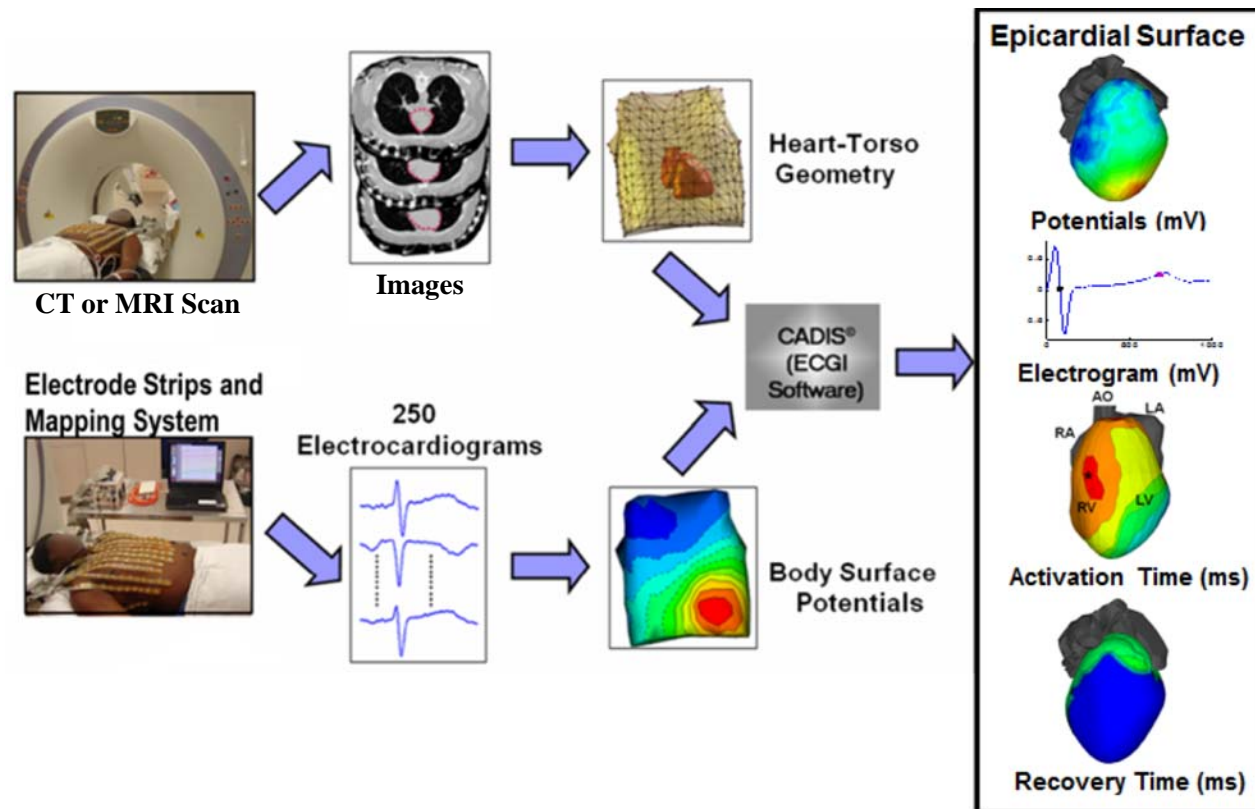# SUPPLEMENTAL MATERIAL

Supplemental Figure S1: The ECGI Procedure

Schematic diagram of the ECGI procedure. A computed tomography (CT) or magnetic resonance imaging (MRI) scan provides the geometry of the epicardial surface and the locations of the recording electrodes on the body surface in the same coordinate system (top). The body surface potential distribution is obtained from 256 simultaneously recorded electrocardiograms (bottom). Solving the inverse problem (middle gray box) yields epicardial potentials and electrograms, from which activation times, recovery times, and other parameters of interest are derived (right frame).

Supplemental Figure S2: Activation Time, Recovery Time, and Activation-Recovery Intervals
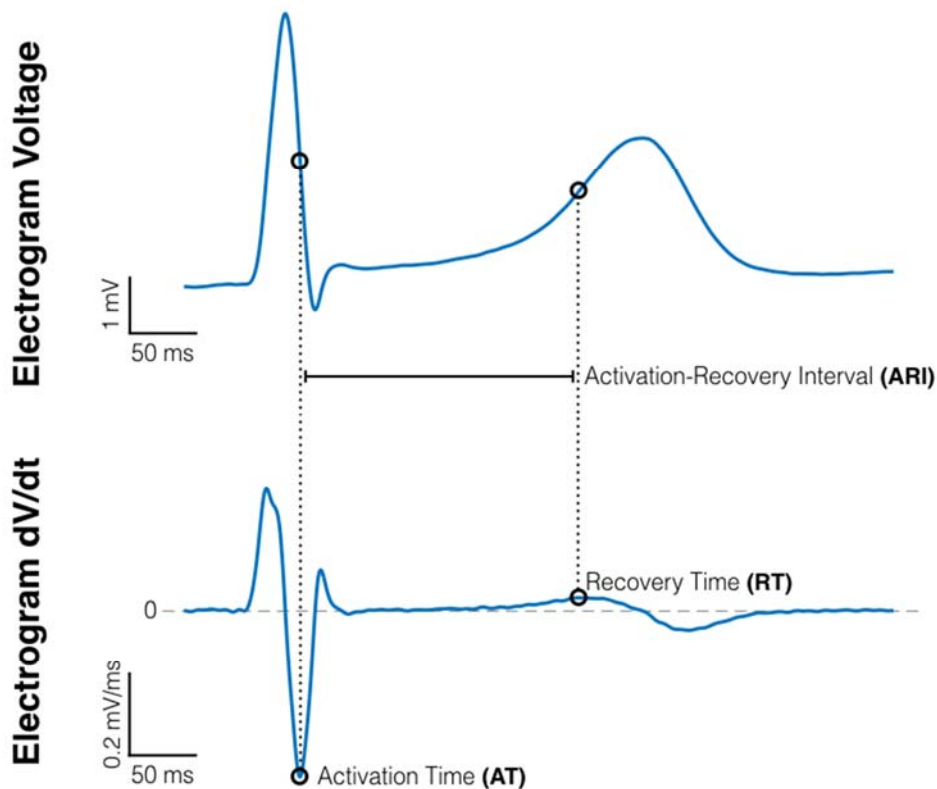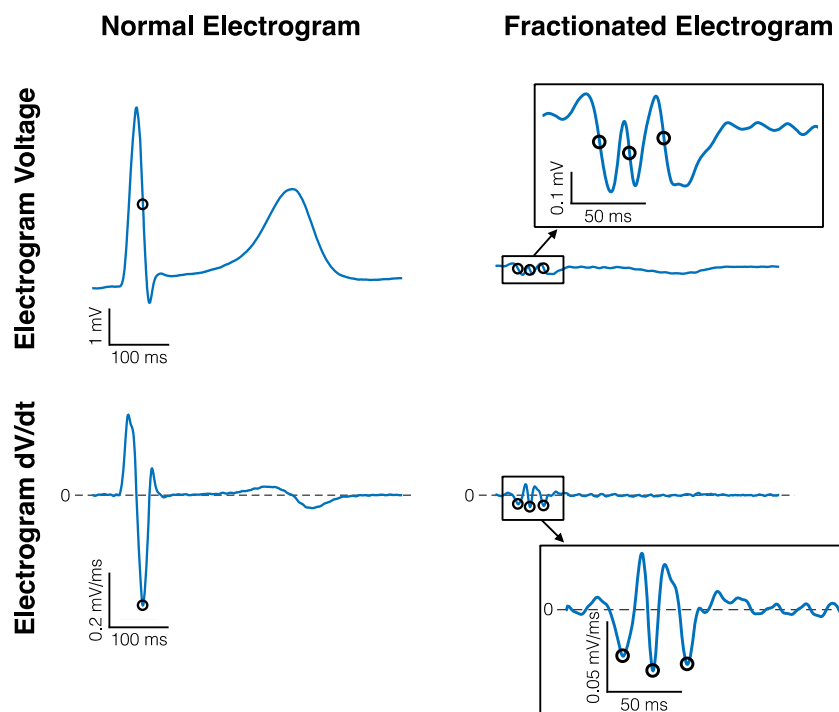

Diagram of unipolar electrogram (EGM) Activation Time (AT), Recovery Time (RT), and Activation-Recovery Interval (ARI). Temporal derivatives (bottom) were computed from EGMs (top). ATs were computed as the time of steepest negative time-derivative of voltage ($-dV/dt_{max}$) in the local QRS complex. Recovery Times were computed as the time of steepest positive time-derivative (dV/dt_{max}) during the T-wave. To eliminate noise effects from RT values, T-waves were lowpass-filtered using a 30 Hz Butterworth filter before determining RT. ARIs (a surrogate for local action potential duration) were computed as the difference between RT and AT.

EGM: electrogram
AT: Activation Time
RT: Recovery Time
ARI: Activation-Recovery Interval

Supplemental Figure S3: Electrogram Fractionation

Normal Electrogram

Fractionated Electrogram

Electrogram Voltage

1 mV
100 ms

0.1 mV
50 ms

Electrogram dV/dt

0

0.2 mV/ms
100 ms

0

0

0.05 mV/ms
50 ms

Diagram of electrogram (EGM) deflections for a normal EGM (left) and a low-amplitude fractionated EGM (right, shown on the same scale). The normal EGM had a single deflection (left, circle) while the fractionated EGM had 3 deflections (right, circles). Insets (large box) show fractionated EGM QRS voltage and dV/dt on enlarged scale. Fractionation was quantified by counting the number of steep downward deflections between the QRS onset and the start of the T-wave. Temporal derivatives (dV/dt, bottom) were computed from unipolar EGMs (top). Downward deflections were regions of EGMs with a negative dV/dt. Multiple deflections occurred when there was a positive dV/dt between downward deflections. The thresholds for steep downward deflections were:

1) Deflection peak-to-peak voltage amplitude ≥ 10% of the EGM peak-to-peak voltage amplitude
2) Deflection –dV/dt ≥ 70% of the EGM maximum –dV/dt

Additionally, both values were required to be ≥ 5% of the corresponding median values for all EGMs to prevent the detection of noise in flat EGMs as fractionation.

EGM: electrogram

Supplemental Table S1: Manuscript Abbreviations

Abbreviation	Meaning
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
RV	Right Ventricle
LV	Left Ventricle
EP	Electrophysiological
ICD	Implantable Cardioverter Defibrillator
ECGI	Electrocardiographic Imaging
MRI	Magnetic Resonance Imaging
CMR	Cardiac Magnetic Resonance
LGE	Late Gadolinium Enhancement
ECG	Electrocardiogram
HR	Heart Rate
EGM	Electrogram
PVC	Premature Ventricular Contraction
AT	Activation Time
RT	Recovery Time
ARI	Activation-Recovery Interval

Supplemental Table S2: Patient Clinical Characteristics (zoom to 200% or larger for clear viewing)

ID	Age	Gender	Gene	Mutation	RV Dilation	RV Wall Thinning	RV RWMA	RV Systolic Dysfunction	RV Anurysm	LV Dilation	LV Wall Thinning	LV RWMA	LV Systolic Dysfunction	LV Anurysm	RV LGE	LV LGE	Biopsy	T wave Inversion	Epsilon Waves	Positive SAECG	Terminal S wave >55ms	NSVT/SVT superior axis	NSVT/SVT indeterminate or inferior axis	>500 VE's per 24 hrs	VT Study Inducible	Family History	TFC Major	TFC Minor
1	59	M	JUP	JUP - c.2039G>A, W680X	+	-	-	-	-	-	-	-	-	-	-	+		-	-	-	-	-	-	-		Major	1	1
2	63	M	PKP2	c.148_151delACAG, p.S50fsX110	+	-	+	-	-	-	-	-	-	-	-	-		-	-	+	-	-	-	+		Major	1	3
3	54	F	PKP2	c.1799delA, p.V600fsX655	+	-	+	-	-	-	-	+	-	-	-	-		V1-3	-	-	-	-	+	+		Major	2	3
4	44	M	DSP	c.817_818insA, p.Q273fsX288	-	-	-	-	-	-	-	-	-	-	-	-		-	-	+	+	-	+	-	-	Major	1	3
5	55	M	DSP	c.G4477T:p.E1493X	+	-	-	-	-	-	-	-	-	-	-	+		-	-	+	-	-	+	+		Major	1	5
6	63	M	PKP2	c.2197_2202delinsG, p.A733fsX740	+	+	+	+	-	-	+	+	-	-	+	-	+	V1-4	-	-	+	-	-	+		Minor	3	3
7	59	M	DSP	c.3045delG, p.S1015fsX1017	+	-	-	-	-	-	-	+	+	-	-	+		V1-5	-	-	-	-	+	+		Minor	1	3
8	69	F	PKP2	c.2146-1G>C	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	+	+		Minor	0	2
9	61	M	DSP	c.G4477T:p.E1493X	-	-	-	-	-	-	-	-	-	-	-	+		V5-6	-	-	-	-	+	+		Major	1	2
10	41	F	DSP	c.C5178A:p.N1726K*	-	-	-	-	-	-	-	-	-	-	-	-		V1-4	-	-	-	-	-	-		Minor	1	1
11	49	F	PKP2	c.2489+1G>A	+	-	+	-	-	-	-	-	-	-	+	-		V1-4	-	+	-	-	-	+		Major	3	2
12	60	M	DSG	c.G3C:p.M1I	+	-	+	-	-	-	-	+	+	+				V5-6	-	+	-	-	-	+		Major	3	2
13	26	M	PKP2	c.2489+1G>A	-	-	-	-	-	-	-	-	-	-	-	-		-	-	+	+	-	-	-		Minor	0	3
14	66	M	PKP2	c.2197_2202delinsG, p.A733fsX740	+	-	+	+	-	-	+	+	-	-	+	+		V1-3	-	-	+	-	-	-		Major	2	1
15	54	M	PKP2	c.2146-1G>C	-	-	+	-	+	-	-	-	-	-	+	-		V1-4	-	-	-	-	-	-		Major	2	0
16	74	M	DSG	c.G3C:p.M1I	-	-	+	-	-	-	-	-	-	-	-	-		-	+	+	-	-	-	+		Minor	1	3
17	24	M	DSP	c.C3337T:p.R1113X	-	-	-	-	-	-	-	-	-	-	-	+		-	-	-	-	-	-	-		Major	1	0
18	54	M	-	Desmosomal gene negative	-	-	+	-	+	-	+	+	-	-	+	+	+	V1-6	-	-	-	-	-	+		None	2	2
19	39	M	-	Desmosomal gene negative	+	-	+	-	-	+	-	+	-	-	-	+		V1-4	-	-	-	-	+	+		None	2	2
20	75	M	-	Desmosomal gene negative	-	-	+	+	-	-	+	+	-	-	+	+	+	V1-5	-	-	-	+	-	+		None	2	3

Clinical characteristics of ARVC study population. Asterisk indicates gene variant of unknown significance.

JUP: Plakoglobin
PKP2: Plakophilin-2
DSP: Desmoplakin
DSG: Desmoglein
RWMA: Regional Wall Motion Abnormality
LV: Left Ventricular
RV: Right Ventricular
LGE: Late Gadolinium Enhancement
SAECG: Signal Averaged Electrocardiogram
NSVT: Non-Sustained Ventricular Tachycardia
SVT: Sustained Ventricular Tachycardia
VE: Ventricular Extrasystole
VT: Ventricular Tachycardia

Supplemental Table S3: Holter PVC Findings

ID	Age	Gender	PVC Count	Monomorphic/Poloymorphic	Morphology
1	59	M	59	Monomorphic	LBBB
2	63	M	620	Polymorphic	LBBB+RBBB
3	54	F	1028	Monomorphic	LBBB
4	44	M	10	Monomorphic	LBBB
5	55	M	1000	Monomorphic	LBBB
6	63	M	2364	Monomorphic	LBBB
7	59	M	1111	Polymorphic	LBBB+RBBB
8	69	F	784	Monomorphic	LBBB
9	61	M	>3000	Monomorphic	LBBB
10	41	F	56	Monomorphic	LBBB
11	49	F	642	Monomorphic	LBBB
12	60	M	681	Polymorphic	LBBB+RBBB
13	26	M	52	Monomorphic	LBBB
14	66	M	26	Monomorphic	LBBB
15	54	M	38	Monomorphic	LBBB
16	74	M	1056	Monomorphic	LBBB
17	24	M	56	Monomorphic	LBBB
18	54	M	3496	Monomorphic	LBBB
19	39	M	890	Monomorphic	LBBB
20	75	M	>3000	Monomorphic	LBBB

Summary of 24-hour Holter findings from patient clinical records.
LBBB: Left bundle branch block morphology
RBBB: Right bundle branch block morphology

Supplemental Table S4: ARVC–Control Group Comparisons

Parameter	Control			ARVC			P	Significance
	Median	Q1	Q3	Median	Q1	Q3		
Total Activation Time (msec)	42	36	47	52	44	64	0.007	**
Total Recovery Time (msec)	134	126	152	129	120	146	0.273	
Mean Epicardial ARI (msec, Fridericia Rate-Correction)	241	230	262	275	237	300	0.014	*
Mean Epicardial EGM Amplitude (mV)	2.28	2.00	3.03	2.58	1.69	2.96	0.735	
Mean Deflections Per-Electrogram	1.06	1.03	1.06	1.09	1.03	1.18	0.086	
Mean Epicardial Activation Time Gradient (ms/mm)	0.24	0.21	0.28	0.31	0.26	0.37	0.018	*
Mean Epicardial Recovery Time Gradient (ms/mm)	1.06	0.95	1.22	0.93	0.85	1.05	0.060	
Mean Epicardial ARI Gradient (msec, Fridericia Rate-Correction)	1.17	1.07	1.38	1.21	1.05	1.48	1.000	

Median, quartiles, and Wilcoxon rank sum comparison of ECGI EP parameters in healthy adults (Controls) and ARVC patients. Highlighted rows (yellow) indicate statistically significant differences between Control and ARVC groups.

Significance levels:
***   p < 0.001
**   p < 0.01
*   p < 0.05

Q1: First Quartile
Q3: Third Quartile

Supplemental Table S5: Mean Fridericia-Corrected Epicardial ARI (msec) in Controls and ARVC Patients with and without T-Wave Inversion

Controls					ARVC: T-Wave Inversion					ARVC: No T-Wave Inversion				
Median	Q1	Q3	Min	Max	Median	Q1	Q3	Min	Max	Median	Q1	Q3	Min	Max
241	230	262	206	274	300	269	313	218	330	238	231	262	226	285

Median, quartiles, Range, and Wilcoxon rank sum comparison of resting ARI (Fridericia rate-correction applied) in Controls and ARVC patients with and without T-Wave Inversion. Group difference ARVC with T-Wave Inversion is significantly different than controls at p < 0.001 level and ARVC without T-Wave Inversion at p < 0.01 level.

Q1: First Quartile
Q3: Third Quartile
Min: Minimum value observed in group
Max: Maximum value observed in group

Supplemental Table S6: Exercise Changes in ARVC Parameters

Parameter	Resting HR			Elevated HR			P	Significance
	Median	Q1	Q3	Median	Q1	Q3		
Total Activation Time (msec)	53	46	66	57	47	66	0.658	
Total Recovery Time (msec)	130	120	150	106	91	120	0.002	**
Mean Epicardial ARI (msec, uncorrected for HR)	275	235	313	186	173	203	< 0.001	***
Mean Epicardial EGM Amplitude (mV)	2.57	1.60	2.94	2.08	1.28	2.50	< 0.001	***
Mean Deflections Per-Electrogram	1.09	1.03	1.18	1.09	1.05	1.22	0.872	
Mean Epicardial Activation Time Gradient (ms/mm)	0.33	0.26	0.38	0.30	0.27	0.35	0.260	
Mean Epicardial Recovery Time Gradient (ms/mm)	0.94	0.87	1.06	0.70	0.60	0.88	0.007	**
Mean Epicardial ARI Gradient (msec, Fridericia Rate-Correction)	1.22	1.07	1.49	1.12	1.01	1.38	0.687	

Median, quartiles, and Wilcoxon signed-rank comparison of ECGI EP parameters in ARVC patients at Resting HR and Elevated HR after exercise. Highlighted rows (yellow) indicate statistically significant differences between Control and ARVC groups.

Significance levels:
*** $p < 0.001$
** $p < 0.01$
* $p < 0.05$

Q1: First Quartile
Q3: Third Quartile

Supplemental Table S7: Correlation of EP Substrate to LV Late Gadolinium Enhancement

Parameter	CC	P	Significance
EGM Amplitude	-0.42	< 0.001	***
Deflections Per-EGM	0.52	< 0.001	***
AT Spatial Gradient	0.24	0.001	**
Resting ARI	0.29	< 0.001	***
Exercise ARI	0.10	0.190	
RT Spatial Gradient	-0.09	0.232	
ARI Spatial Gradient	0.05	0.485	
Exercise ARI Shortening	0.31	< 0.001	***

Spearman correlation coefficients of LV LGE and EP substrate parameters. Highlighted rows (yellow) indicate statistically significant correlations between LV LGE and EP substrate parameters.

Significance levels:
*** $p < 0.001$
** $p < 0.01$
* $p < 0.05$

Supplemental Table S8: Correlation of EP Substrate to RV Late Gadolinium Enhancement

Parameter	CC	P	Significance
EGM Amplitude	-0.02	0.755	
Deflections Per-EGM	-0.05	0.472	
AT Spatial Gradient	-0.15	0.051	
Resting ARI	0.30	< 0.001	***
Exercise ARI	0.17	0.027	*
RT Spatial Gradient	-0.05	0.502	
ARI Spatial Gradient	-0.10	0.197	
Exercise ARI Shortening	0.36	< 0.001	***

Spearman correlation coefficients of RV LGE and EP substrate parameters. Highlighted rows (yellow) indicate statistically significant correlations between RV LGE and EP substrate parameters.

Significance levels:
*** $p < 0.001$
** $p < 0.01$
* $p < 0.05$

Supplemental Table S9: Correlation of LGE and EP Substrate with Regional Rate of Ventricular Ectopy

Parameter	CC	P	Significance
EGM Amplitude	-0.21	< 0.001	***
Deflections Per-EGM	0.20	< 0.001	***
AT Spatial Gradient	0.04	0.457	
Resting ARI	0.35	< 0.001	***
Exercise ARI	0.28	< 0.001	***
RT Spatial Gradient	-0.06	0.232	
ARI Spatial Gradient	0.00	0.943	
Exercise ARI Shortening	0.30	< 0.001	***
LV LGE	0.50	< 0.001	***
RV LGE	0.35	< 0.001	***

Spearman correlation coefficients of PVC rate within anatomical regions and EP substrate parameters and LGE. Highlighted rows (yellow) indicate statistically significant correlations between PVC Rate and substrate parameters.

Significance levels:
*** $p < 0.001$
** $p < 0.01$
* $p < 0.05$

Supplemental References (ECGI Methodology)

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