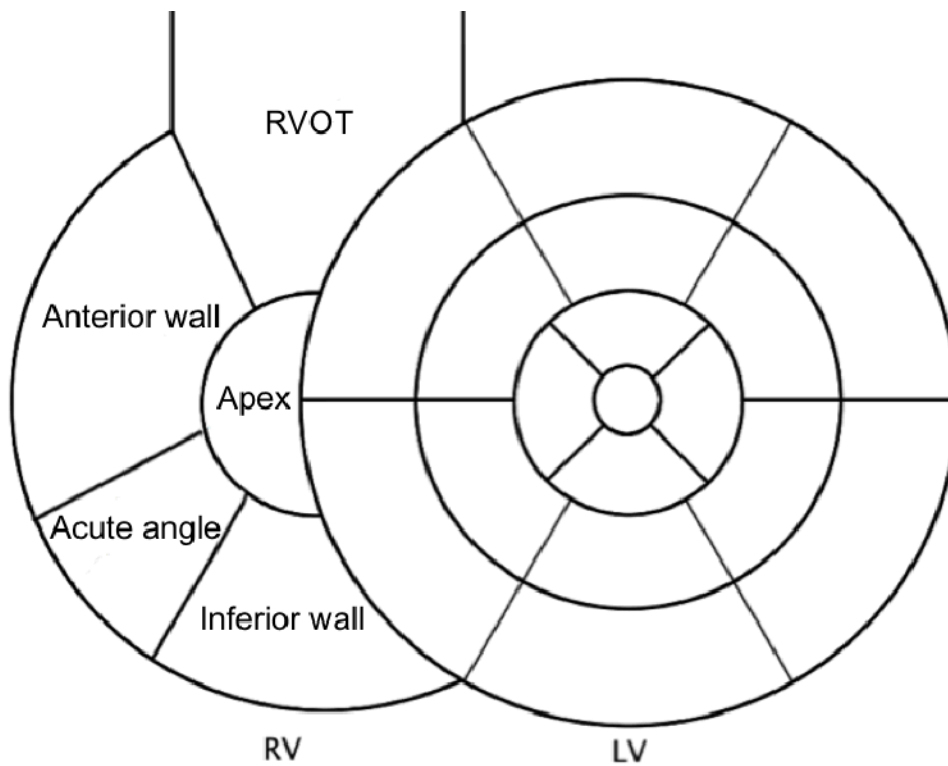


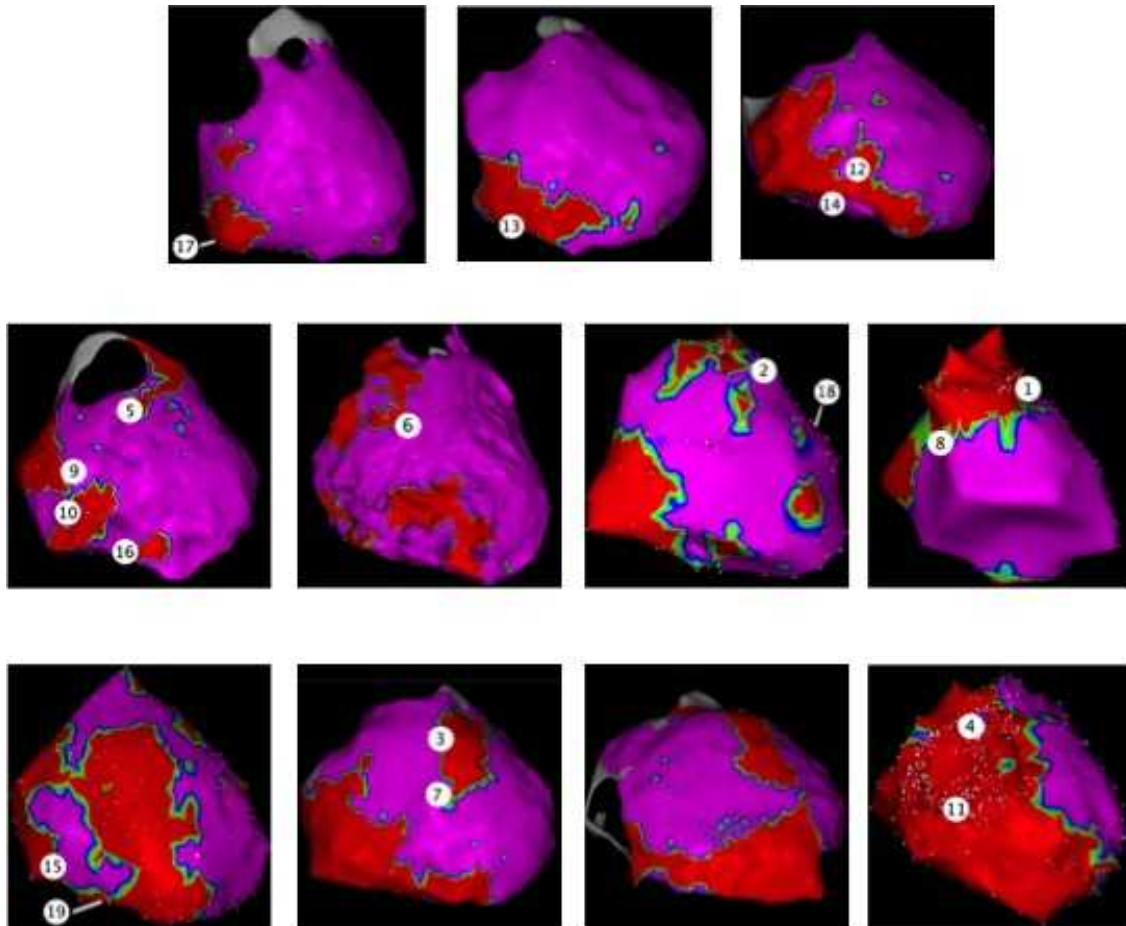
## Supplementary Material

### Supplementary Figures

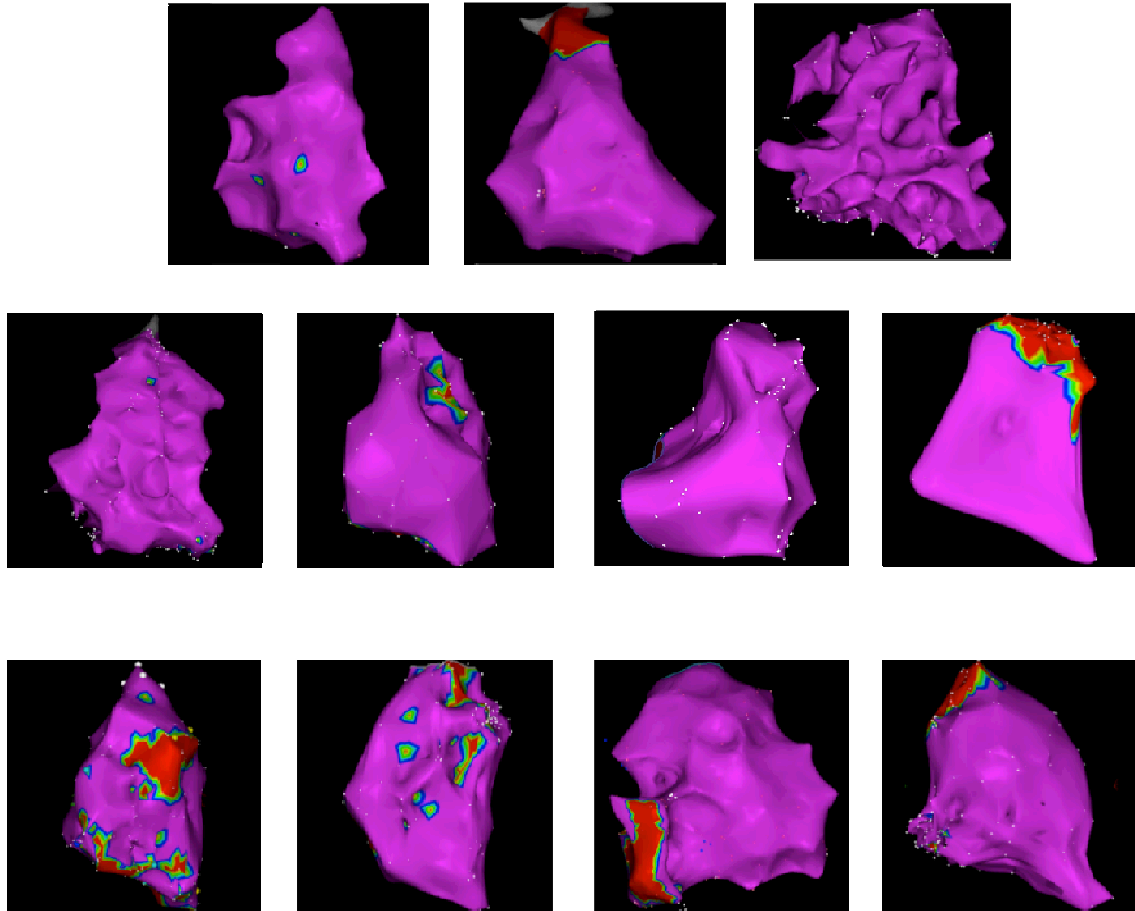
**Supplementary Figure 1.** Schematic representation of our scoring system for regional cardiac involvement. A 5-segment RV and 17-segment LV model<sup>13</sup> was used to score cardiac regional involvement. Abbreviations: LV: left ventricular, RV: right ventricular, RVOT: right ventricular outflow tract.



**Supplementary Figure 2.** Epicardial electroanatomic voltage maps for 11 patients who underwent a complete electrophysiological study. Numbers in the images refer to sites of successful VT ablation in these patients (Figure 5B in the main manuscript). Electroanatomic scar (<0.5 mV) is colored red; normal and low-voltage myocardium ( $\geq 0.5$  mV) is colored purple. Abbreviations: VT: ventricular tachycardia.

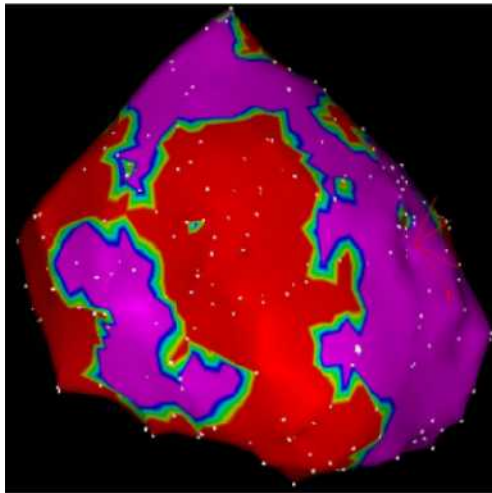


**Supplementary Figure 3.** Endocardial electroanatomic voltage maps for 11 patients who underwent a complete electrophysiological study. Electroanatomic scar (<0.5 mV) is colored red; normal and low-voltage myocardium ( $\geq 0.5$  mV) is colored purple.

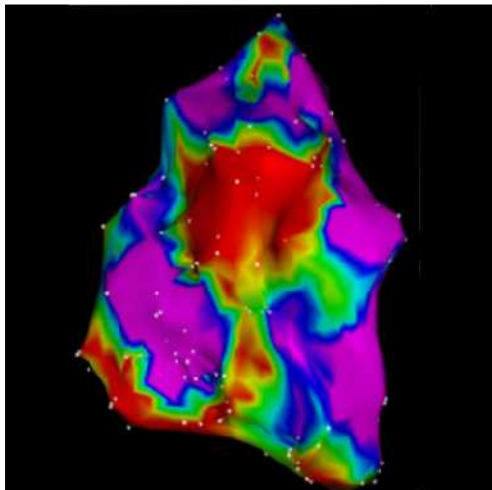


**Supplementary Figure 4.** Representative example of correspondence between epicardial scar (<0.5 mV) and endocardial low voltage area (<1.5 mV) in an ARVD/C patient. Abbreviations: ARVD/C: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy.

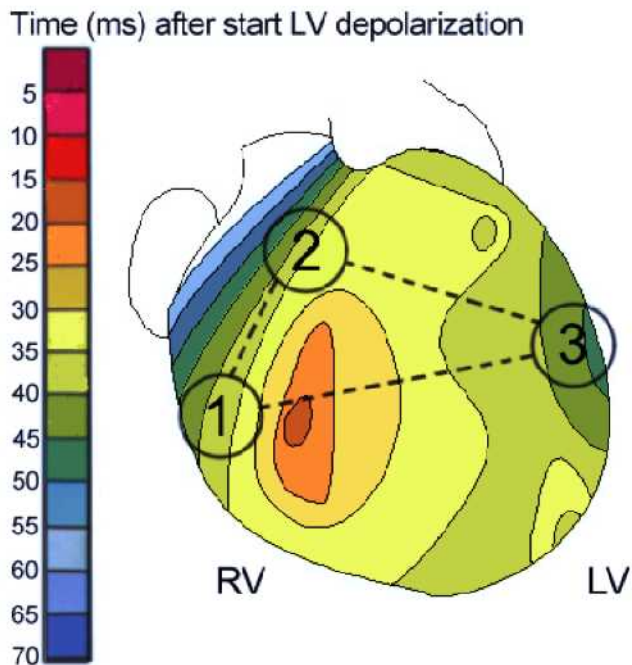
**(A).** Anteroposterior view of the epicardial electroanatomic voltage map showing a large area of epicardial scar involving the subtricuspid region, RV inferior wall, and RV free wall. An encircled area of normal voltage can be appreciated in the RV anterior wall. Abbreviations: RV: right ventricular, RVOT: right ventricular outflow tract.



**(B).** Anteroposterior view of the endocardial electroanatomic voltage map revealing low voltage in the subtricuspid region, RV inferior wall, and RV anterior wall. Epicardial scar and endocardial low voltage show a very similar regional distribution. Abbreviations: RV: right ventricular.



**Supplementary Figure 5.** New Triangle of Structural Abnormalities in Early ARVD/C. Structural abnormalities in ARVD/C preferentially locate to the epicardial subtricuspid region (1), the RV basal anterior wall (2), and the LV posterolateral wall (3). These regions are all late activated region of the normal heart during sinus rhythm, depicted by isochronic activation times (based on Durrer et al, Circulation 1970; 41:899-912). This activation delay is aggravated in ARVD/C. Abbreviations: ARVD/C: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, LV: left ventricular, RV: right ventricular.



## Supplementary Tables

**Supplementary Table 1.** Mutations among the study population

Gene; n (%)	Amino Acid Change	Nucleotide Change	Overall (n=80)	CMR (n=74)	EPS (n=11)
<b>PKP2; 66 (83)</b>	R79X	235C>T	10	9	1
	Mutant splice product	2146-1G>C	8	7	1
	W538X	1613G>A	5	5	0
	A733fsX740	2197_2202delinsG	3	3	0
	Mutant splice product	2489+1G>A	3	3	0
	V837fsX930	2509delA	3	3	0
	S406fsX4	1211-1212insT	3	3	0
	R413X	1237C>T	3	3	0
	P323fsX350	968_971delAGGC	3	3	0
		deletion exon 1-14	3	3	0
	P672fsX683	2013delC	3	2	1
	F424S	1271T>C	2	2	0
	Mutant splice product	2489+4A>C	2	2	0
	V587I	1759G>A	2	2	0
	Q617X	1849C>T	1	1	1
	S50fsX110	148_151delACAG	1	1	0
	S615F	1844C>T	1	1	0
	W538X	1613G>A	1	1	0
	S587fsX69	1759delG	1	1	0
	Q133X	397C>T	1	1	0
	E601fsX55	1803delC	1	1	0
	V587fsX69	1760delT	1	1	0
	V725SfsX19	2169_2172dupAGTT	1	1	1
	C796R	2386T>C	1	1	0
	R651X	1951C>T	1	0	1
	L437HfsX11	1307_1315delinsATTTAGTT	1	0	1
	Y221X	663C>A	1	0	1
<b>DSG2; 5 (6)</b>	T335A	1003A>G	3	3	1
	R46W	136C>T	1	1	1
	T1047R	3140C>G	1	1	1
<b>DSP; 3 (4)</b>	E422K	1264G>A	1	1	0
	R160X	478C>T	1	1	0
	Q51X	151C>T	1	1	0
<b>DSC2; 2 (3)</b>	G220R	658G>A	1	1	0
	E426K	1276G>A	1	1	0
<b>Compound/ Digenic Heterozygote; 4 (5)</b>	Mutant splice product (DSG2) + 1038_1040delGAA (DSG2)	523+2T>C (DSG2) + K346del (DSG2)	1	1	0
	S50fsX110 (PKP2) + T335A (DSG2)	148_151delACAG (PKP2) + 1003A>G (DSG2)	1	1	0
	C796R (PKP2) + T335A (DSG2)	2386T>C (PKP2) + 1003A>G (DSG2)	1	1	0
	A358T (DSG2)	1072G>A (DSG2) + deletion exon 1-14 (PKP2)	1	1	0

Abbreviations: CMR: cardiac magnetic resonance imaging, *DSC2*: Desmocollin-2, *DSG2*: desmoglein-2, *DSP*: Desmoplakin, EPS: electrophysiological study, *PKP2*: Plakophilin-2.

**Supplementary Table 2.** Patient Characteristics in the Johns Hopkins and Dutch CMR cohort.

	<b>Overall (n=74)</b>	<b>USA cohort (n=56)</b>	<b>Dutch cohort (n=18)</b>	<b>p-value</b>
Male	31 (42)	28 (49)	3 (17)	0.013
Age at presentation (yrs)	30.5 ± 14.7	28.9 ± 13.6	35.6 ± 17.3	NS
Proband	34 (46)	29 (52)	5 (28)	NS
Symptomatic	50 (68)	37 (66)	13 (72)	NS
Syncope	22 (30)	18 (32)	4 (22)	NS
Presyncope	19 (26)	16 (29)	3 (17)	NS
Palpitations	39 (53)	28 (50)	11 (61)	NS
Chest pain	8 (11)	6 (11)	2 (11)	NS
TFC	6 (range 4-10)	6 (range 4-10)	7 (range 4-10)	NS
Epsilon wave	5 (7)	4 (7)	1 (6)	NS
Prolonged TAD	28 (37)	18 (32)	10 (56)	NS
Negative T waves	68 (92)	53 (95)	15 (83)	NS
V1-3	53 (72)	42 (75)	11 (61)	NS
V1-2	14 (19)	9 (16)	5 (28)	NS
V4-6 with complete RBBB	2 (3)	2 (4)	0 (0)	NS
Late potentials on SAECG*	25/38 (66)	25/38 (66)	0/0 (0)	-
LBBB VT with superior axis	17 (23)	11 (20)	6 (33)	NS
LBBB VT	25 (34)	20 (36)	5 (28)	NS
PVC >500/24 h†	44/60 (73)	31/45 (69)	13/15 (87)	NS
Structural major TFC	38 (51)	26 (46)	12 (67)	NS
Structural minor TFC	12 (16)	8 (14)	4 (22)	NS

\* In the Netherlands, SAECG is not clinical practice and thus not performed in the Dutch cohort. † 60 patients underwent Holter monitoring. Abbreviations: CMR: cardiac magnetic resonance, LBBB: left bundle branch block, PVC: premature ventricular complex, RBBB: right bundle branch block, SAECG: signal-averaged electrocardiograms, TAD: terminal activation duration, TFC: Task force criteria, VT: ventricular tachycardia.

**Supplementary Table 3.** CMR results for the study population.

	<b>Overall n=74</b>	<b>Limited (0-1 region) n=27</b>	<b>Moderate (2-3 regions) n=20</b>	<b>Advanced (4-5 regions) n=27</b>	<b>P-value</b>
Age at CMR (yrs)	33.7 ± 15.0	35.9 ± 16.9	31.8 ± 13.0	32.9 ± 14.5	NS
<b>Quantitative parameters</b>					
RV EDV/BSA (ml/m <sup>2</sup> )	103.6 ± 30.7	85.2 ± 16.9	100.3 ± 21.8	124.0 ± 34.2	<0.001
RV EF (%)	41.7 ± 11.4	50.6 ± 6.8	40.4 ± 11.3	34.1 ± 8.9	<0.001
LV EDV/BSA (ml/m <sup>2</sup> )	85.8 ± 14.4	86.9 ± 12.9	80.2 ± 14.0	88.3 ± 15.7	NS
LV EF (%)	53.1 ± 7.4	53.9 ± 6.6	54.4 ± 9.1	51.5 ± 6.8	NS
<b>Qualitative parameters</b>					
Global RV dilatation	32 (43)	2 (7)	10 (50)	20 (81)	<0.001
Global RV hypokinesia	26 (35)	0 (0)	8 (40)	18 (67)	<0.001
RV regional wall motion abnormalities	50 (68)	3 (11)	20 (100)	27 (100)	<0.001
RV regional aneurysm	11 (15)	1 (4)	3 (16)	7 (26)	NS
RV regional fat infiltration	20/71 (28)	3/26 (12)	7/19 (37)	10/26 (39)	NS
RV regional delayed enhancement	9/63 (14)	0/25 (0)	1/15 (7)	8/23 (35)	0.002
Global LV dilatation	5 (7)	3 (11)	0 (0)	2 (7)	NS
Global LV hypokinesia	6 (8)	2 (7)	1 (5)	3 (11)	NS
LV regional wall motion abnormalities	13 (18)	2 (7)	0 (0)	11 (41)	<0.001
LV regional aneurysm	1 (1)	0 (0)	0 (0)	1 (4)	NS
LV regional fat infiltration	25/72 (35)	3/26 (12)	5/20 (25)	17/26 (65)	<0.001
LV regional delayed enhancement	18/65 (28)	2/26 (8)	3/16 (19)	13/23 (57)	<0.001
<b>Fulfilment of TFC for CMR</b>					
Minor TFC	3 (4)	1 (4)	2 (11)	0 (0)	NS
Major TFC	36 (49)	0 (0)	13 (68)	23 (85)	<0.001

Abbreviations: BSA: body surface area, CMR: Cardiac Magnetic Resonance, EDV: end-diastolic volume, EF: ejection fraction, LV: left ventricle, RV: right ventricle.



**Supplementary Table 4.** Comparison of patients with increasing structural severity with respect to clinical variables.

	<b>Limited (0-1 region) n=27</b>	<b>Moderate (2-3 regions) n=20</b>	<b>Advanced (4-5 regions) n=27</b>	<b>P-value</b>
Male	5 (19)	10 (50)	16 (59)	0.007
Age at CMR (yrs)	35.9 ± 16.9	31.8 ± 13.0	32.9 ± 14.5	NS
TFC points	5 (range 4-9)	7 (range 4-9)	8 (range 5-10)	<0.001
<b>Symptomatic</b>	12 (44)	14 (70)	24 (89)	0.002
Syncope	4 (15)	6 (30)	12 (44)	NS
Presyncope	4 (15)	6 (30)	9 (33)	NS
Palpitations	9 (33)	9 (45)	21 (78)	0.003
Chest pain	4 (15)	1 (5)	3 (11)	NS
<b>ECG</b>				
Negative T V1-3 or beyond	14 (52)	13 (65)	26 (96)	0.001
Negative T V1-2	9 (33)	4 (20)	1 (4)	0.021
Epsilon wave	2 (7)	0 (0)	3 (11)	NS
Prolonged TAD	8 (30)	5 (25)	15 (56)	NS
<b>Holter*</b>				
PVC count	602 (range 0-14000)	2230 (range 29-12579)	4436 (range 769-20527)	0.003
>500 PVC/24 hrs	11/23 (48)	14/18 (78)	19/19 (100)	0.001
<b>SAECG†</b>				
Filtered QRS duration (ms)	114 ± 22	111 ± 10	125 ± 30	NS
Low amplitude signal duration (ms)	41 ± 14	34 ± 10	53 ± 30	NS
Root mean square of terminal 40 ms (µV)	26 ± 18	29 ± 15	24 ± 30	NS
≥1/3 parameters abnormal	10/17 (59)	6/11 (55)	9/12 (75)	NS

\* 60 patients underwent Holter monitoring. † 40 patients underwent SAECG. Abbreviations: CMR: cardiac magnetic resonance, FU: follow-up, PVC: premature ventricular complex, RBBB: right bundle branch block, SAECG: signal-averaged ECG, TAD: terminal activation duration, TFC: Task Force Criteria, VT: ventricular tachycardia.