, 2010. **31**(7): p. 806-14.
6. Birnie, D.H., et al., *HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis.* Heart Rhythm, 2014. **11**(7): p. 1305-23.
7. Levine, B.D., et al., *Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 1: Classification of Sports: Dynamic, Static, and Impact: A Scientific Statement From the American Heart Association and American College of Cardiology.* J Am Coll Cardiol, 2015. **66**(21): p. 2350-2355.
8. Sawant, A.C., et al., *Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations.* J Am Heart Assoc, 2014. **3**(6): p. e001471.
9. Piers, S.R., et al., *Epicardial substrate mapping for ventricular tachycardia ablation in patients with non-ischaemic cardiomyopathy: a new algorithm to differentiate between scar and viable myocardium developed by simultaneous integration of computed tomography and contrast-enhanced magnetic resonance imaging.* Eur Heart J, 2013. **34**(8): p. 586-96.
10. Polin, G.M., et al., *Endocardial unipolar voltage mapping to identify epicardial substrate in arrhythmogenic right ventricular cardiomyopathy/dysplasia.* Heart Rhythm, 2011. **8**(1): p. 76-83.
11. Casella, M., et al., *Feasibility of combined unipolar and bipolar voltage maps to improve sensitivity of endomyocardial biopsy.* Circ Arrhythm Electrophysiol, 2015. **8**(3): p. 625-32.
12. Heidbuchel, H., D.L. Prior, and A. La Gerche, *Ventricular arrhythmias associated with long-term endurance sports: what is the evidence?* Br J Sports Med, 2012. **46 Suppl 1**: p. i44-50.
13. James, C.A., *Nature and Nurture in Arrhythmogenic Right Ventricular Cardiomyopathy - A Clinical Perspective.* Arrhythm Electrophysiol Rev, 2015. **4**(3): p. 156-62.
14. La Gerche, A., et al., *Lower than expected desmosomal gene mutation prevalence in endurance athletes with complex ventricular arrhythmias of right ventricular origin.* Heart, 2010. **96**(16): p. 1268-74.
15. Kumar, S., et al., *Ventricular tachycardia in cardiac sarcoidosis: characterization of ventricular substrate and outcomes of catheter ablation.* Circ Arrhythm Electrophysiol, 2015. **8**(1): p. 87-93.
16. Bohm, P., et al., *Right and Left Ventricular Function and Mass in Male Elite Master Athletes: A Controlled Contrast Enhanced CMR Study.* Circulation, 2016.
17. Baldesberger, S., et al., *Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists.* Eur Heart J, 2008. **29**(1): p. 71-8.

18. Zaidi, A., et al., *Clinical Differentiation Between Physiological Remodeling and Arrhythmogenic Right Ventricular Cardiomyopathy in Athletes With Marked Electrocardiographic Repolarization Anomalies.* J Am Coll Cardiol, 2015. **65**(25): p. 2702-11.
19. Wilson, M., et al., *Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes.* J Appl Physiol (1985), 2011. **110**(6): p. 1622-6.
20. Swift, A.J., et al., *LGE patterns in pulmonary hypertension do not impact overall mortality.* JACC Cardiovasc Imaging, 2014. **7**(12): p. 1209-17.
21. Marra, M.P., et al., *Imaging study of ventricular scar in arrhythmogenic right ventricular cardiomyopathy: comparison of 3D standard electroanatomical voltage mapping and contrast-enhanced cardiac magnetic resonance.* Circ Arrhythm Electrophysiol, 2012. **5**(1): p. 91-100.
22. Tokuda, M., et al., *Direct comparison of adjacent endocardial and epicardial electrograms: implications for substrate mapping.* J Am Heart Assoc, 2013. **2**(5): p. e000215.

Supplemental Material

Supplemental Methods

Sport Questionnaire

1.) Please list the sports you played or exercise you did up until your ablation:

Sport/exercise	For how long?	Number of practices	Number of months/ year	Duration of practice (on average)
1.	…. years	….. /week		
2.	…. years	….. /week		
3.	…. years	….. /week		
4.	…. years	….. /week		

2.) How many hours per week do you exercise?

On average _____ hours per week

3.) What is the highest level at which you have competed in the above listed sports?

- o Professional
- o Competition level
- o Recreational

4.) Have you previously (i.e. in your youth) exercised more intensively? If yes, how much

- o Yes
- o No

Sport/exercise	For how long?* (dates)	Number of practices	Number of months/ year	Duration of practice (on average)
1.	From…… Until…….	….. /week		
2.	From…… Until…….	….. /week		
3.	From…… Until…….	….. /week		
4.	From…… Until…….	….. /week		

* During which period (years) did you performed this sport? (For example from 1998 until 2005)

5.) What is the highest level at which you have ever competed in any sport?

- o Professional
- o Competition level
- o Recreational

6.) Have you ever had an arrhythmia during exercise?

- o Yes
- o No
- o Unknown

7.) Have you ever had any of the following symptoms during exercise? You may check multiple options.

- o Light-headedness
- o Fainting or syncope
- o Dizziness
- o Sudden extreme fatigue
- o Palpitations

8.) Have you decreased your exercise due to arrhythmias?

- o Yes
- o No

If yes why:

Genetic analysis consisted of Next Generation Sequencing of 55 or 60 cardiomyopathy-related genes:

ABCC9 (ATP-binding cassette, subfamily C, member 9), ACTC1 (Actin, alpha, cardiac muscle), ACTN2 (Actinin, alpha-2), ANKRD1 (Ankyrin repeat domain-containing protein 1), ANO5 (Anoctamin 5)†, BAG3 (BCL2-associated athanogene 3), CALR3 (Calreticulin 3), CAV3 (Caveolin 3), CRYAB (Crystalline, alpha-B), CSRP3/MLP (Cysteine- and glycine-rich protein 3), CTNNA3 (Catenin, alpha 3)†, DES (Desmin), DMD (Dystrophin), DSC2 (Desmocollin 2), DSG2 (Desmoglein 2), DSP (Desmoplakin), DTNA (Dystrobrevin, alpha), EMD (Emerin), EYA4 (eye absent 4)*, FHL1 (Four and a half LIM Domains 1)†, FKTN (Fukutin)†, GATAD1 (GATA zinc finger domain-containing protein 1)*, GLA (Galactosidase, alpha), HCN4 (Hyperpolarization activated cyclic nucleotide gated potassium channel 4)†, ILK (Integrin-linked kinase)†, JPH2 (Junctophilin 2), JUP (Junction plakoglobin), LAMA4 (Laminin alpha-4), LAMP2 (Lysosome-associated membrane protein 2), LDB3 (LIM domain-binding 3), LMNA (Lamin A/C), MIB1 (Mindbomb E3 ubiquitin protein ligase 1)†, MYBPC3 (Myosin-binding protein C, cardiac), MYH6 (Myosin, heavy chain 6, cardiac muscle, alpha), MYH7 (Myosin, heavy chain 7, cardiac muscle, beta), MYL2 (Myosin, light chain 2, regulatory, cardiac, slow), MYL3 (Myosin, light chain 3, alkali, ventricular, skeletal, slow), MYLK2 (Myosin light chain kinase 2)†, MYOZ1 (Myozenin 1), MYOZ2 (Myozenin 2), MYPN (gamma-2, Myopalladin), NEXN (Nexilin, rat, homolog of), PKP2 (Plakophilin 2), PLN (Phospholamban), PRDM16 (PR domain containing 16)†, PRKAG2 (Protein kinase, AMP-activated, noncatalytic), PSEN1 (Presenilin 1)*, PSEN2 (Presenilin 2)*, RBM20 (RNA-binding protein 20), RYR2 (Ryanodine receptor 2), SCN5A (Sodium channel, voltage gated, type V, alpha subunit), SGCD (Sarcoglycan, delta), SOD2 (superoxide dismutase 2, mitochondrial)*, TAZ (Tafazzin), TBX20 (T-box 20), TCAP (Titin-cap), TMEM43 (Transmembrane protein 43), TNNC1 (Troponin C, slow), TNNI3 (Troponin I, cardiac), TNNT2 (Troponin T2, cardiac), TPM1 (Tropomyosin 1), TTN (Titin), TTR (Transthyretin)†, TXNRD2 (Thioredoxin reductase 2), VCL (Vinculin).

*denotes genes only tested in 55 cardiomyopathy related gene-panel ; †, genes only tested in 60 gene-panel.

ECG

A resting non-paced 12-lead ECG (25mm/s, 0.1mV/mm) prior to the index ablation was analyzed for QRS axis, voltages, QRS duration, PR- and QT intervals, (incomplete) left/right bundle branch block, left/right ventricular hypertrophy (Sokolow-Lyon criteria), presence and type of early repolarization, epsilon waves, terminal activation duration including all depolarized deflections, T wave inversion (TWI, ≥1mm), deep TWI (≥2mm), biphasic T-waves and fragmentation of the QRS complex.[1-5] RBBB and incomplete RBBB was defined as QRS duration >120ms and >100 and ≤120ms respectively, with rSR' pattern in V1 and qRS in V6. Complete LBTB was defined as >0.12ms with broad

R in I, aVL, V5 and V6 and absent Q. ST-segment elevation was defined as an elevation of the ST junction of ≥0.1mV and upward sloping of the ST segment. Microvoltations were defined as amplitudes lower than <5mm in any of the limb leads and <10mm in any of the precordial leads. ER was defined as an elevation of the terminal portion of the QRS complex of >0.1mV in ≥2 contiguous inferior (II, III, and aVF) or lateral (I, aVL, and V_4–V_6) leads, manifested as QRS notching or slurring. A notched ER was defined as an upward deflection and slurring as a conduction delay beginning on the QRS down stroke.[6] Fragmented QRS was defined in narrow QRS (<120ms) complex as various RSR' patterns (including: the presence of an additional R wave (R') in the nadir of the S wave notching in the R wave; or >1 R' in at least 2 contiguous leads. In a broad QRS (≥120ms) complex it was defined as >2 notches or multiple notches of the R wave or i in the nadir of the S wave in at least 2 consecutive leads.[7] All ECGs were reviewed by 2 experienced observers (JV, YN). In case of disagreement, a third observer (KZE) reviewed for consensus

Genetic testing and imaging

Genetic testing by combined next-generation and Sanger sequencing of ≥55 cardiomyopathy-related genes became available in 2012 and was performed in all patients, including those ablated before 2012, unless a pathogenic mutation in a desmosomal gene had already been previously identified. Mutations were categorized as benign (benign or likely benign), variant of unknown significance (unknown whether benign or pathogenic), or pathogenic (pathogenic or likely pathogenic).[8] ARVC-associated mutations included desmosomal mutations (*PKP2*, *DSC2*, *DSG2*, *JUP* and *DSP*) and mutations in *CTNNA3*, *DES*, *LMNA*, *PLN*, *TGFB3*, *TMEM43*, and *TTN*.[9]

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. When CMR was contraindicated, echocardiography was used. RV angiograms were reviewed, if performed. All imaging studies performed before 2010 were reanalyzed according to the 2010 TFC by an independent physician blinded to all study data. Before endocardial-epicardial ablation, ECG-gated cardiac computed tomography (CT) imaging was performed and imported into the EA mapping system as previously described [10, 11] to provide detailed information on epicardial fat thickness and the location of the tricuspid annulus and pulmonary valve.

Electrophysiological evaluation

Epicardial access was obtained through a subxiphoid puncture if prior endocardial ablation had failed or an epicardial substrate was suspected based on endocardial voltage and/or activation mapping. EA voltage mapping of the RV endocardium and

epicardium was performed during sinus rhythm or RV pacing (if pacing dependent; n = 3) using a 3.5 mm irrigated-tip catheter and the CARTO system. Electrograms were filtered at 30 to 400 Hz (bipolar) and 1 to 240 Hz (unipolar). Abnormal electrograms (fragmented [high frequency, low amplitude], late potentials [inscribing after QRS and separated by an isoelectric segment >20ms]) were tagged on the map.[11]

VT ablation

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 substrate and pace-mapping. Whenever possible, a briefly tolerated VT was reinduced to perform entrainment maneuvers and/or terminate VT by radiofrequency application (≤45W, temperature ≤43°C, flow 20 to 30 ml/min). VT-related sites and fragmented and late potentials were targeted by ablation. At the epicardium radiofrequency application was applied at a safe distance from the coronary arteries.

Reference list

1. Zaidi, A., et al., *Clinical Differentiation Between Physiological Remodeling and Arrhythmogenic Right Ventricular Cardiomyopathy in Athletes With Marked Electrocardiographic Repolarization Anomalies.* J Am Coll Cardiol, 2015. **65**(25): p. 2702-11.
2. Corrado, D., et al., *Recommendations for interpretation of 12-lead electrocardiogram in the athlete.* Eur Heart J, 2010. **31**(2): p. 243-59.
3. Uberoi, A., et al., *Early repolarization in an ambulatory clinical population.* Circulation, 2011. **124**(20): p. 2208-14.
4. Heng, S.J., E.N. Clark, and P.W. Macfarlane, *End QRS notching or slurring in the electrocardiogram: influence on the definition of "early repolarization".* J Am Coll Cardiol, 2012. **60**(10): p. 947-8.
5. Das, M.K., et al., *Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease.* Heart Rhythm, 2007. **4**(11): p. 1385-92.
6. Naruse, Y., et al., *Early repolarization increases the occurrence of sustained ventricular tachyarrhythmias and sudden death in the chronic phase of an acute myocardial infarction.* Circ Arrhythm Electrophysiol, 2014. **7**(4): p. 626-32.
7. Hayashi, T., et al., *Fragmented QRS predicts cardiovascular death of patients with structural heart disease and inducible ventricular tachyarrhythmia.* Circ J, 2013. **77**(12): p. 2889-97.
8. Bhonsale, A., et al., *Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers.* Eur Heart J, 2015. **36**(14): p. 847-55.
9. Lazzarini, E., et al., *The ARVD/C genetic variants database: 2014 update.* Hum Mutat, 2015. **36**(4): p. 403-10.
10. van Huls van Taxis, C.F., et al., *Real-time integration of MDCT-derived coronary anatomy and epicardial fat: impact on epicardial electroanatomic mapping and ablation for ventricular arrhythmias.* JACC Cardiovasc Imaging, 2013. **6**(1): p. 42-52.
11. Piers, S.R., et al., *Epicardial substrate mapping for ventricular tachycardia ablation in patients with non-ischaemic cardiomyopathy: a new algorithm to differentiate between scar and viable myocardium developed by simultaneous integration of computed tomography and contrast-enhanced magnetic resonance imaging.* Eur Heart J, 2013. **34**(8): p. 586-96.

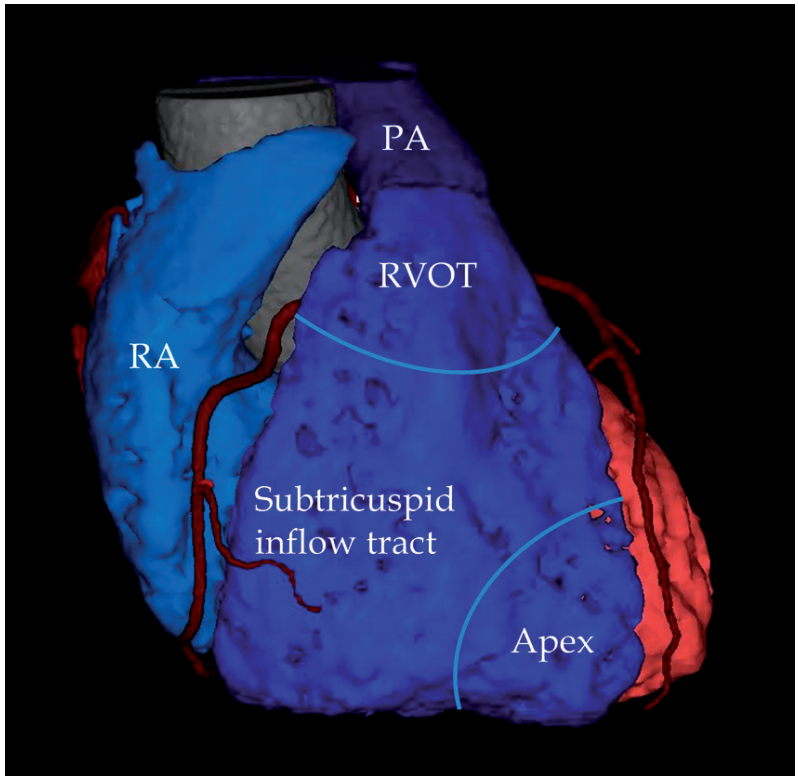
Supplemental results

Genetics

Genetic testing was performed in 56 (98%) of the patients, except in one sarcoidosis patient. In group A, 28/45 (62%) patients and all patients in group B were tested by combined next generation and Sanger sequencing of ≥55 cardiomyopathy-related genes. In group A, 16/45 (36%) were tested with a 55 genes panel, 9/45 (20%) with a 60 genes panel and 3/45 (7%) were evaluated by another panels for respectively 41, 47 and 65 cardiomyopathy genes. In group B, 6/11 (55%) patients were tested with a 55 genes panel and 5/11 (45%) with a 60 genes panel.

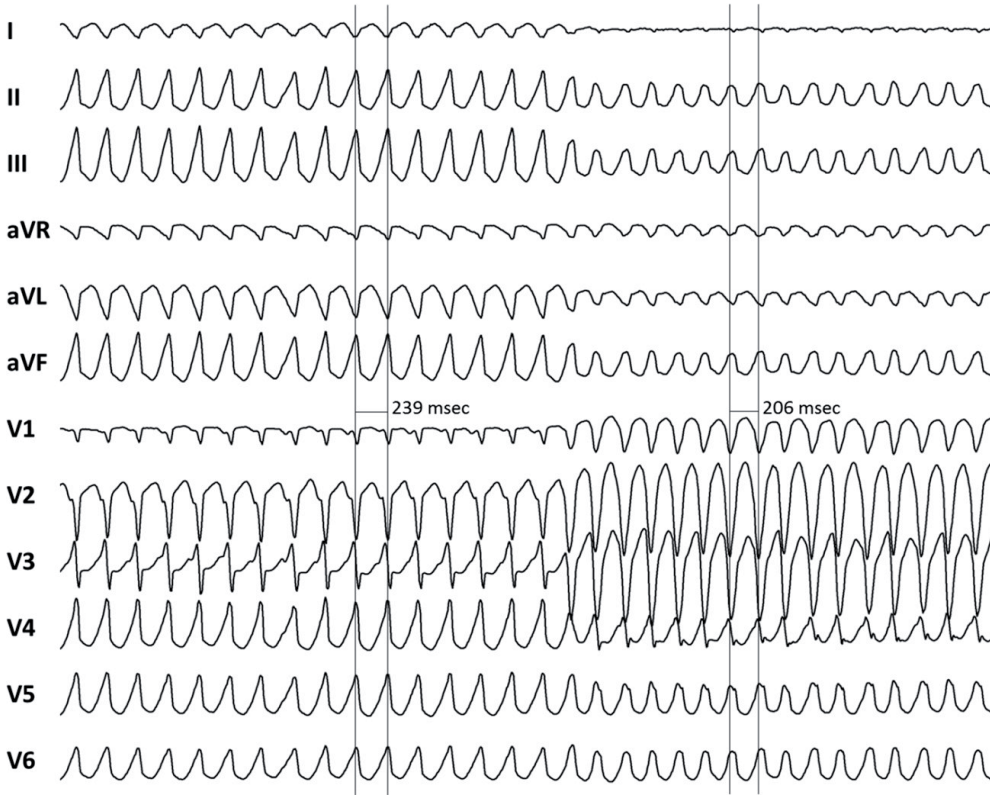
Supplemental Figures

Supplemental Figure 1. 3-plus 1-segment model of the RV



The 3-plus-1 (=septum) segment model of the RV.

Supplemental Figure 2. VT of athlete of group B with spontaneous change in morphology and acceleration



12-lead ECG of spontaneous VT in endurance athlete with a VT cycle length of 239ms with spontaneous conversion and acceleration to the second VT- morphology with a cycle length of 206ms.

Supplemental Table 1. Scar distribution per individual patient

	PT.	Subtricuspid		Apex		RVOT		Septum	Diagnosis	Athlete	Training hours/ week†	Mutation
		ENDO	EPI	ENDO	EPI	ENDO	EPI	ENDO				
Group A	1	1	1	1	1	1	1	0	ARVC	No		1
	2	1	1	0	0	1	1	0	ARVC	No		1
	3	0	1	0	0	0	1	0	ARVC	No		1
	4	1	1	1	1	1	1	0	ARVC	No		1
	5	1	1	0	0	1	1	0	ARVC	No		1
	6	1	1	0	0	1	1	0	ARVC	No		1
	7	1	1	0	0	0	0	0	ARVC	No		0
	8	1	1	0	0	0	0	0	ARVC	No		1
	9	1	1	0	0	1	1	0	ARVC	No		0
	10	0	1	0	0	1	0	0	ARVC	No		1
	11	1	1	0	1	0	1	0	ARVC	No		1
	12	1	1	0	0	1	1	1	ARVC	No		0
	13	1	NA	1	NA	1	NA	0	ARVC	No		1
	14	1	NA	0	NA	0	NA	0	ARVC	No		1
	15	1	NA	0	NA	1	NA	0	ARVC	No		1
	16	1	NA	0	NA	0	NA	0	ARVC	No		1
	17	1	NA	1	NA	1	NA	0	ARVC	No		1
	18	1	NA	0	NA	0	NA	0	ARVC	No		1
	19	1	NA	0	NA	1	NA	0	ARVC	No		0
	20	1	NA	0	NA	0	NA	0	ARVC	No		0
	21	1	NA	1	NA	1	NA	0	ARVC	No		1
	22	1	NA	0	NA	0	NA	0	ARVC	No		1
	23	1	1	1	1	1	0	0	ARVC	Yes	8	1
	24	1	1	0	0	0	0	0	ARVC	Yes	10	0
	25	1	1	1	0	1	1	0	ARVC	Yes	10	0
	26	0	1	0	0	0	1	0	ARVC	Yes	10	1
	27	1	1	0	0	0	0	0	ARVC	Yes	6	1
	28	0	1	0	0	1	1	0	ARVC	Yes	8	1
	29	1	1	0	1	0	1	0	ARVC	Yes	6	1
	30	1	NA	0	NA	0	NA	0	ARVC	Yes	9	1
	31	1	NA	1	NA	1	NA	1	ARVC	Yes	12	1
	32	1	NA	0	NA	1	NA	0	ARVC	Yes	20	1
	33	1	NA	1	NA	1	NA	1	ARVC	Yes	7	0
	34	1	1	0	0	1	1	0	ARVC	Yes	12	0
	35	1	NA	0	NA	1	NA	0	ARVC (bor)	Yes	8	1
	36	1	1	0	0	0	0	0	ARVC (bor)	No		0
	37	1	1	0	1	1	1	0	ARVC (bor)	Yes	8	0
	38	0	1	0	0	0	0	0	Sarcoidosis	Yes	10	1
	39	1	1	1	1	0	0	1	Sarcoidosis	No		0
	40	1	1	0	1	1	1	1	Sarcoidosis	No		0
	41	1	1	0	1	0	0	1	Sarcoidosis	No		NA
	42	1	NA	0	NA	1	NA	0	Sarcoidosis	No		0
	43	1	1	0	0	0	0	1	Myocarditis	Yes	7	0
	44	1	1	0	0	0	0	0	SuO	No		0
	45	0	1	0	0	0	0	0	SuO	No		1
	46	1	NA	1	NA	1	NA	0	SuO	No		1

Group B	1	0	0	0	0	0	1	0	RVOT scar	Yes	25	0
	2	0	0	0	0	0	1	0	RVOT scar	Yes	15	0
	3	0	0	0	0	0	1	0	RVOT scar	Yes	14	0
	4	0	0	0	0	0	1	0	RVOT scar	Yes	7	0
	5	0	0	0	0	0	1	0	RVOT scar	Yes	15	0
	6	0	0	0	0	0	1	0	RVOT scar	Yes	10	0
	7	0	0	0	0	0	1	0	RVOT scar	Yes	15	0
	8	0	0	0	0	0	1	0	RVOT scar	Yes	14	0
	9	0	0	0	0	0	1	0	RVOT scar	Yes	8	0
	10	0	0	0	0	0	1	0	RVOT scar	Yes	40	0
	11	0	NA	0	NA	1*	NA	0	RVOT scar	Yes	20	0

The presence of scar is denoted as 1; NA, not acquired (only endocardial mapping performed).

† indicates training hours per week only in endurance athletes; * patient with preserved endocardial bipolar voltages but underwent extensive ablation of a low unipolar voltage in the RVOT; ARVC, arrhythmogenic right ventricular cardiomyopathy; ARVC (bor), borderline ARVC; SuO, scar of unknown origin

Supplemental Table 2. Genetic mutations

Classification	Genes	Amino acid change	Nucleotide change	NM number	Mutations (n)
Desmosomal	PKP2	p.(Val406Serfs*4)	c.1211dupT	NM_004572.3	7
		p.(Cys796Arg)	c.2386T>C	NM_004572.3	2
		p.(Pro318Glnfs*29)	c.917_918delCC	NM_004572.3	2
		p.(Arg79*)	c.235C>T	NM_004572.3	2
		p.(Trp678*)	c.2034G>A	NM_004572.3	1
		p.(Arg651*)	c.1951C>T	NM_004572.3	1
		p.?; mutant RNA splice product	c.2489+1G>A	NM_004572.3	1
		p.(His733Alafs*8)	c.2197_2202delinsG	NM_004572.3	1
		p.(Asp460Asn; p.Val445fs)	c.1378G>A: r.1333_1378del	NM_004572.3	1
		p.(Ser826Argfs*105)	c.2478delT	NM_004572.3	1
	DSG2	p.?; mutant RNA splice product	c.82-1G>T	NM_001943.1	1
	DSC2	p.?; mutant RNA splice product	c.2125+1delG	NM_004949.3	1
	DSP	p.(Ser711Cysfs*4)	c.2131 _2132delAG	NM_004415.2	1
ARVC-associated	PLN	p.(Arg14del)	c.40_42delAGA	NM_002667.3	1
Non-ARVC associated	MYL2	p.(Glu22Lys)	c.64G>A	NM_000432.3	1
	MYH7	p.(Arg723Cys)	c.2167C>T	NM_000257.2	1
	CSRP3	p.(Asn64Lysfs*15)	c.191dupA	NM_ 213599.2	1
	MIB1	p.(Gln473*)	c.1417C>T	NM_020774.3	1
Multiple mutations	PKP2	p.(Val406Serfs*4)	c.1211dupT	NM_004572.3	1
	LMNA	p.(Arg435Cys)	c.1303C>T	NM_ 170707.3	1
	PLN	p.(Arg14del)	c.40_42delAGA	NM_002667.3	1
	DES	p.(Ala273Argfs*10)	c.816dupC	NM_001927.3	1

CRSP3 indicates cysteine and glycine rich protein 3, DES desmin, DSC2 Desmocollin 2, DSG2 Desmoglein 2, DSP Desmoplakin, LMNA, lamin A/C, MIB1 mindbomb homolog 1, PLN Phospholamban, MYL2 Myosin light chain 2, MYH7 Myosin heavy chain 7, PKP2 Plakophilin 2

Supplemental Table 3. ECG

	All patients (n= 57)	Group A (Subtricuspid) (n= 46)	Group B (Isolated RVOT) (n= 11)	P-value*
Atrial paced	9 (16%)	9 (20%)	0 (0%)	0.11
Heart rate bpm.	60±12	61±13	56±8	0.238
PR-segment ms.	174 (138-201)	180 (140-204)	144 (134-159)	0.072
Hearts axis, °	39±58	31±60	71±38	0.040
QRS-duration, ms	111±20	114±25	103±14	0.193
QTc, ms	432±37	437±38	414±23	0.068
RBBB incomplete	4 (7%)	4 (9%)	0 (0%)	0.31
RBBB complete	12 (21%)	11 (24%)	1 (9%)	0.279
LVH	1 (2%)	0 (0%)	1 (9%)	0.039
RVH	5 (9%)	4 (9%)	1 (9%)	0.967
Pathological Q	2 (4%)	2 (4%)	0 (0%)	0.481
ER	10 (18%)	6 (13%)	4 (36%)	0.068
ER notch	6 (11%)	5 (11%)	1 (9%)	0.863
ER slur	4 (7%)	1 (2%)	3 (27%)	0.003
ER inferolateral	5 (9%)	4 (9%)	1 (9%)	0.967
ER with STj elevation	2 (4%)	1 (2%)	1 (9%)	0.263
ER without STj elevation	8 (14%)	5 (11%)	3 (27%)	0.159
QRS_{frag}	41 (72%)	35 (76%)	6 (55%)	0.153
QRS_{frag} inferior	36 (63%)	31 (67%)	5 (46%)	0.175
QRS_{frag} lateral	26 (46%)	22 (48%)	4 (36%)	0.493
QRS_{frag}(V1-V3)	17 (30%)	15 (33%)	2 (18%)	0.347

Variables are expressed as number (percentage), mean±standard deviation, or median (interquartile range).

*Isolated RVOT (Group B) vs. subtricuspid group (group A). ER denotes early repolarization; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; RVOT, right ventricular outflow tract; QRS_{frag}, fragmented QRS; QTc, corrected QT interval; STj, ST junction; TAD, terminal activation duration; TWI, T-wave inversion; VT, ventricular tachycardia.

Supplemental Table 4. Echocardiography

	All patients (n= 57)	Group A (Subtricuspid) (n= 46)	Group B (Isolated RVOT) (n= 11)	P-value*
Echocardiography	17	15	2	
WMA and/or Aneurysms	9/17 (53%)	9/15 (60%)	0/2 (0%)	0.11
WMA	2/17 (12%)	2/15 (13%)	0/2 (0%)	0.582
Aneurysms	8/17 (47%)	8/15 (53%)	0/2 (0%)	0.156
TAPSE mm	17±8	16±7	25±0	0.138
RVFAC	30±11	29±11	33±11	0.658
PLAX	43±6	43±6	38±6	0.281
PLAX BSA	22±4	22±4	22±6	0.929
PSAX	41±6	22±4	38±5	0.454
PSAX BSA	21±3	21±3	22±6	0.646
RVD1	49±8	50±9	45±7	0.475
LVEDD	48±5	49±5	45±7	0.394
RVD1/ LVEDD	1.0±0.2	1.0±0.2	1.0±0.0	0.821
LVEDV	101±31	99±32	114±20	0.546
LVESV	48±21	47±22	53±8	0.748
LVEF	53±10	53±9	53±15	0.954

Variables are expressed as number (percentage), mean±standard deviation.

*Isolated RVOT (Group B) vs. subtricuspid group (Group A). BSA indicates body surface area; LVEDD, LV end diastolic diameter; LVEDV, LV end diastolic volume; LVEF, LV ejection fraction; LVESV, LV end systolic volume; PLAX, posterior long axis; PSAX, posterior short axis; RVD1, RV ventricular basal dimension; RVFAC, RV fraction area change; RVFAC, RV fractional area change; TAPSE, tricuspid annular plane systolic excursion; WMA, wall motion abnormality.

Supplemental Table 5.Task Force criteria and final diagnosis

	Definite	Borderline	Possible		Negative
			1 major	double minor	
Number of pts (%)	38 (67%)	3 (5%)	4 (7%)	4 (7%)	8 (14%)
ARVC	34 (60%)	-	-	-	-
ARVC borderline	-	3 (5%)	-	-	-
Sarcoid	4 (7%)	-	1 (2%)	-	-
Myocarditis	-	-	1 (2%)	-	-
SuO	-	-	2 (4%)	1 (2%)	-
Sport induced	-	-	-	3 (5%)	8 (14%)

Variables are expressed as number (percentage).

ARVC Task Force Criteria; Definite = 2 major, 1 major and 2 minor or 4 minor from different categories, borderline = 1 major and 1 minor or 3 minor, possible is 1 major or 2 minor and negative 1 or no minor criteria. Abbreviation as in supplemental Table 1.