SUPPLEMENTAL MATERIAL

Phase I/II Trial of Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia

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Procedural Workflow

An example of the treatment workflow is shown graphically in Figure S1, as previously published.[1] A detailed description is provided below, modified where appropriate from the original workflow.

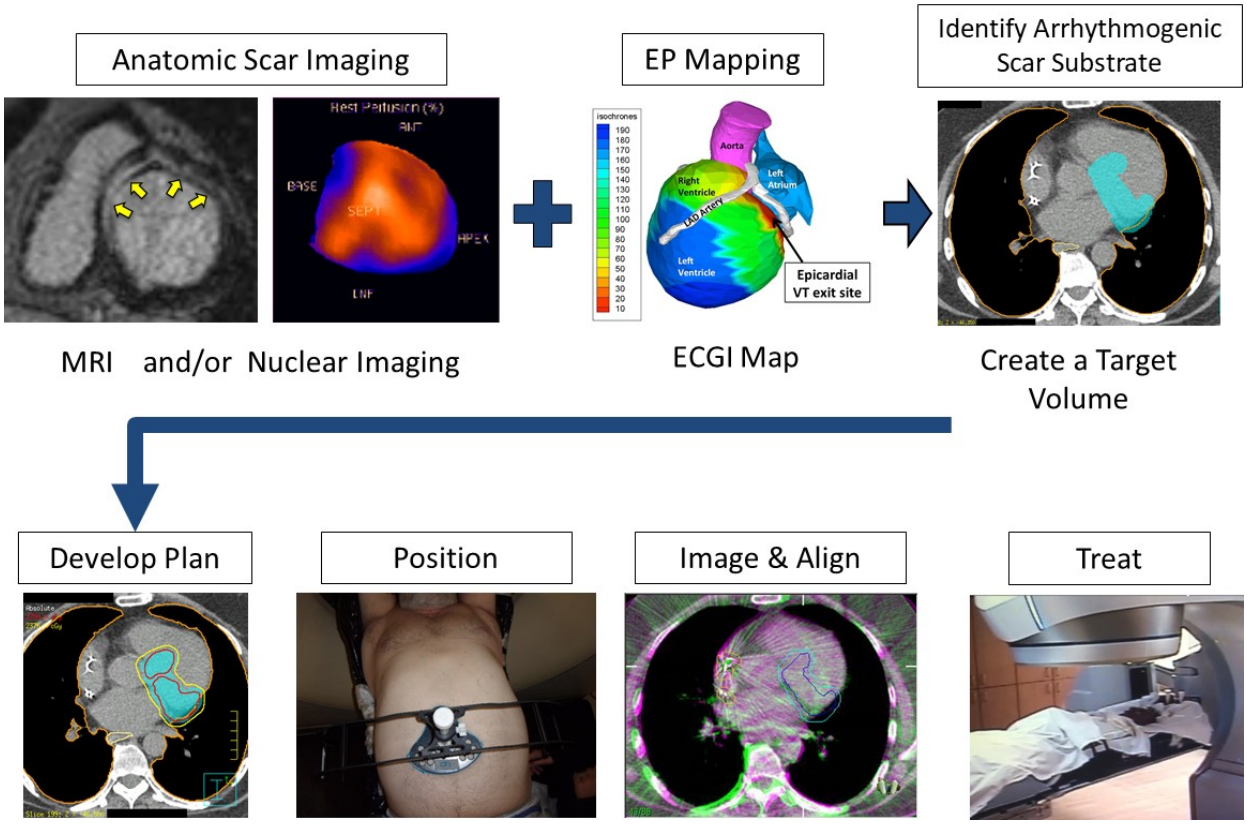

Figure S1. Workflow for Electrophysiology-Guided, Noninvasive Cardiac Radioablation. Patients undergo noninvasive visualization of the ventricular scar by means of Magnetic Resonance Imaging (MRI), Computed Tomography (CT), single-photon emission CT (SPECT), positron-emisson tomography (PET/CT) or a combination of methods, according to protocol. In this example, the zone of scarring is indicated by arrows on MRI and by blue regions on SPECT, including the base, inferior wall, and apex. Noninvasive electrophysiologic (EP) mapping is performed with electrocardiographic imaging (ECGI) of induced ventricular tachycardia (VT) with programed stimulation from the indwelling implantable cardioverter–defibrillator. The color scale shows the range of activation times of each area of the ventricular wall (isochrones), ranging from 10 msec (red) to 190 msec (deep blue) from the onset of VT activation. The electrophysiologist develops an ablation volume by targeting the full thickness of the ventricular wall harboring the first 10 msec of VT activation (the “exit site”) and the colocalized ventricular scar. The target volume is shown in light blue in the figure panel showing the arrhythmogenic scar substrate. This volume is transferred by the radiation oncologist onto a respiratory-correlated, four-dimensional CT scan, which allows an assessment of the

total cardiac and pulmonary motion. In this example, a dose of 25 Gy in a single fraction is prescribed for delivery to the enhanced treatment volume, with a goal of achieving maximal coverage inside the volume while avoiding exposure to the surrounding organs at risk. The target volume is indicated in light blue in the figure panel showing the treatment plan; red and yellow boundaries indicate the distribution of zones projected to receive 2750 cGy and 2375 cGy of radiation, respectively; the lung is outlined in orange, and the yellow boundary behind the heart is the esophagus. If all plans pass standard internal physics quality assurance on a calibrated phantom, the patient is immobilized with the use of a vacuum-assisted device or foam cushion coupled with an abdominal compression device (shown here), and stereotactic radioablation is performed by means of an image-guided, radiotherapy-equipped linear accelerator that uses a cone-beam CT to align the radiotherapy treatment beams with the target volume. The dark blue boundary indicates the target, which includes the total cardiac and pulmonary motion. The light blue boundary indicates the target with an additional expansion to account for motion, setup uncertainty, and delivery uncertainty. Treatment is then delivered with the use of the radiotherapy delivery system. LAD denotes left anterior descending.

Electrocardiographic Imaging (ECGI)

Prior to treatment, patients underwent noninvasive ECGI during induced ventricular tachycardia (VT) to precisely identify the critical electrical elements of VT (Figure S1). Patients wore a series of electrode strips containing 256 electrodes (BioSemi, Netherlands), with small radiopaque markers attached at the location of the electrodes, to assist with visualization on cardiac imaging. A gated chest CT scan with 3 mm axial resolution was obtained to provide patient-specific heart-torso geometry and the location of the body surface electrodes relative to the heart. If renal function allowed, IV contrast was used to delineate additional cardiac structures and morphology. After the CT scan, patients were brought to the EP laboratory, provided light sedation, and prepped for a noninvasive-programmed stimulation (NIPS) procedure. In the NIPS procedure, the patient's ICD was used to pace the heart using a standard protocol of single, double and triple ventricular extrastimuli at two pacing intervals (600 ms and 400 ms) with the intent of inducing VT. Once sustained VT was induced, a 12-lead ECG and 256-lead body surface electrical map were rapidly obtained for use with ECGI. The torso surface potentials were sampled at 1-ms intervals. While only a single recorded beat is necessary for ECGI, we usually acquired a recording of 10 seconds of VT. The ICD was then used to terminate the VT with a brief overdrive-pacing maneuver. The NIPS procedure was terminated at the discretion of the physician based on the reproducibility of the induced VT and the medical condition of the patient.

Information from the CT scan and the body surface potential mapping during VT was combined using methods described previously (3-6, Figure S2). The recorded torso potential and CT-derived geometrical information provide the input data for the ECGI algorithm, which constructs three-dimensional plots of epicardial potentials, electrograms, activation sequences (isochrone maps) and repolarization patterns. The reconstruction is performed during a single beat and does not require accumulating data from many beats. This allowed for exact noninvasive identification of the earliest site of electrical activation

in VT, which was considered to be the site of origin of the VT. For all patients, the induced VTs originated in areas of preexisting ventricular scar.

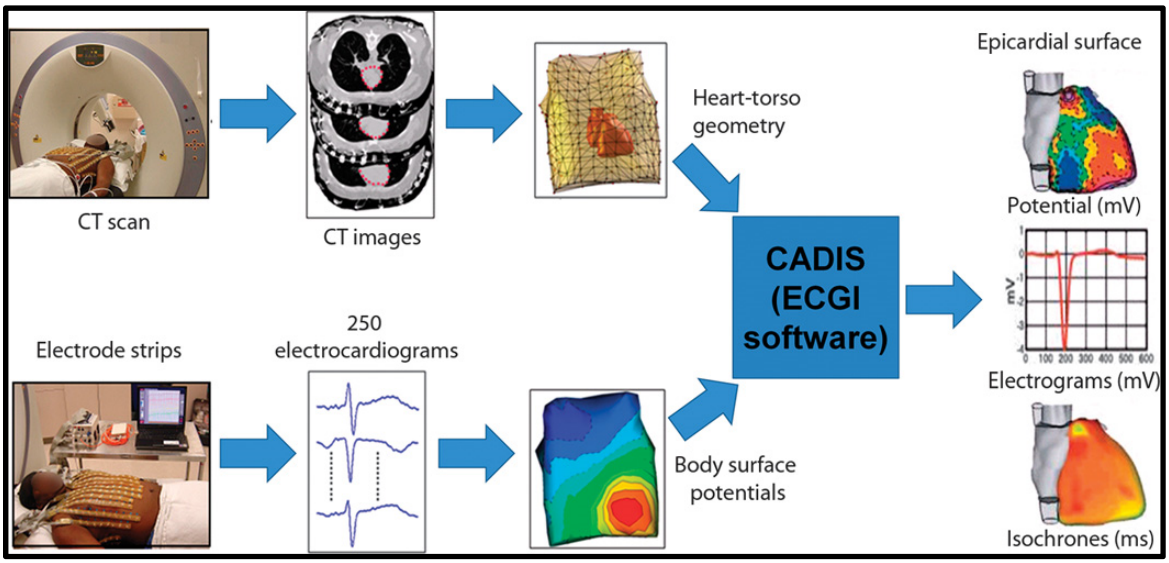

Figure S2. Electrocardiographic Imaging (ECGI) workflow (Reprinted from Wang et al[2]) *CT = Computed Tomography*

In addition to cardiac electrical maps generated from ECGI, any clinically available 12-lead ECGs obtained while the patient was in VT, as well as data from prior catheter ablations, were collected when available.

Anatomic Scar Imaging

Ventricular scar was identified using the cardiac imaging techniques listed below. All scans were performed using clinical scanners and standard techniques.

a) Positron-emission tomography computed tomography (PET-CT)
b) Contrast-enhanced cardiac computed tomography (CT)
c) Contrast-enhanced cardiac magnetic resonance imaging (MRI) in patients without contraindication.
d) Cardiac ultrasound/echocardiography when available.

Regions of abnormal ventricular myocardium were identified using standard criteria. For PET-CT studies, regions of persistently reduced radiotracer uptake were identified as ventricular scar, while hyper-enhancing areas were identified as regions of inflammation. For CT studies, regions with >50% wall thinning were identified as ventricular scar. For MRI studies, regions with persistent enhancement after administration of IV gadolinium were identified as ventricular scar. For echocardiography, regions with reduced systolic function were identified as abnormal; regions with akinesis and wall thinning were identified as ventricular scar. Affected regions were identified and compared using a standard 17-segment left ventricle model for each imaging modality (Figure S3).

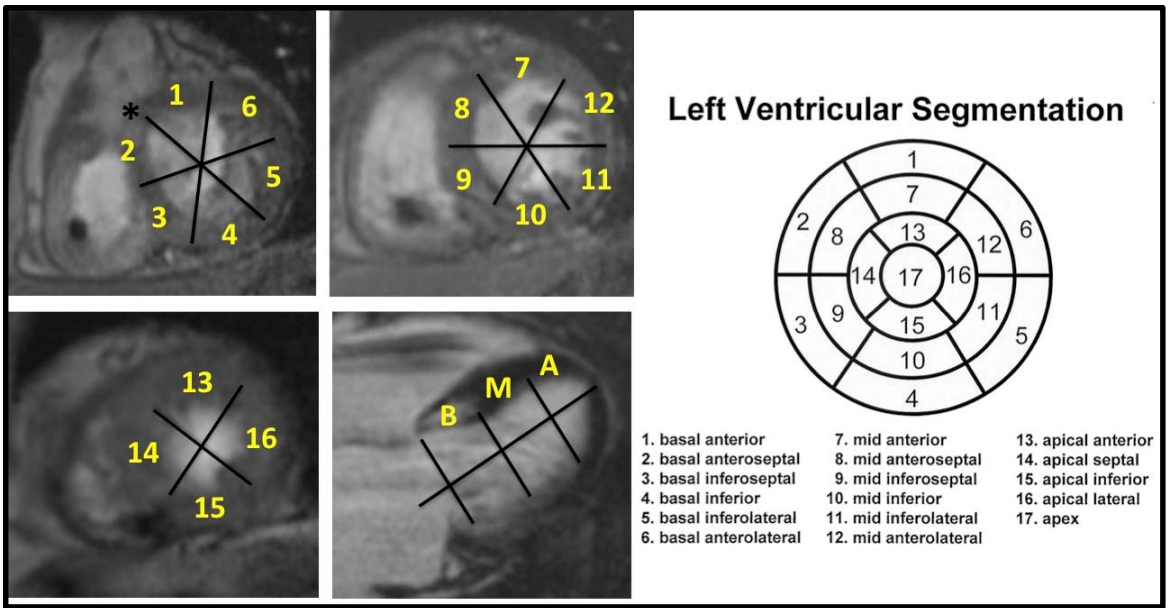

Figure S3. Standard 17-segment left ventricle model

Targeting a Contoured Ablation Volume

The sum total of electrical information (ECGI, 12-lead ECG, and prior ablations) and the anatomic scar information (PET-CT, MRI, CT, and/or echocardiogram) was used to build a target for radioablation. In general, this was constructed by targeting a clinically rational combination of the (1) location of the first 10 ms of VT from ECGI and (2) the full myocardial thickness of the associated ventricular scar. For all patients, the contoured volume was strictly limited to regions of abnormal myocardium.

Radioablation Delivery

Several days prior to treatment, all patients underwent a standard stereotactic body radiotherapy (SBRT) simulation, which is an imaging procedure intended to simulate the patient's anatomy at the time of radiation treatment delivery. The simulation process starts with the creation of a custom immobilization device for the patient, which allows the patient to be positioned on the treatment table in a manner that is identical to their position at the time of imaging. The immobilization system used for all five patients was either a (1) vacuum-assisted cushion, shaped to the patient's body, (BodyFIX, Elekta, Stockholm, Sweden) and reinforced with a vacuum-sealed layer that prohibits the patient from moving during treatment, or (2) a foam cushion (Alpha Cradle, Smithers Medical Products, North Canton) coupled with abdominal compression (FreedomX, CDR Systems, Calgary). Once the custom immobilization device is made, a series of CT scans are acquired including a free-breathing CT and a respiration-correlated CT (4D-CT), which provides information about the sum of cardiac and pulmonary motion. CT contrast was used during the free-breathing CT to facilitate definition of cardiac structures when not otherwise contraindicated.

The treatment target volume was defined as described in the previous section, and the location and shape of the target was outlined on the free-breathing CT scan using the treatment planning system (TPS) (Pinnacle, Phillips, Amsterdam, or Eclipse, Varian

Medical Systems, Palo Alto), which is specialized commercially available computer software used to generate the radiation treatment plan. The target is referred to as the gross target volume (GTV). After outlining the GTV, an additional area around the GTV was added to account for internal motion of the GTV caused by breathing and cardiac motion, as assessed by review of the 4D-CT. This is called the internal target volume (ITV). Finally, an additional safety margin of 5 mm was added to the ITV region for treatment planning to create a planning target volume (PTV), which accounts for any residual uncertainties in patient setup, motion, and delivery.

The SBRT radiation treatment plan was generated in the TPS to deliver a total dose of 25 Gy in a single treatment fraction to cover the entire region of the PTV. The orientation and direction of the radiation beams relative to the patient were selected with the goal of achieving maximal coverage of the PTV region while reducing the dose to surrounding normal tissue. In addition to these standard radiotherapy principles, the SBRT plan was created with the intention of being highly conformal to the target and having rapid fall-off of dose away from the target. Due to inherent issues with SBRT planning, this often results in doses far in excess of the prescription dose being delivered within the target itself. This is generally considered a favorable characteristic of SBRT inasmuch as this additional “boost” of radiation is achieved while simultaneously delivering a smaller dose to surrounding normal tissue. In the context of VT ablation, the normal tissues of concern (organs at risk, OARs) generally included the esophagus, stomach, lungs, and spinal cord. The treatment plans all utilized intensity modulated radiotherapy (IMRT), which is a form of radiotherapy in which the shape and intensity of radiotherapy is changed during treatment to “modulate” or “paint” the dose in a highly accurate, conformal manner. Beams were arranged using a multiple-plane, fixed pattern (fixed-field) or a volumetric modulated arc radiotherapy (VMAT) technique, in which the radiation beam assembly rotates around the patient during radiation delivery. Each technique attempts to minimize the overlap between the entrance and exit dose of various radiation beams, which helps reduce the dose to the OARs. Following review and approval of plans in the TPS, all plans were subjected to, and passed, standard internal quality assurance, to ensure accurate delivery of the dose to the patient prior to treatment delivery.

The radiation treatment was delivered using an image-guided radiotherapy (IGRT)-equipped linear accelerator (TrueBeam or Edge, Varian Medical Systems, Palo Alto). This system is equipped with an onboard imaging device capable of acquiring both volumetric images (cone beam CT, CBCT) and kV fluoroscopic images, which allows for acquisition of high fidelity images of the patient on the treatment table, for verification of the accuracy of patient setup prior to delivery. The images acquired in the treatment position are directly compared with the simulation images to ensure that the patient anatomy is aligned with the treatment beams as intended by the treatment plan. At the time of treatment, patients were placed in their custom immobilization device, aligned using the CBCT with additional verification of this alignment using fluoroscopy, and treated without use of any additional imaging during the treatment delivery.

Programming of cardiac devices after therapy

ICDs were programmed to three zones:

1) A VF zone with a single ATP followed by shocks;
2) A VT zone with several ATPs followed by shocks. The number of ATPs in the VT zone was at the discretion of the treating physician, based largely on the hemodynamic tolerance of that particular patient's VT. The VT zone was set at >=20bpm below the slowest induced VT or clinical VT;
3) A VT monitor zone (no therapy) was employed in all patients, adjusted to 30bpm greater than the highest sinus rate.

The time to VT/VF detection or number of VT/VF intervals to detect was programmed in a standardized fashion and is manufacturer-specific:

- Medtronic: VT and VF zone 30/40 NID
- Boston Scientific: VT and VF zone 2.5 seconds
- St. Jude/Abbott: VT and VF zone 16 beats

Safety

Table S1. All Adverse Events. Summary of all adverse events, regardless of attribution, grade, or time after treatment.
CTCAE v4.0 = Common Terminology Criteria for Adverse Events version 4.0, NOS = Not Otherwise Specified

CTCAE v4.0 System/Toxicity	Grade 1				Grade 2					Grade 3				Grade 4			Grade 5		
	Unrelated	Unlikely	Possible	Probable	Unrelated	Unlikely	Possible	Probable	Definite	Unrelated	Unlikely	Possible	Probable	Unrelated	Unlikely	Possible	Unrelated	Unlikely	Possible
Blood and lymphatic system disorders																			
Anemia														1					
Cardiac disorders																			
Acute coronary syndrome							1												
Atrial Fibrillation		2									1								
Cardiac Arrest														1				1	
Heart Failure			1			1	3			1		5				1			2
Other - Chest Pain NOS	1	1	3							1		4							
Palpitations	1																		
Pericardial Effusion			3					1				1		1					
Pericarditis													1						
Sinus tachycardia						1													
Ear and labyrinth disorders																			
Ear Pain					1														
Gastrointestinal disorders																			
Abdominal Pain					1	1													
Constipation					1														
Diarrhea										1									
Dyspepsia	1	1	1		2		1												
Gastric hemorrhage														1					
Nausea	1		2		1			1		2									
Other - Congestive Gastropathy					1														

Other - Dark Stools	1											
Other - Polydipsia		1										
Retroperitoneal hemorrhage					1					1		
Vomiting	2				1		1		1			
General disorders and administration site conditions												
Chills			1									
Fatigue	3	2	11	1								
Malaise			1									
Multi-organ failure										1		
Other - Accident											1	
Hepatobiliary disorders												
Cholecystitis							1					
Immune system disorders												
Allergic Reaction							1					
Infections and infestations												
Sepsis							1					
Sinusitis					1							
Upper Respiratory Infection		1			2		1					
Urinary tract infection					1		1					
Injury, poisoning and procedural complications												
Fracture						1						
Intraoperative cardiac injury										1		
Investigations												
Alanine Aminotransferase increased								1				
Alkaline Phosphatase increased	1											

Aspartate Aminotransferase increased							1					
Blood bilirubin increased				1								
Metabolism and nutrition disorders												
Acidosis										1		
Dehydration								1				
Hyperglycemia						1						
Musculoskeletal and connective tissue disorders												
Arthritis	1											
Back Pain	1	3										
Chest wall pain		1										
Other - Shoulder Pain								1				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Cyst	1											
Nervous system disorders												
Dizziness	3	1	4	1	2							
Dysesthesia	1	1	1									
Headache	2											
Hypersomnia			1									
Presyncope								1				
Seizure				1								
Spasticity			1									
Syncope		1										
Tremor	2											
Cognitive disturbance							1					
Psychiatric disorders												

Agitation					1																			
Renal and urinary disorders																								
Acute Kidney Injury													1				2							
Hematuria	1																							
Reproductive system and breast disorders																								
Testicular pain													1											
Respiratory, thoracic and mediastinal disorders																								
Cough			2				1																	
Dyspnea	1	1	3		1		2							1										
Hypoxia													1		1		1							
Other - Chemical Pneumonitis																							1	
Other - Influenza	1																							
Other - Pneumonia						1							1		1									
Other - Radiation Pneumonitis								1	1															
Pleural Effusion			1	1																				
Pleuritic pain			1																					
Pneumothorax														1										
Pulmonary edema															1									
Wheezing		1																						
Skin and subcutaneous tissue disorders																								
Hyperhidrosis		1	1																					
Vascular disorders																								
Flushing														1										
Hematoma													1											
Hypertension		1											1				2							
Hypotension			3				7								1						1			
Thromboembolic event													1											

Efficacy

Table S2. All-cause mortality summary. *LVAD = Left ventricular assist device. ICD = Implantable Cardioverter Defibrillator, RCO = Rate cut-off, SBRT = Stereotactic Body Radiotherapy, AAD = Antiarrhythmic drug, NICM = Non-ischemic cardiomyopathy, Mech AVR/MVR = Mechanical aortic valve replacement/mitral valve replacement, NYHA = New York Heart Association class, LVEF = ejection fraction, mo = month, VT = ventricular tachycardia, CA = catheter ablation, ICM = ischemic cardiomyopathy, VF = ventricular fibrillation, IV = intravenous.*

Pt	Age	Hx	Attribution	Mo	Details
Cardiac Deaths					
002	66	NICM, Mech AVR/MVR. NYHA 4 LVEF=15%, 6 mo VT=172	Possible	8.3	Advancing heart failure. Recurrent VT in the setting of IV inotropes. Not offered LVAD due to prior cardiac surgery, poor right ventricular function. Electively turned off ICD, enrolled in palliative care
006	60	ICM, NYHA 3, LVEF=19%, 1 prior CA, 6 mo VT=12*	Unlikely	5.5	Had continuous VT at the time of SBRT for >3 months. VT stopped 2-4 weeks after treatment. Recurrent VT/VF while driving, after decreasing AAD.
011	80	NICM, NYHA 4,LVEF=20%, 2 prior CA, 6 mo VT=11*	Possible	15	Heart failure and late recurrent VT. Electively turned off ICD, enrolled in palliative care.
Non-Cardiac Deaths					
003	81	ICM, NYHA 4, LVEF=38%, 1 prior CA, 6 mo VT = 4*	Unlikely	0.6	Had sustained VT below RCO before SBRT. Patient found down at nursing home with gown wrapped around neck, ruled accidental asphyxiation.
015	50	NICM, NYHA 4 LVEF=29%, 2 prior CA, 6 mo VT = 132	Unlikely	7	Amiodarone pulmonary toxicity.
020	65	ICM, LVEF=22%, NYHA 3 1 prior CA, 6 mo VT = 76	Unrelated	7.8	Biliary stent complicated by pancreatitis, sepsis, respiratory failure, renal failure; withdrew care

Figure S4. 24-Hour PVC Burden and Left Ventricular Ejection Fraction Changes. Two patients with PVC-related cardiomyopathy were enrolled and treated. The burden of PVC as measured by a 24-hour Holter monitor was 24% and 26% at baseline. Longitudinal PVC burden is shown **(red lines)**. Left ventricular ejection fraction was measured with echocardiography. Longitudinal LV ejection fraction is shown **(green lines)**. Both patients had improvement in LV ejection fraction as the PVC burden declined. *PVC = Premature ventricular contraction, LV = Left ventricular*

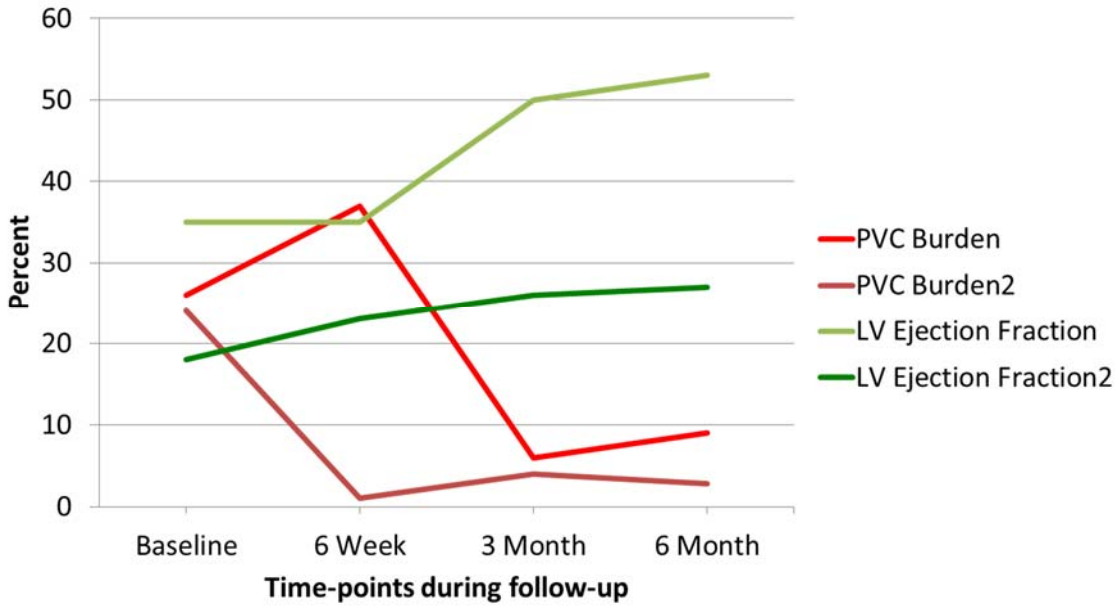

Figure S5. Quality of Life for all 9 Short Form (SF)-36 domains. Each ENCORE-VT participant received the SF-36 quality of life (QoL) assessment at baseline (pre-treatment), at 6 weeks, and at 6 months. This 36-item patient reported survey assesses eight health components and an additional element to assess perceived changes in health. Instrument scores reflect the composite score of specific questions. Scores range from 0 to 100, with lower scores indicating greater disability and higher scores indicating less disability within that section. Data is reported for the 16 patients who lived through 6 months. **Asterisks** next to the individual section in the figure legend indicate a statistically significant improvement from baseline to 6 months. No measure demonstrated a significant decrease over time.

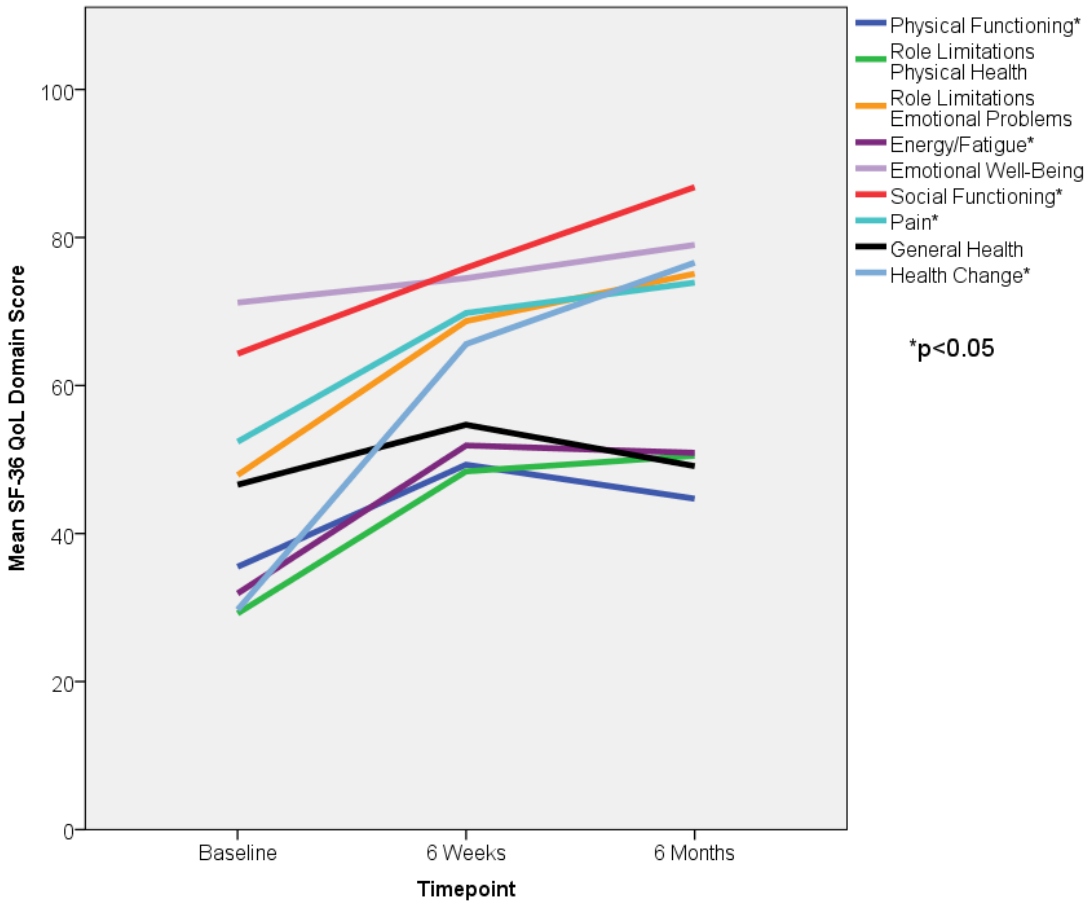

Table S3. Quality of Life for all 9 Short Form-36 domains. *QoL=Quality of Life. SD = Standard Deviation*

QoL Domain Score, Mean, SD	Baseline	6 Weeks	6 Months
Physical Functioning	35.5, 29.6	49.3, 28.7	44.7, 26.4
Role Limitations Physical Health	29.2, 39.4	48.4, 48.7	50.5, 47.2
Role Limitations Emotional Problems	47.9, 45.5	68.7, 43.0	75.1, 35.5
Energy / Fatigue	31.9, 19.2	51.9, 25.1	50.9, 21.5
Emotional Well-Being	71.2, 16.8	74.5, 19.9	79, 15.9
Social Functioning	64.3, 23.2	75.9, 28.3	86.8, 14.8
Pain	52.4, 23.3	69.8, 23.7	73.9, 19.7
General Health	46.6, 18.9	54.7, 21.6	49.1, 22.4
Health Change	29.7, 22.8	65.6, 27.2	76.6, 32.2

References

1. Cuculich PS, Schill MR, Kashani R, Mutic S, Lang A, Cooper D, Faddis M, Gleva M, Noheria A, Smith TW, Hallahan D, Rudy Y and Robinson CG. Noninvasive Cardiac Radiation for Ablation of Ventricular Tachycardia. *N Engl J Med*. 2017;377:2325-2336.

2. Wang Y, Cuculich PS, Zhang J, Desouza KA, Vijayakumar R, Chen J, Faddis MN, Lindsay BD, Smith TW and Rudy Y. Noninvasive electroanatomic mapping of human ventricular arrhythmias with electrocardiographic imaging. *Sci Transl Med*. 2011;3:98ra84.