

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Noninvasive Cardiac Radiation for Ablation of Ventricular Tachycardia

Supplementary Appendix

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AUTHOR CONTRIBUTIONS

The treatment plan was conceived by PSC and CGR. Data was collected and analyzed by PSC, MS, DC, MF, MG, AN, TS, CGR. Treatment plans were developed by CGR, RK, SM, DC, PSC. AL interpreted pathology. All authors vouch for the data. First draft of the manuscript was written by PSC and CGR, and decision to publish was further guided by YR, SM, DH.

DETAILED METHODS

Procedural Workflow

An example of the treatment workflow is shown graphically in Figure 1. A detailed description is provided below.

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 S1). 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.

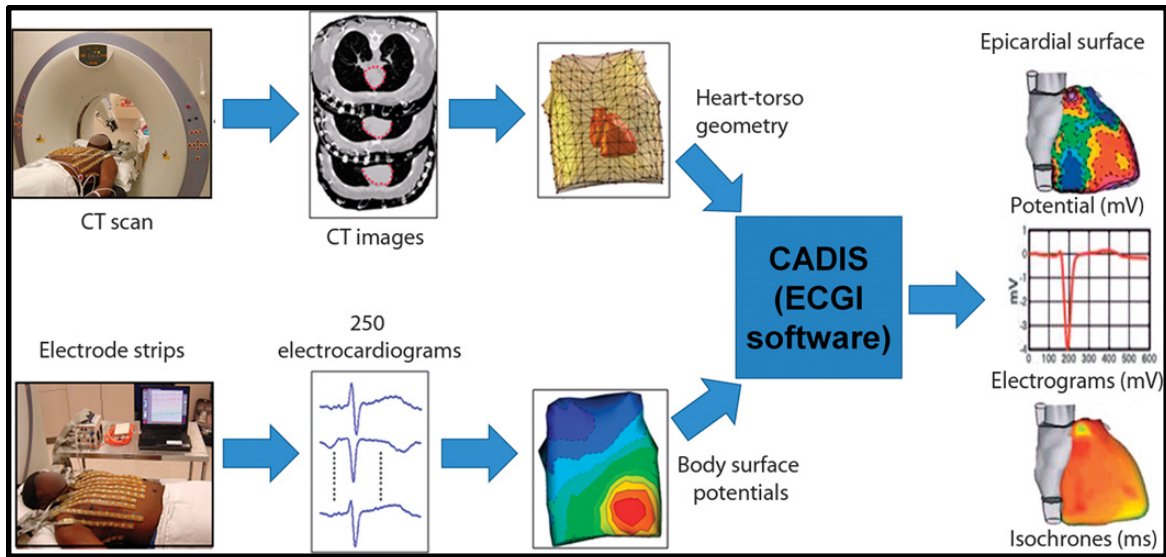


Figure S1. Electrocardiographic Imaging (ECGI) workflow (from Reference 5).

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) Single-photon emission computed tomography (SPECT)
- b) Contrast-enhanced cardiac computed tomography (CT)
- c) Contrast-enhanced cardiac magnetic resonance imaging (MRI) in patients without ICD
- d) Cardiac ultrasound/echocardiography

Regions of abnormal ventricular myocardium were identified using standard criteria. For SPECT studies, regions of persistently reduced radiotracer uptake were identified as ventricular scar. 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 S2).

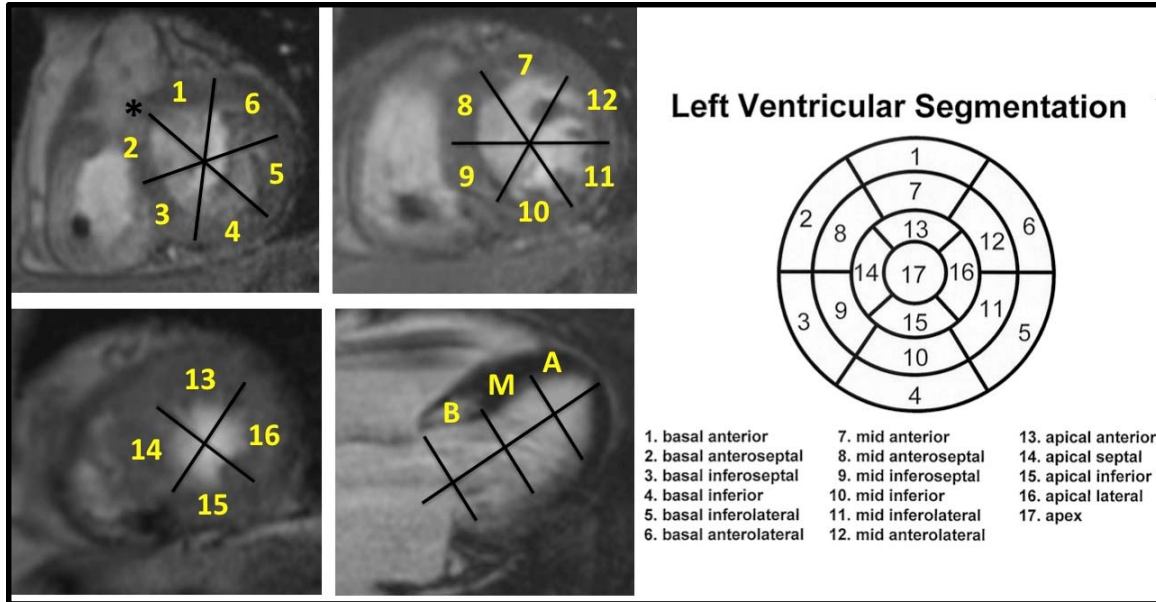


Figure S2. Standard 17-segment left ventricle model

Targeting a Contoured Ablation Volume

The sum total of electrical information (ECGI, 12-lead ECG, and prior ablations) and the anatomic scar information (SPECT, 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 example, patient 1 had two distinct induced VT morphologies, originating from segments 1 and 6, respectively. His MRI identified midmyocardial scar distribution in segments 1, 2 and 6. Therefore, segments 1, 2 and 6 were targeted for full-thickness ablation. For all patients, the contoured volume was strictly limited to regions of abnormal myocardium. For patients with prior catheter ablations, we made an effort to include the previous radiofrequency ablation locations in the contoured ablation volume.

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 a 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. 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), 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). Notably, in all patients the portion of the heart being targeted was akinetic or hypokinetic due to preexisting cardiac scar in that region. 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, 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.

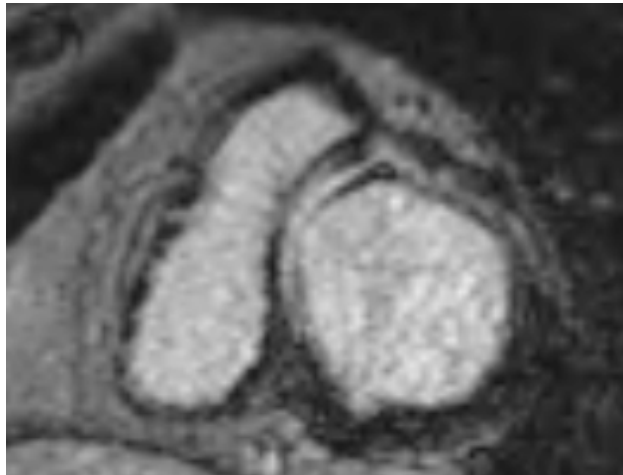
FULL DATA DISCLOSURE

Patient 1

This patient was a 61-year-old man with nonischemic cardiomyopathy, NYHA class 4 heart failure symptoms, and repeated ICD shocks for VT despite treatment with amiodarone and mexiletine. Previous to those medications, he failed sotalol. ICD interrogation showed at least two different VT cycle lengths. Previous endocardial ablation one year before SBRT targeted four distinct VT circuits in the basal anterior septum and anterolateral left ventricle. Because of the presumed “protected” site of origin of his VT (intramural circuit, epicardial location with overlying epicardial adipose tissue), the presence of multiple VT circuits, and strong patient preference to avoid another long invasive ablation procedure, he sought alternative ways to treat his VT storm. After discussions about the risks, he was offered SBRT.

Cardiac MRI with delayed enhancement of gadolinium (prior to first ablation)

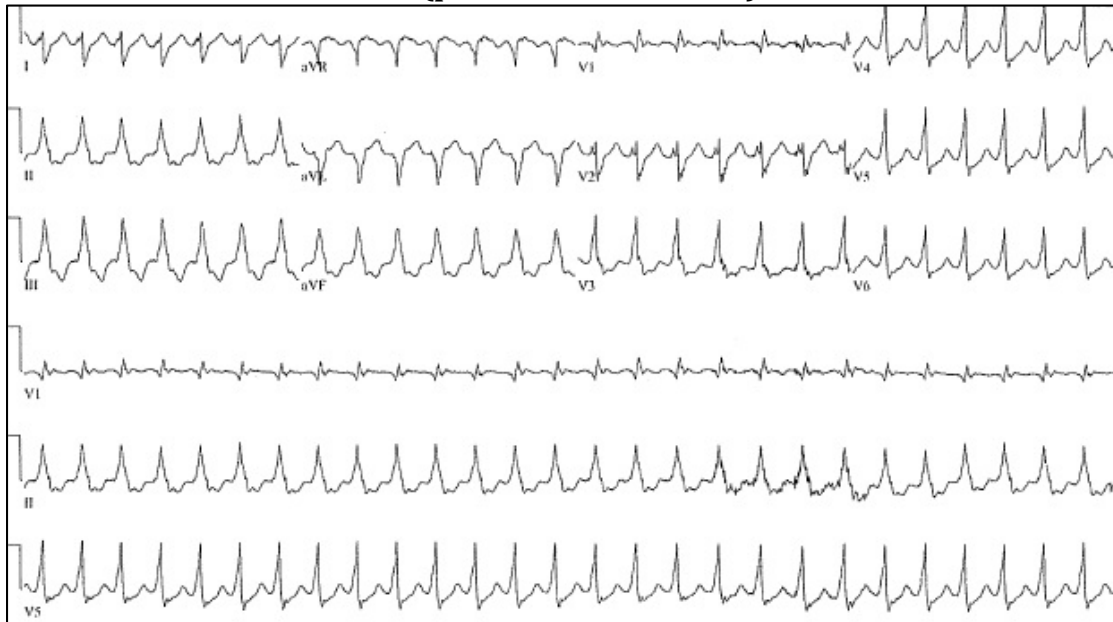
Image shown below. Delayed enhancement in the basal anterior LV, midmyocardial distribution, from mid-septal to mid-lateral location. Epicardial fat and epicardial coronary arteries directly over the scar region.



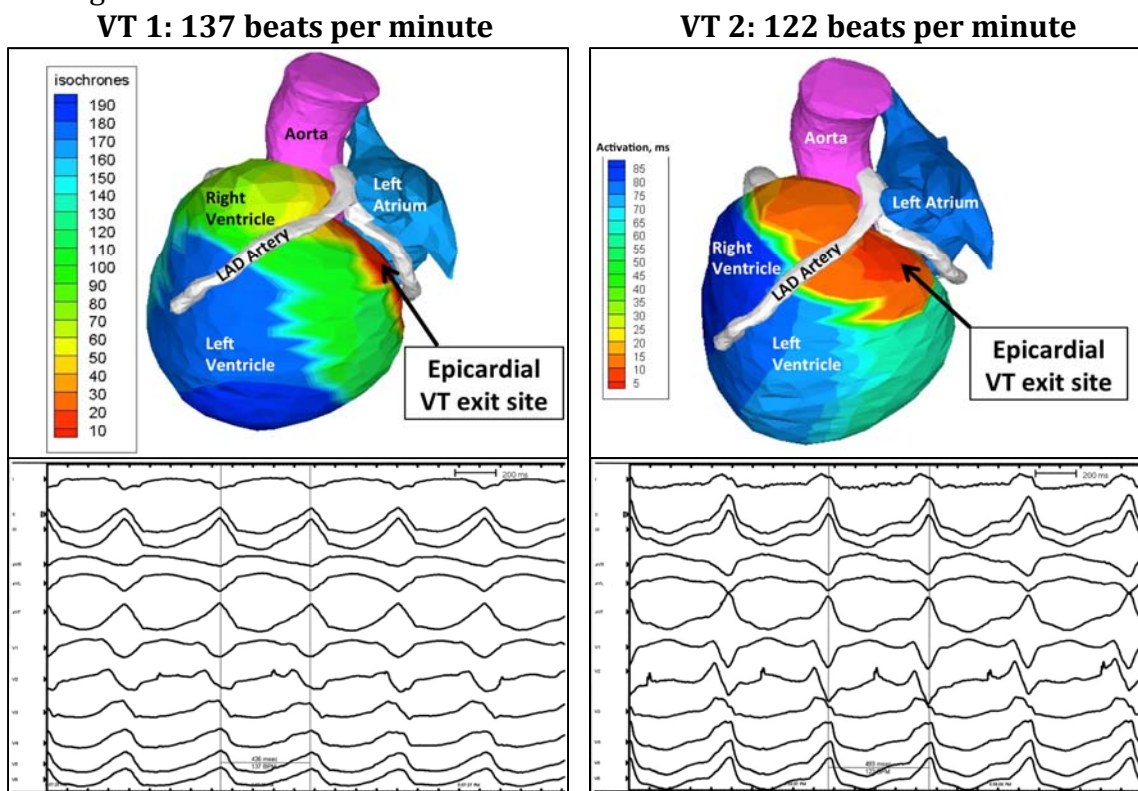
Echocardiogram (prior to SBRT treatment)

Left ventricular ejection fraction 37%. Global LV hypokinesis. Altered relaxation with upper-normal estimated LV pressure. LV end-diastolic dimension 6.1cm.

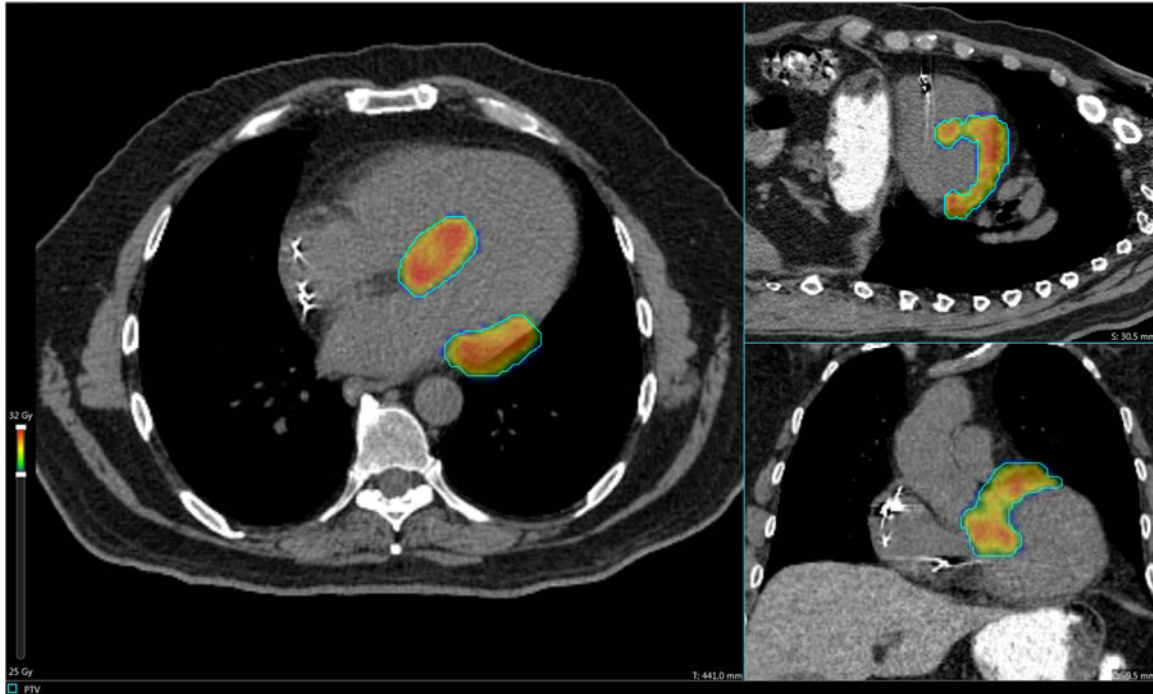
12-lead ECG of the clinical VT (prior to first ablation)



Two Induced VT in the EP lab with NIPS (below). Noninvasive ECGI activation maps are shown on top; the corresponding 12-lead ECGs are shown on the bottom. ECGI mapped two distinct VT patterns: one localizing to the basal anterolateral LV (left); the other localizing to the basal anteroseptal LV (right). The isochrone (activation time) color scale, shown to the left of each map, is in milliseconds (ms) in both figures.



Targeting Volume for noninvasive ablation with SBRT Three orthogonal views are shown below, demonstrating the custom volumetric ablation target that included the full thickness of the myocardium harboring the first 10 ms of each VT and associated scar areas. The radiation dose is displayed as a color wash, with a lower threshold of 25 Gy (blue), with doses in excess of 25 Gy displayed in gradations of color in the spectrum, with red being the highest dose. The ablation volume was 51.3 cc. After immobilization and alignment of the patient, treatment was delivered over 12 minutes.



Clinical follow-up (at 12 months)

Patient 1 had two antitachycardia pacing (ATP) episodes and one ICD shock 12 months after treatment. ICD interrogation demonstrated a VT that had a longer cycle length (slower VT) than the pre-treatment VTs. The stored electrograms had similar characteristics to the pre-treatment VTs. Whether this represents recurrence of the same VT circuit or a new VT circuit is unclear.

Patient 2

This patient was a 60-year-old man with mixed ischemic/nonischemic cardiomyopathy, NYHA class 3 heart failure symptoms, and repeated ICD shocks for VT despite treatment with amiodarone and mexiletine. Prior to this, he had failed sotalol. ICD interrogation showed a single VT morphology, though with progressively longer cycle lengths as medication doses escalated. He had recently undergone a mechanical mitral valve replacement and surgical left atrial appendage ligation. A 12-lead ECG of his VT suggested possible epicardial involvement, though significant pericardial inflammation and adhesions were anticipated with recent surgery. The surgical team strongly recommended against endocardial catheter mapping near the recent mechanical valve replacement. After discussions about the risks, he was offered SBRT.

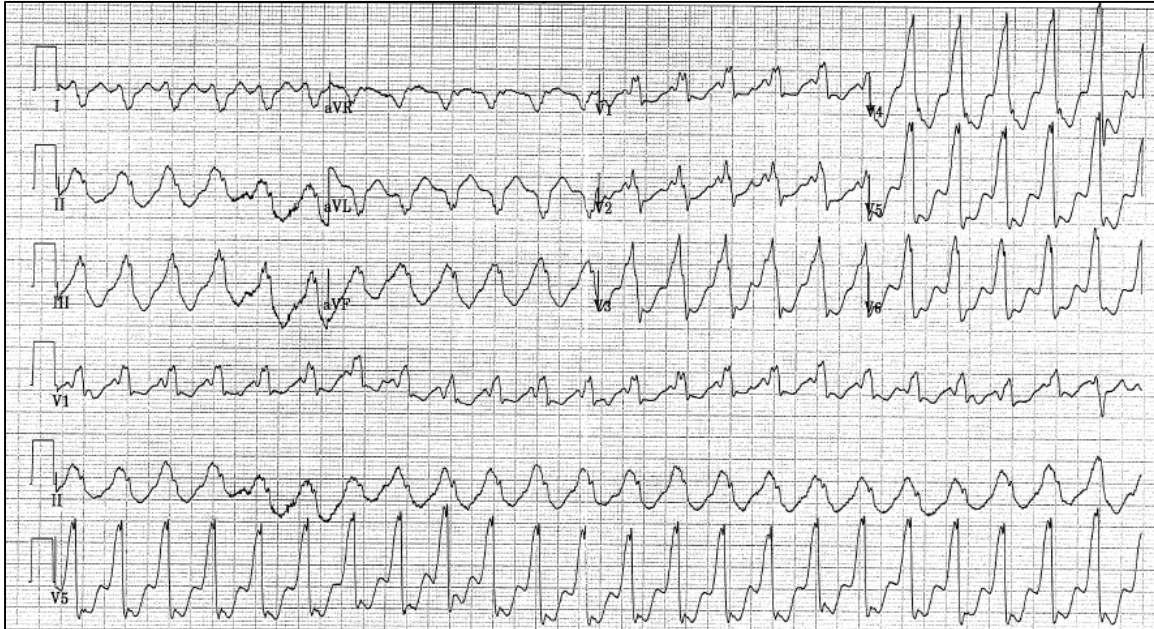
Myocardial radionuclide imaging (nuclear stress test, 8 years prior to SBRT)

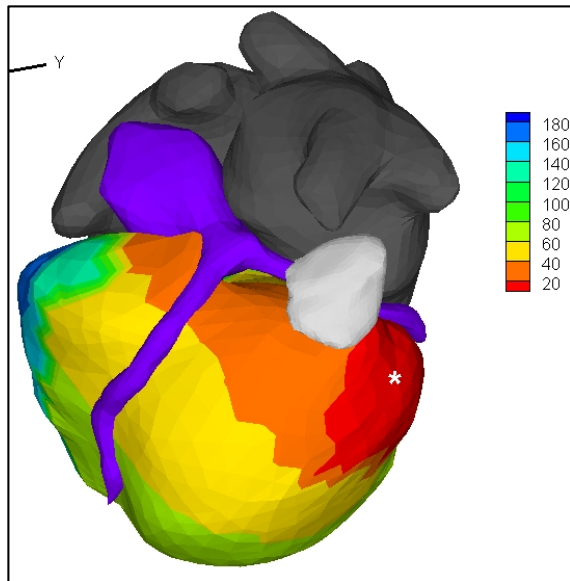
Moderate-sized infarction in the basal and mid-inferior wall. Moderate left ventricular enlargement. Akinesis of the inferior wall (LVEF 41%).

Echocardiogram (prior to SBRT treatment)

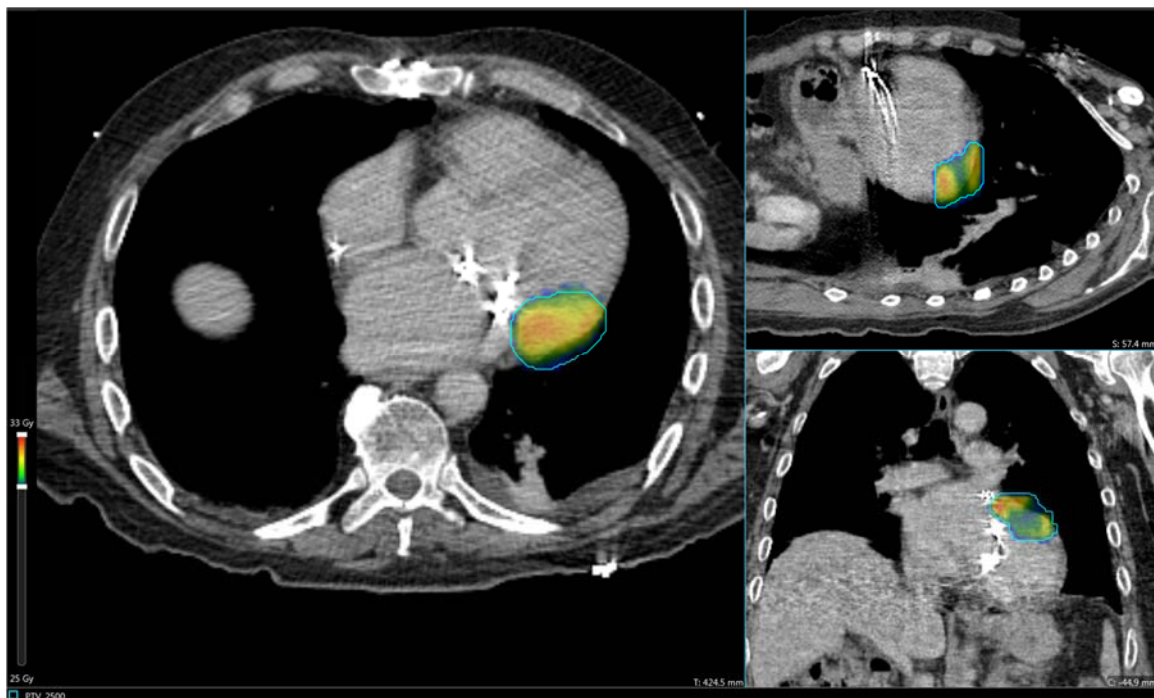
LVEF 17%, with akinesis of the basal anterolateral, inferolateral, inferior wall and inferior septum. MV mechanical prosthesis with mean gradient of 4 mmHg. Left ventricular end-diastolic dimension 6.8 cm.

Clinical VT (12-lead ECG, VT 1: 148 bpm)





One induced VT in the EP lab with NIPS (above). The noninvasive ECGI activation map is shown in an AP superior view. The left coronary artery is shown in purple; the atria are dark grey; the area of the closed left atrial appendage is light grey. ECGI mapped the area of earliest activation during VT to the anterolateral LV base (red region, white asterisk). Color scale is activation time in milliseconds.



Targeting volume for noninvasive ablation with SBRT. Three orthogonal views are shown above (axial left; sagittal top right; coronal bottom right), demonstrating the custom volumetric ablation target that included the full thickness of myocardium harboring the first 10 ms of the VT. The radiation dose is displayed as a color wash,

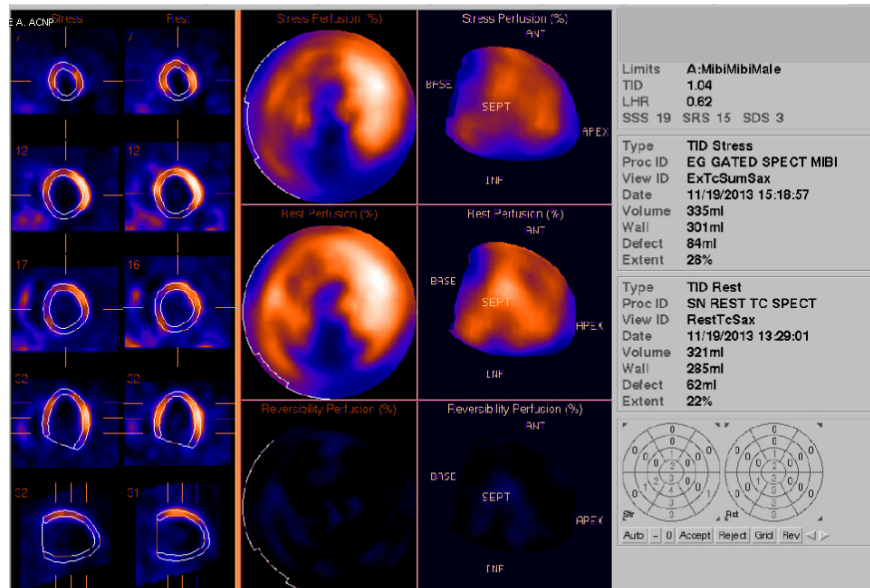
with a lower threshold of 25 Gy (blue), with doses in excess of 25 Gy displayed in gradations of color in the spectrum with red being the highest dose. The targeted area was in the anterolateral LV, near the surgically closed left atrial appendage and mechanical prosthetic mitral valve. The treatment spared the entirety of the inferior scar region. In this case, we opted to treat the electrical map primarily, and not treat the entirety of the anatomic scar. The ablation volume was 17.3 cc. After immobilization and alignment of the patient, treatment was delivered over 11 minutes.

Clinical follow-up (at 12 months)

Patient 2 had three ATP events during the six-week blanking period, but had no subsequent VT events.

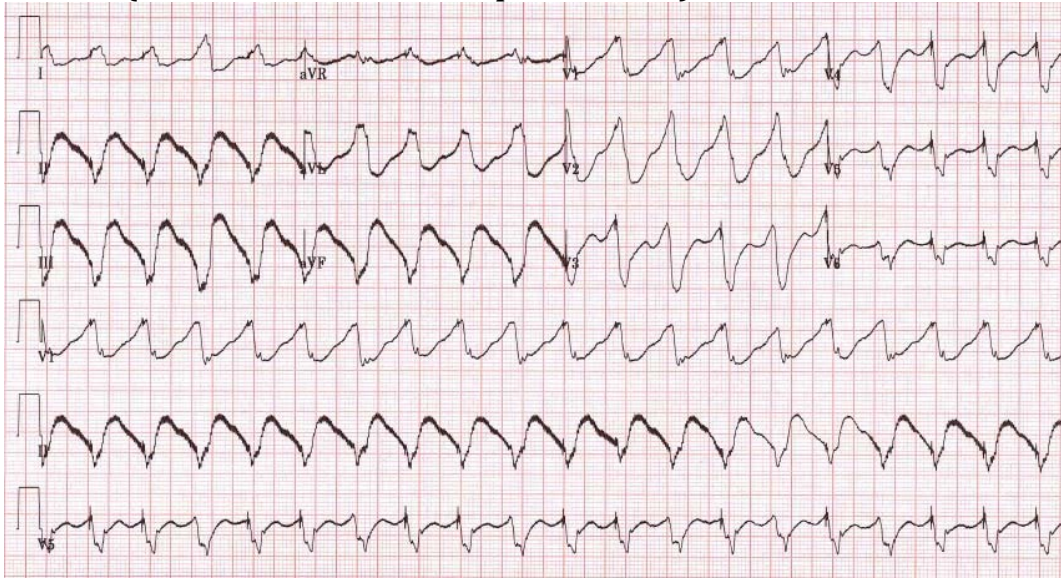
This patient was a 65-year-old man with nonischemic cardiomyopathy, NYHA class 4 heart failure symptoms, and repeated ICD shocks for VT despite treatment with amiodarone and mexiletine (he was intolerant of sotalol). He had undergone two prior invasive catheter ablations, including invasive mapping that targeted the posterior LV, from septal to lateral. His heart failure was advanced, and he required intermittent IV inotropic support. After discussions about the risks, and prior to undergoing surgical implantation of a left ventricular assist device (LVAD), he was offered SBRT in an attempt to control his electrical storm. At the time of his NIPS, his VT was not inducible with single and double extrastimuli from the right ventricular ICD lead.

Image shown below. Moderate-sized severe infarct of the mid to distal inferior wall. Marked left ventricular enlargement. Severe diffuse hypokinesia, worse in the apex (LVEF 21%).

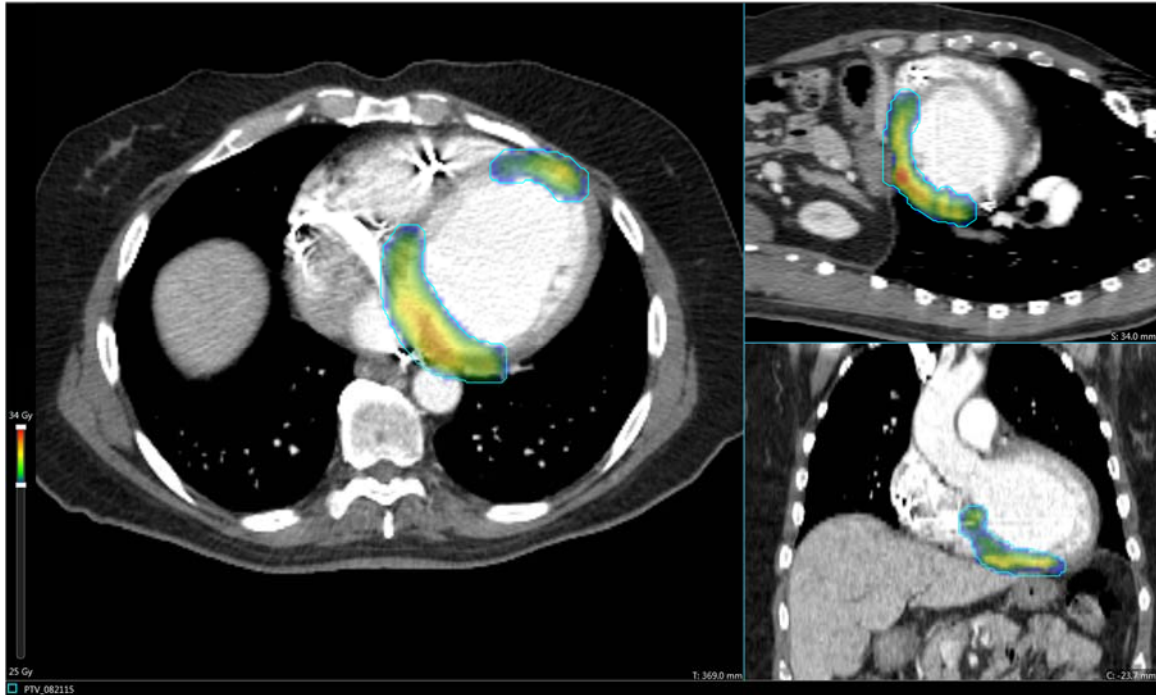


LVEF 22%, with global severe hypokinesis. Akinetic segments in the basal inferolateral and mid-inferolateral regions. Left ventricular end-diastolic dimension 7.8 cm.

Clinical VT (12-lead ECG; VT 1: 135 bpm, variable)



Targeting volume for noninvasive ablation with SBRT. Three orthogonal views are shown below, demonstrating the custom volumetric ablation target that included the full thickness of myocardium harboring the scar area in the inferior posterior lateral LV. The radiation dose is displayed as a color wash, with a lower threshold of 25 Gy (blue), with doses in excess of 25 Gy displayed in gradations of color in the spectrum with red being the highest dose. The 12-lead ECG suggested an inferoseptal LV site of origin, though the VT could not be induced in the EP lab, so no ECGI was available for precise targeting. In this case, we opted to treat the anatomic map primarily, with only a 12-lead ECG and prior invasive catheter mapping to guide volumetric ablation. The ablation volume was 44.5 cc. After immobilization and alignment of the patient, treatment was delivered over 14 minutes.



Clinical follow-up (at 12 months)

Patient 3 had one appropriate ATP event nine months after treatment. ICD interrogation demonstrated a VT that had a much longer cycle length (slower VT) than the pre-treatment VTs. The stored electrograms had different characteristics from the pre-treatment VTs. At that point, amiodarone was restarted.

Patient 4

This patient was a 62-year-old man with nonischemic cardiomyopathy, NYHA class 4 heart failure symptoms, and repeated ATP events and shocks for VT despite treatment with combinations of sotalolol, mexiletine, amiodarone and quinidine. He had undergone four prior invasive catheter ablation procedures targeting numerous VT sites of origins along the anterior and inferior LV septum (first two ablations), anterior RV outflow tract (third ablation), and posterior RV outflow tract (fourth ablation). He continued to have polymorphic VT storm with at least two different VT morphologies. Because of the multiple failed ablations, the site of origin was thought to be protected from the effect of a catheter delivery of radiofrequency energy. After discussions about the risks, he was offered SBRT.

Myocardial radionuclide imaging (nuclear stress test, after 4 ablations)

Small sized, mild severity anterior wall ischemia. Decreased perfusion on both stress and rest images of the basal/mid septal and inferoseptal walls with relative sparing of the distal septal segments which may represent infarcted myocardium. Marked left ventricular enlargement with severe left ventricular dysfunction (LVEF 21%).

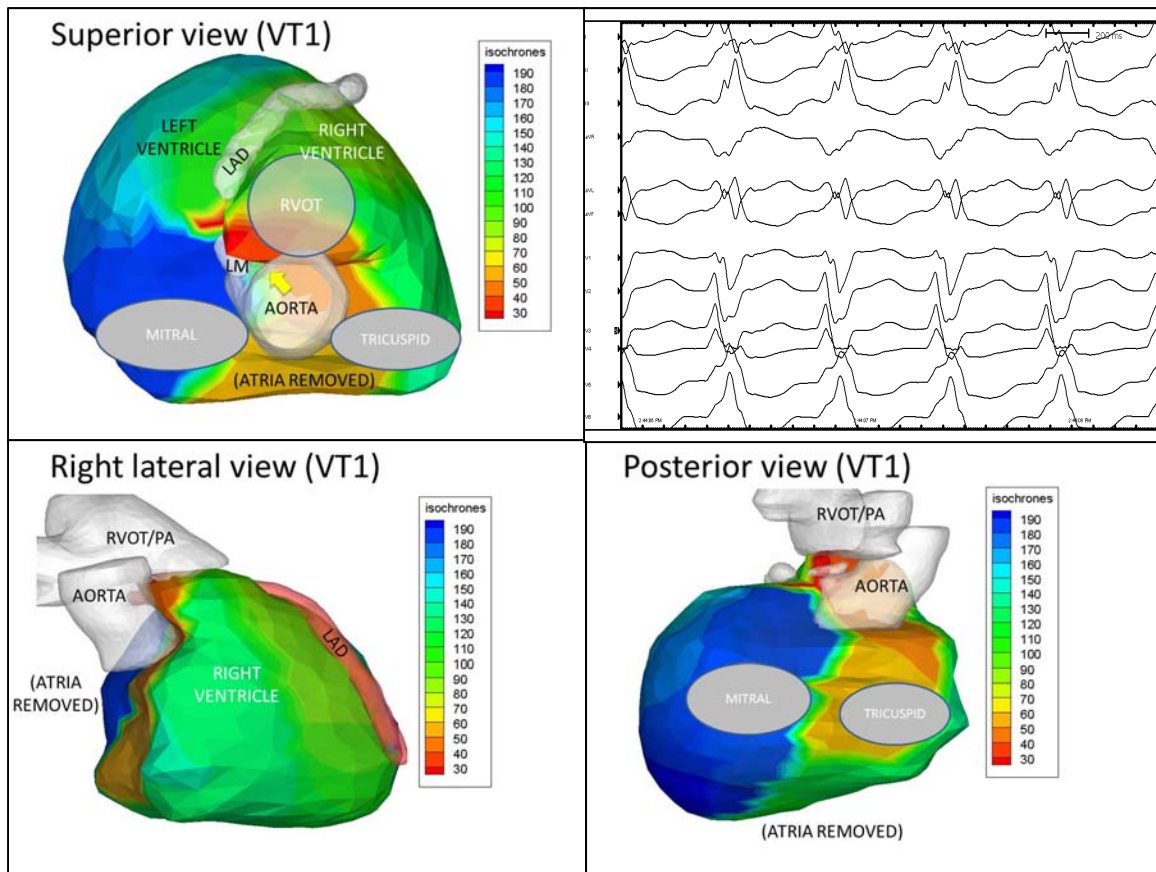
Echocardiogram (prior to SBRT treatment)

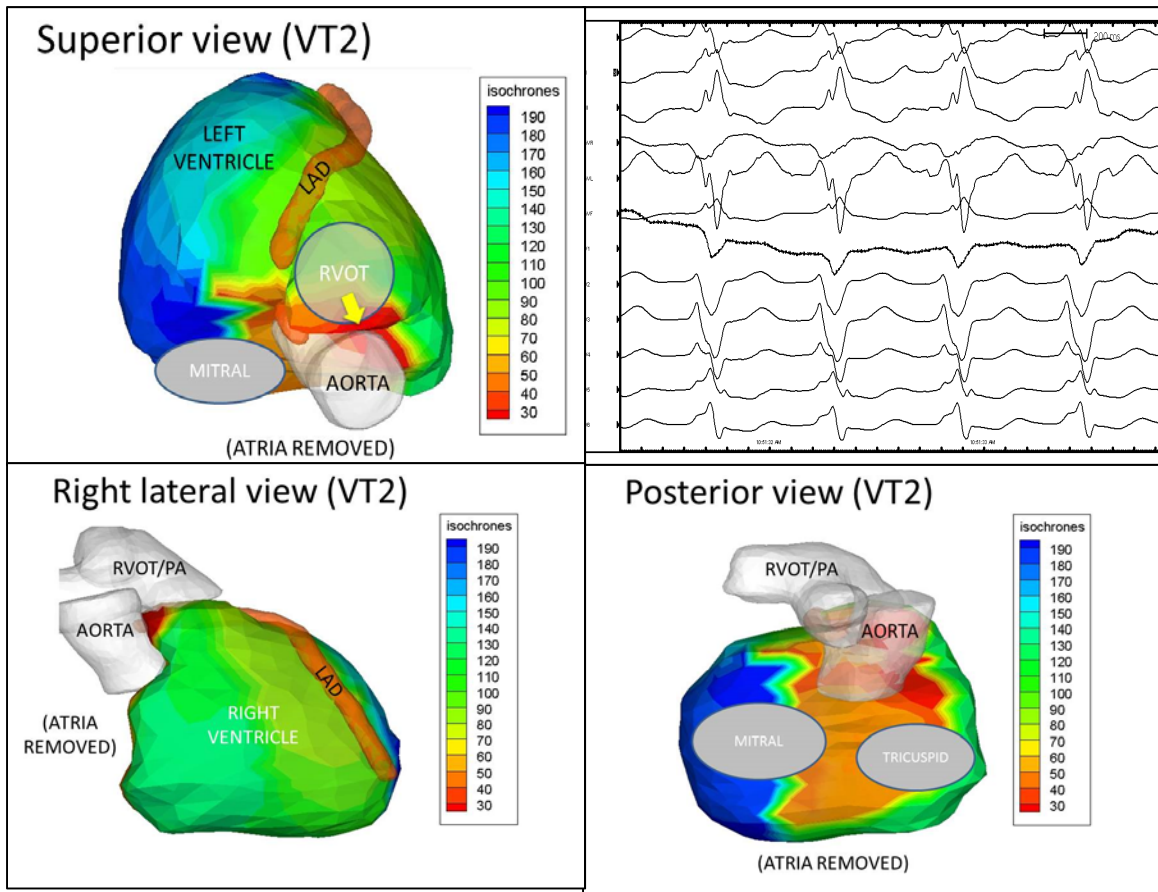
LVEF 26%, with global severe hypokinesis. Eccentric LVH. Restrictive diastolic dysfunction. Left ventricular end-diastolic dimension 6.3 cm.

Clinical VT (12-lead ECG; VT 1: 120 bpm)

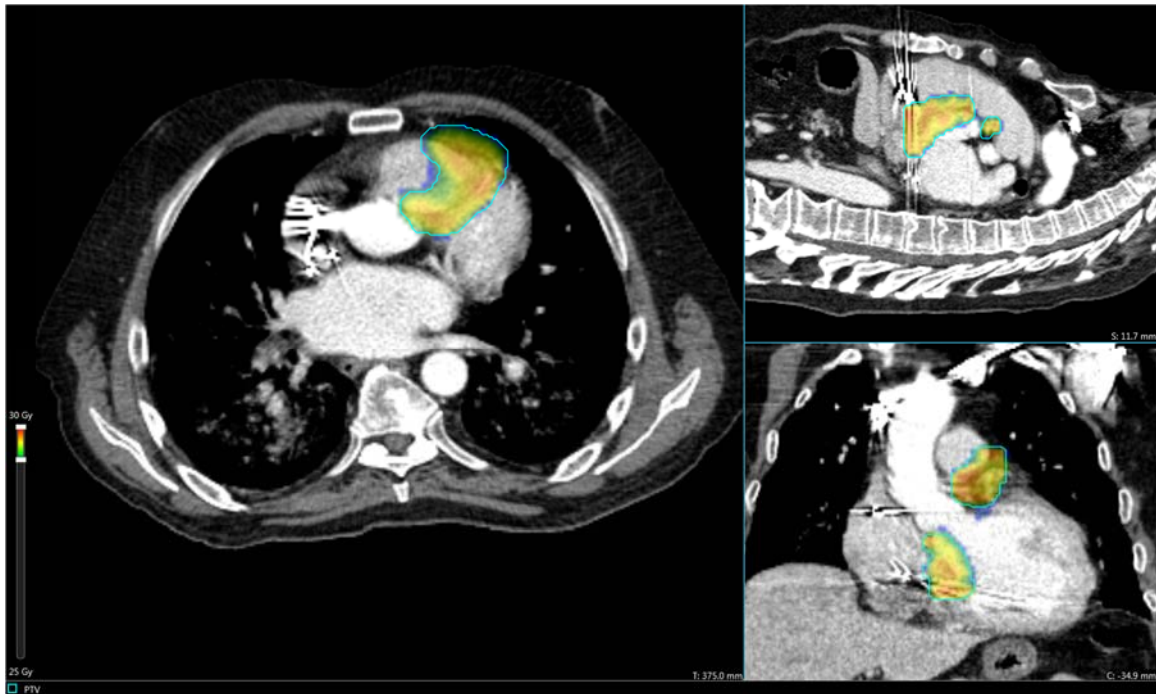


Induced VT in the EP lab with NIPS. In total, five different PVCs and nonsustained VTs were observed during NIPS. Noninvasive ECGI activation maps of the two sustained VTs are shown below (color scale showing activation time in milliseconds), in three orthogonal views (superior, right lateral and posterior). The earliest activation site for VT 1 is in the left coronary cusp of the aortic outflow tract (yellow arrow). The earliest activation site for VT 2 is in the posterior right ventricular outflow tract (RVOT, yellow arrow). Interestingly, both VTs activate the interventricular septum first (orange areas), which is atypical for VT of true outflow tract origin.⁵





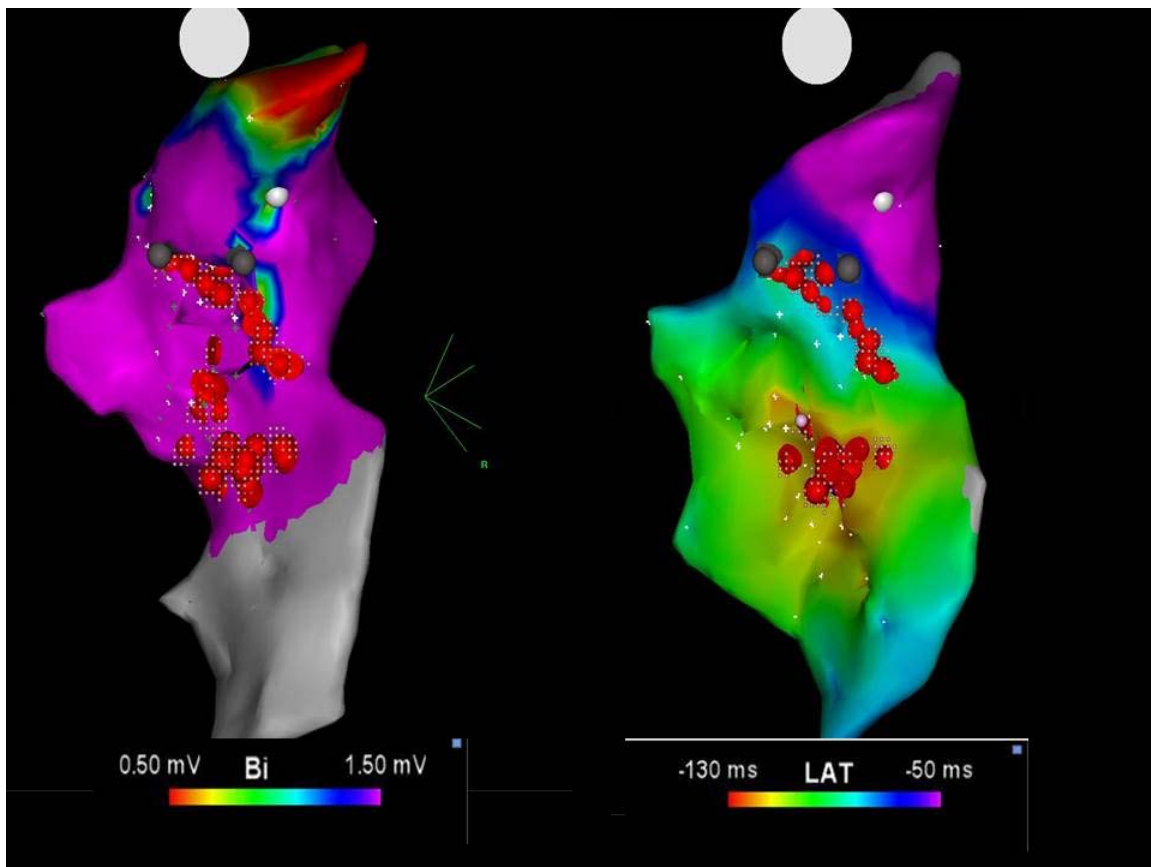
Targeting volume for noninvasive ablation with SBRT. Three orthogonal views are shown below, demonstrating the custom volumetric ablation target that included the full thickness of myocardium harboring all the PVCs that were mapped, which extended along the interventricular septum from the inferior wall to the outflow tract. The radiation dose is displayed as a color wash, with a lower threshold of 25 Gy (blue), with doses in excess of 25 Gy displayed in gradations of color in the spectrum with red being the highest dose. The ablation volume was 53.0 cc. After immobilization and alignment of the patient, treatment was delivered over 12 minutes.



Patient 4 underwent a fifth invasive mapping and ablation procedure 4 weeks after treatment due to incomplete control of his VT (over 2000 episodes before SBRT versus 355 episodes in the month after SBRT). His previously polymorphic VT was now monomorphic. The area of successful invasive ablation was located in the posterior right ventricular outflow tract (RVOT, activation map shown below on the right). At the time of the invasive mapping the amplitude (voltage, shown below on the left) and characteristics of the electrograms in the RVOT tissue appeared unremarkable. When compared to the noninvasive treatment volume, the location of the successful ablation fell just outside the original treatment area. It is likely that the partially successful result of the noninvasive ablation was due to treatment of some, but not all, of the arrhythmogenic region.

PA view, Voltage map
No signs of low-voltage regions
Points of noncaptured pacing in grey.

PA view, Activation map
Earliest PVC activation in red.
Ablation points as red circles.



Clinical follow-up (at 12 months)
Patient 4 had no further VT episodes.

Patient 5

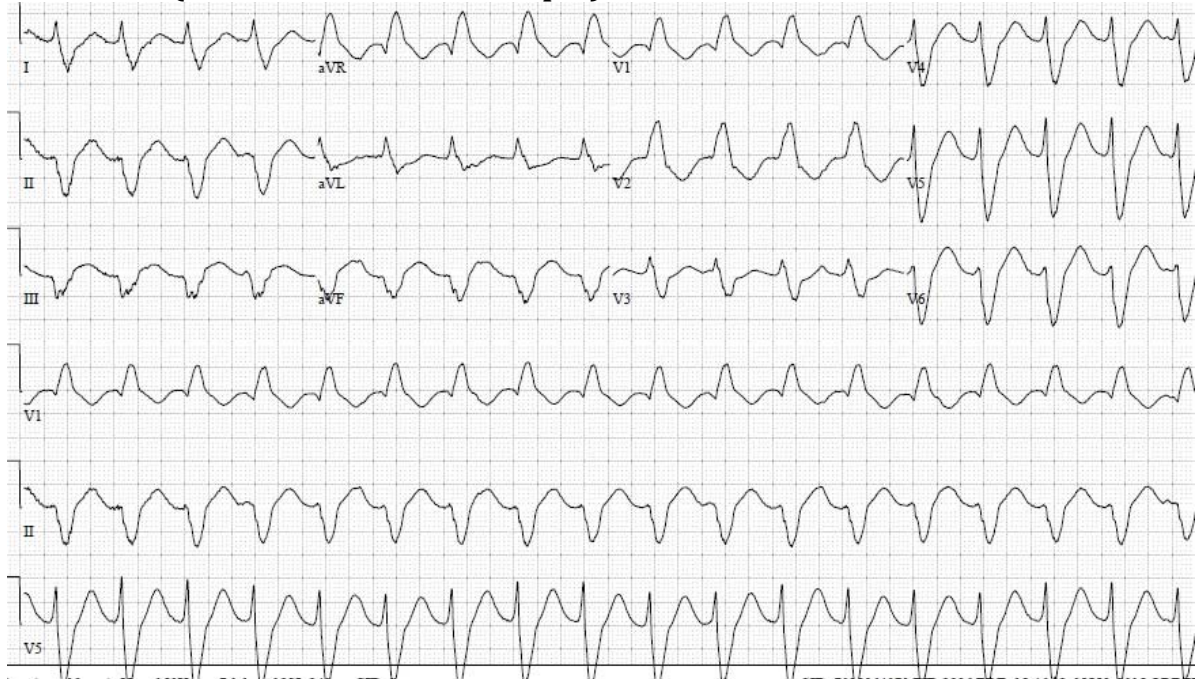
This patient was an 83-year-old woman with ischemic cardiomyopathy, NYHA class 4 heart failure symptoms, and repeated ATP events and shocks for VT despite treatment with combinations of amiodarone and mexiletine. She had other underlying illnesses, including atrial fibrillation (not on oral anticoagulants due to frailty and prior traumatic subarachnoid hemorrhage), chronic kidney disease stage 4, and hypertension. Because of her advanced age and other illnesses, she was offered hospice care, but she refused. After discussions of the risks she wished to undergo SBRT.

Myocardial radionuclide imaging (nuclear stress test)

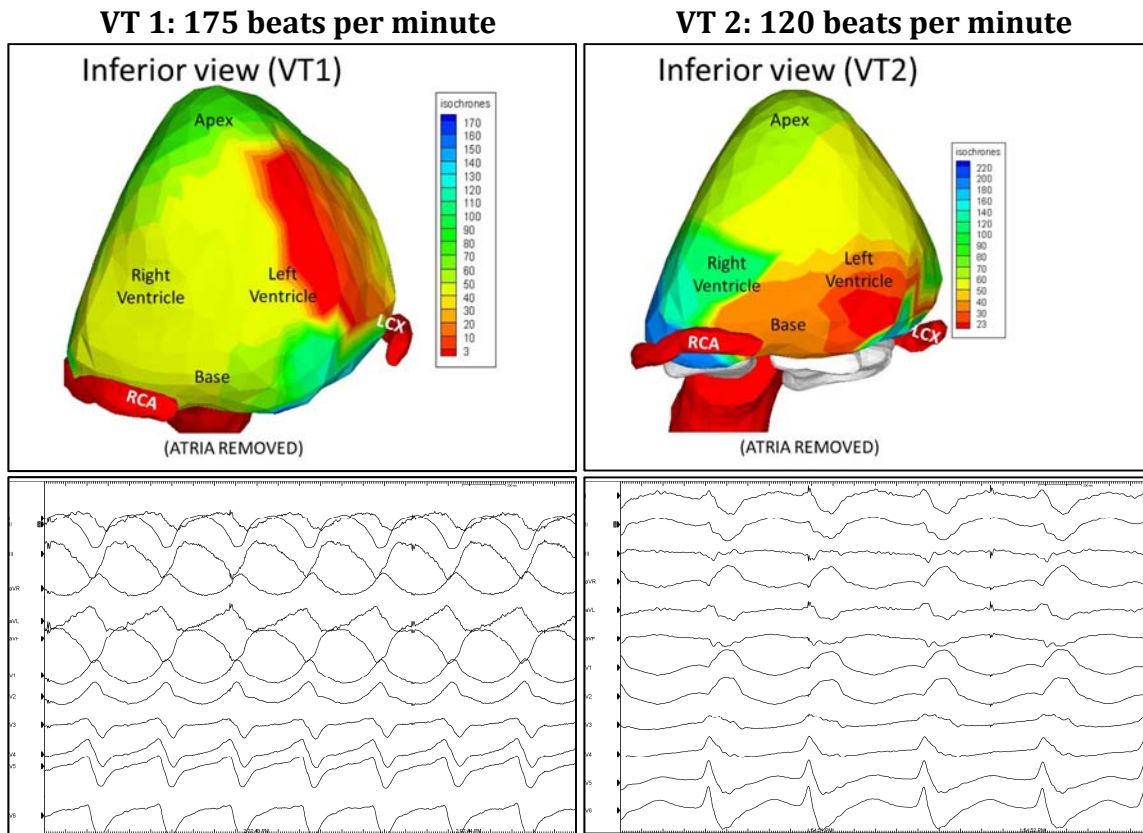
Image shown below. Moderate sized inferior-lateral resting transmural fixed defect. Severe left ventricular dysfunction (LVEF 15%).



Clinical VT (12-lead ECG; VT 1: 115 bpm)

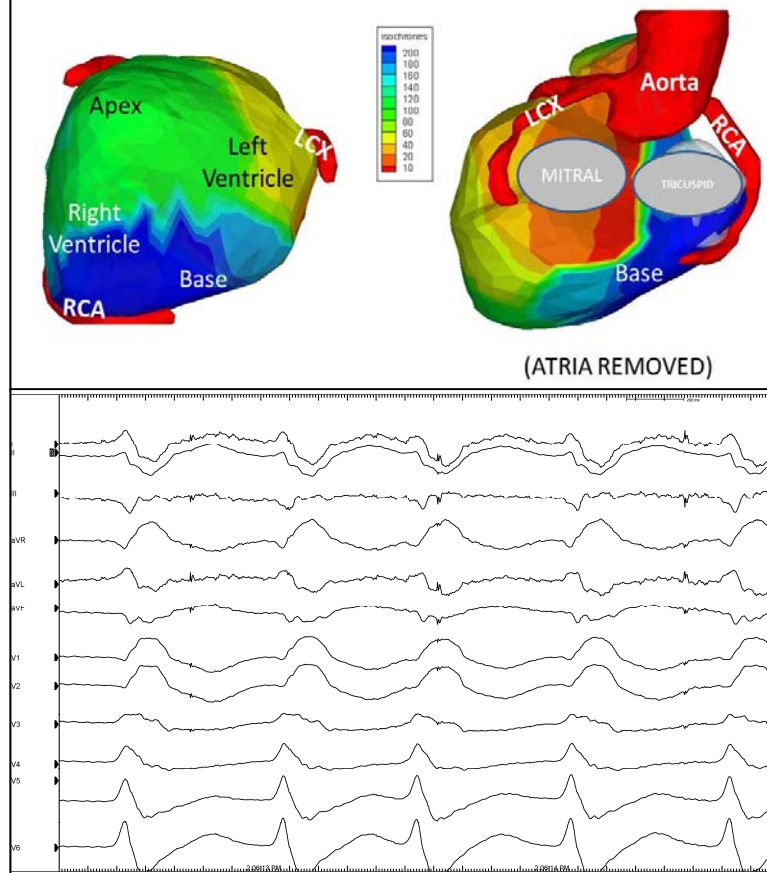


Induced VT in the EP lab with NIPS. In total, six different sustained VTs were observed in during NIPS. Noninvasive ECGI activation maps of three sustained VTs are shown below (color scale showing activation time in milliseconds). The earliest epicardial activation sites are seen as the red regions in the maps. VT 2 matched the “clinical” VT, at 120 beats per minute. These three sustained VTs demonstrated earliest activation from various edges of the inferolateral LV scar, highlighting the complexity of several circuits within the ventricular scar. Three additional induced VTs are shown below, with exit sites that are not in proximity to the inferolateral LV scar.



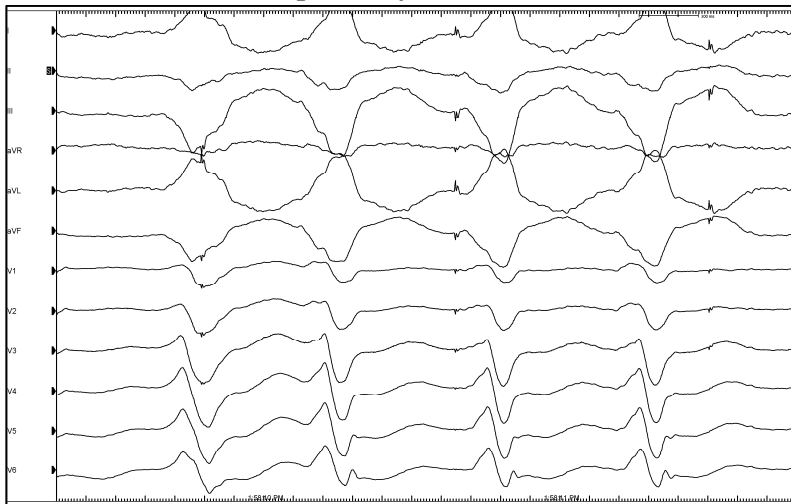
VT3: 155 beats per minute

LAO inferior and PA views (VT3)

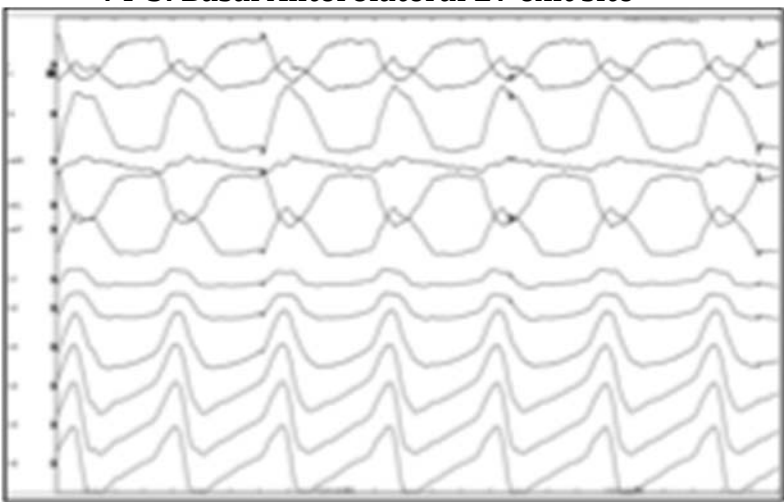


NONTARGETED VT:

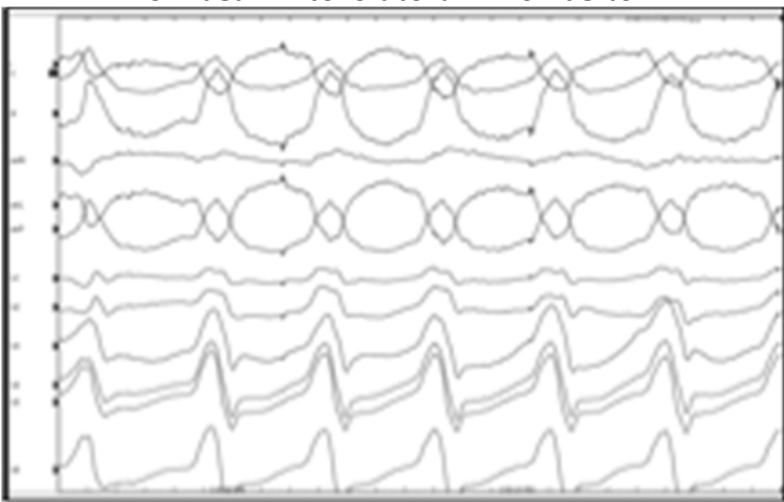
VT4: Inferoseptal LV/RV exit site



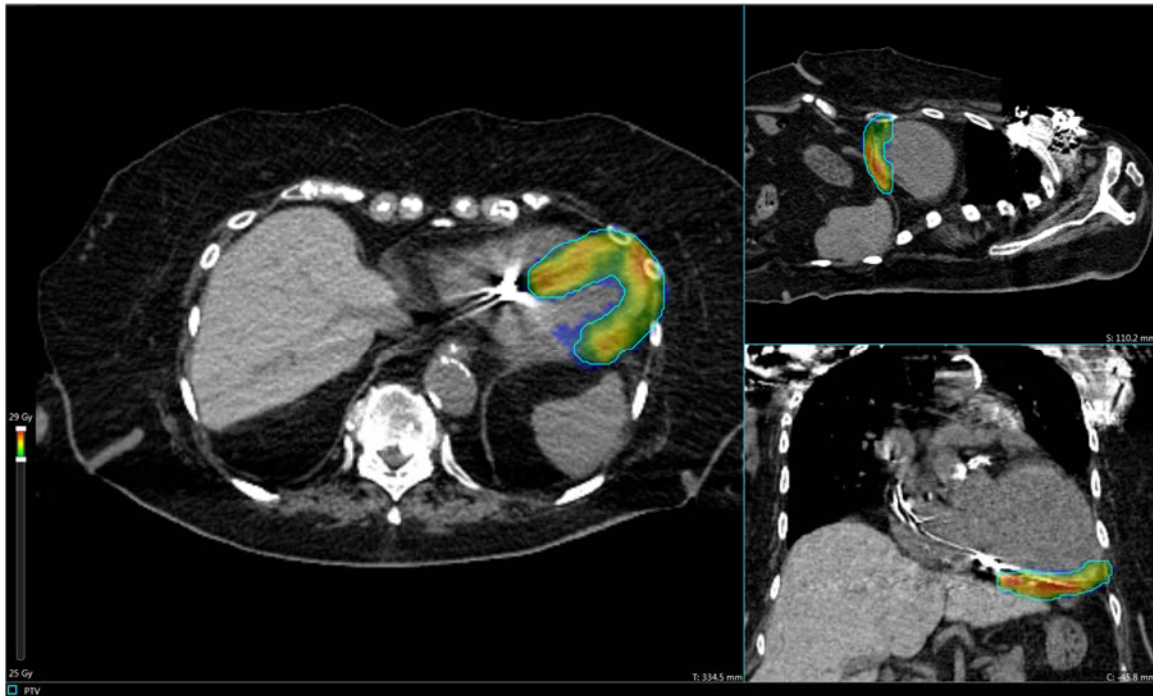
VT 5: Basal Anterolateral LV exit site



VT 6: Basal Anterolateral LV exit site



Targeting volume for noninvasive ablation with SBRT. Three orthogonal views are shown below, demonstrating the custom volumetric ablation target that included the full thickness of myocardium in the inferior wall. The radiation dose is displayed as a color wash, with a lower threshold of 25 Gy (blue), with doses in excess of 25 Gy displayed in gradations of color in the spectrum with red being the highest dose. The ablation volume was 81.0 cc, with an attempt to include the entirety of the myocardial scar and the three distinct exit sites identified by ECGI. This was the largest volume treated in the group, but there remained concern that not all ECGI identified sites could be covered. After immobilization and alignment of the patient, treatment was delivered over 18 minutes.



Clinical follow-up (at 12 months)

Patient 5 had 322 VT episodes in the first three weeks after treatment (decreased from over 2000 before SBRT). As described in the main text, she suffered a severe ischemic stroke three weeks after treatment. She ultimately decided on comfort care options and died shortly thereafter. She generously donated her heart for autopsy. Prior to her death, her LVEF had improved from 15% to 30% in three weeks after treatment with the reduction of her VT burden.