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Electrical Substrate Ablation for Refractory Ventricular Fibrillation: Results of the AVATAR Study

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Abstract

Background ––Refractory ventricular fibrillation (VF) is a challenging clinical entity, for which ablation of triggering premature ventricular complexes (PVCs) is described. When PVCs are infrequent and multifocal, the optimal treatment strategy is uncertain.

Methods ––We prospectively enrolled consecutive patients presenting with multiple ICD shocks for VF refractory to antiarrhythmic drug therapy, exhibiting infrequent (≤3%), multifocal PVCs (≥3 morphologies). Procedurally, VF was induced with rapid pacing and mapped, identifying sites of conduction slowing and rotation or rapid focal activation. VF electrical substrate ablation (VESA) was then performed. Outcomes were compared against reference patients with VF who were unable or unwilling to undergo catheter ablation. The primary outcome was a composite of ICD shock, electrical storm, or all-cause mortality.

Results ––VF was induced and mapped in 6 patients (60±10 y, LVEF 46±19%) with ischemic (n=3) and nonischemic cardiomyopathy. An average of 3.3±0.5 sites of localized reentry during VF were targeted for radiofrequency ablation (38.3±10.9 minutes) during sinus rhythm, rendering VF non-inducible with pacing. Freedom from the primary outcome was 83% in the VF ablation group versus 17% in 6 non-ablation reference patients at a median of 1.0 years (IQR 0.5–1.5 years, p=0.046) follow-up.

Conclusions ––VESA is associated with a reduction in the combined endpoint compared with the non-ablation reference group. Additional work is required to understand the precise pathophysiologic changes which promote VF in order to improve preventative and therapeutic strategies.

Graphical Abstract

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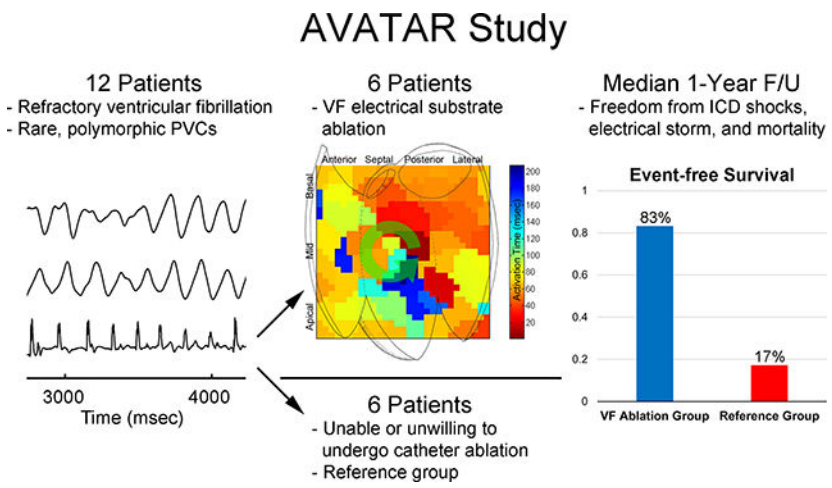

Keywords

ventricular fibrillation; catheter ablation; electrophysiology mapping; Catheter Ablation and Implantable Cardioverter-Defibrillator

Background

Ventricular fibrillation (VF) is a common, life-threatening arrhythmia[1] in patients with structural heart disease. For patients with recurrent implantable cardioverter-defibrillation (ICD) shocks, antiarrhythmic drug therapy is indicated,[2] but may be ineffective.[3] Patients who fail antiarrhythmic drugs are at particularly high risk of arrhythmia recurrence, ICD shocks, and death.[3]

Premature ventricular complex (PVC) trigger ablation has been reported for VF with frequent, monomorphic ventricular ectopy.[4, 5] Prior work has also demonstrated ablation in patients with idiopathic VF[6, 7] and VF following myocardial infarction[8] or with structural heart disease[7] by targeting low-voltage substrate. However, for patients with extensive substrate remodeling and rare, polymorphic triggers, the optimal ablation approach is unclear. Stellate ganglia modulation[9] and cardiac transplantation[10] are options for refractory cases, but may be suboptimal or associated with potential morbidity.

Case reports have demonstrated VF electrical substrate mapping and ablation,[11–13] but outcomes in larger series compared with non-ablation reference patients are unknown. We designed the AVATAR Study to evaluate this approach in patients with recurrent, drug-refractory VF and rare, polymorphic PVCs at 2 tertiary medical centers.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Enrollment

AVATAR (Ablation of Ventricular fibrillation by Accurate Targeting of Arrhythmogenic Regions) is a prospective, 2-center study of targeted substrate ablation in consecutive patients with ischemic and nonischemic cardiomyopathy presenting with multiple (≥2) ICD shocks for VF, refractory to 1 or more antiarrhythmic drugs and with rare (<3% of total beats), multifocal PVCs (≥3 morphologies) at the University of California San Diego (UCSD)/VA San Diego Healthcare Systems and Stanford University Medical Center (NCT01492764: registered December 2011; supplemental material figure S1). Patients unable or unwilling to participate in ablation were enrolled as reference patients.

VF was defined as rapid, irregular ventricular activation with marked variability in electrocardiographic (ECG) waveform, ventricular rate by ICD electrogram >250 bpm (cycle length: <240 ms).[6] Exclusion criteria consisted of the presence of prior monomorphic ventricular tachycardia (VT), cardiogenic shock or volume overload precluding the safe administration of anesthesia, ventricular thrombus, significant unrevascularized ischemia, recent myocardial infarction (<7 days[14]), ventricular pseudoaneurysm, or other risks to patient safety.[15] The study protocol was approved by the institutional review boards at both centers, and all patients provided written, informed consent.

Procedural Protocol

Because of the requirement for VF induction and subsequent defibrillation to allow arrhythmia mapping, patients were intubated, ventilated, and maintained under a consistent general anesthetic protocol. Invasive arterial pressure and vital signs were monitored continuously throughout the case. Patients were anticoagulated following intravascular access, targeting an activated clotting time of ≥250 seconds.[16]

A deflectable, externally irrigated 3.5 mm quadripolar ablation catheter (ThermoCool, Biosense-Webster, or Tacticath, St. Jude Medical) was advanced sequentially into the right (RV) and left ventricles (LV) to create ventricular geometries and perform bipolar (figure S2) and unipolar voltage mapping and electrogram mapping. For endocardial bipolar mapping, voltage cutoffs were: normal (bipolar voltage ≥1.5 mV), borderzone (>0.5 and <1.5 mV), and dense scar (≤0.5 mV).[17] For unipolar mapping in patients with minor endocardial voltage abnormalities, borderzone voltage cutoffs were: >3.5 and <8.3 mV LV, >3.5 and <5.5 mV RV.[18] In patients with significant endocardial voltage abnormalities, borderzone unipolar cutoffs were: >3.4 and <5.1 mV LV, >3.2 and <4.4 mV RV.[19] The ventricular geometries and voltage/electrogram maps were then fused with 3-dimensional anatomical data from preprocedural cardiac imaging.[20, 21]

After voltage mapping, basket catheters (64-electrode; Constellation, Boston Scientific or FIRMap, Abbott; 6 mm interelectrode spacing) were advanced into the ventricles (figure 1A) for VF electrical substrate mapping. Basket catheters were maneuvered under fluoroscopic (figure S3) and intracardiac echocardiographic visualization to optimize ventricular contact.[13] Basket spline and electrode positions were then recorded within the 3-dimensional ventricular geometry for reference during ablation. The ventricular endocardial

surface was analyzed according to 144 discrete regions referenced to the basket catheter electrodes for VF mapping and voltage analysis[13] as shown in figure S4.

The VF induction protocol[11] consisted of 2 VF inductions using a defined protocol (figure S5, and supplemental material pages S12-S13) beginning with triple extrastimulus pacing and utilizing 15 seconds of progressively more rapid burst pacing if required (figures 1B and S6). VF was recorded during defibrillator charging (10–15 seconds) and defibrillated externally. VF cycle length was calculated as the average of 10 cycles of VF from the ICD interrogation (for spontaneous VF) or intracardiac recordings (for induced VF during electrophysiology study).

Electrogram Analysis and Interpretation

Unipolar electrograms (figure 1C) were recorded at 1000 Hz and filtered from 0.5 to 250 Hz (LabSystem Pro, Boston Scientific, Marlborough, MA or CardioLab, GE Marquette, Milwaukee, WI). Signals were then exported for analysis; details of the algorithms are not yet available due to their proprietary nature (RhythmView, Abbott, Abbott Park, IL).

We evaluated maps of ventricular activation during VF for potential sources, which included sites of functional reentry (figures 1D and S7) and focal activation.[15] We defined *functional reentry* as migratory, continuous activation consistent with prior description,[22] excluding anatomical reentry such as scar-based monomorphic VT.[22] We defined *focal sources* as regions of centrifugal activation.[15]

VF source locations were then transposed to the fused electroanatomic maps (figure 1E) and cardiac imaging data to identify potential structural abnormalities at each site (please see supplemental material, page S7–8 for detailed criteria). We defined the term *VF electrical substrate sites* as locations within the ventricle which possessed the structural and functional abnormalities to stabilize and perpetuate functional reentry and/or focal sources. This definition of electrical substrate sites excludes patients with functional abnormalities alone, such as a patient with VF solely due to electrolyte abnormalities, from consideration for this study.

We evaluated VF electrical substrate stability according to 3 criteria: (1) the maximum number of consecutive revolutions of electrical activity or focal activations within a region bounded by 2 electrodes in each axis;[15] (2) repeatability of VF electrical sources after transient interruption during ongoing VF; and (3) between separate VF inductions. The locations of the 3–4 VF electrical substrate sites with the greatest stability according to these 3 metrics and ≥3 rotations or focal activations were targeted for ablation (figure 1F); sites of transient functional reentry or focal activation ≤ 2 VF cycles were not targeted.

Ablation and VF Reinduction

VF electrical substrate ablation (VESA, figure 1F) was performed using 35–45 Watts power for 30–60 seconds per lesion targeting: (a) 10–15 Ohm impedance drop;[23] with impedance decreasing ≥ 5 Ohms in the first 10 seconds[24] and plateauing at 30–40 seconds;[23, 25] (b) reduction in target region electrogram amplitude to <0.15 mV in regions of bipolar electrogram voltage < 1.5 mV;[26] and (b) pacing non-capture at an output of 20 V at 10

msec[27] in the targeted area. The final number of ablation lesions for each targeted site was determined by the attending electrophysiologist.

Following ablation of all targeted sites, VF reinduction testing (figure S8) was performed using the entire pacing protocol as determined by the study induction protocol (figure S5, bottom).

Follow-up

All patients had follow-up at 1, 3, 6, and 12 months, and thereafter at 6 months intervals with defibrillator interrogation at each visit. Additionally, we reviewed all documented patient encounters, remote monitoring reports, and outside medical records. The primary outcome was a composite of ICD shocks, three or more documented episodes of ventricular arrhythmia within 24 hours (electrical storm), or all-cause mortality.[28]

Statistical Analysis

Continuous variables are expressed as mean±standard deviation, unless otherwise indicated. Follow-up duration for the primary endpoint analysis is reported as median±interquartile range. Fisher's exact test was used to compare categorical variables. McNemar's test was used to compare pre- and post-ablation VF inducibility. Kaplan-Meier plots were used to evaluate cumulative survival from the primary endpoint. The permutation test incorporating 10,000 Monte Carlo samples was used to compute p-values comparing group means and survival. Statistical analyses were performed using SPSS version 19 (IBM, Somers, New York), R statistical software (R Foundation, Vienna, Austria), and NCSS (NCSS LLC, Kaysville, UT). Note that the study was underpowered to optimally detect confounding factors between the experimental and reference groups (e.g. potential type II error); p-values are provided for exploratory analysis and should be interpreted with caution.

Results

Patient Characteristics

Between January 2014 and March 2018, 14 patients were screened; 6 patients were enrolled and underwent VESA. Six contemporaneous patients meeting the study inclusion criteria who were unable (LV thrombus=2, LV pseudoaneurysm=1, femoral vein/IVC DVT=1) or unwilling (n=2) to undergo VF ablation were followed as reference patients and managed using optimal medical therapy including antiarrhythmic drugs (figure S1). Patient characteristics are shown in tables 1 and 2.

Locations of prior transmural myocardial infarction in ablation patients with ischemic cardiomyopathy are shown in table S2. There were no significant differences between groups with the exception of a greater number of ICD shocks in the VF ablation group. All patients either met a study endpoint or completed 6 months of post-procedure follow-up. (please see supplemental material section III for additional patient data).

Average PVC burden at enrollment was 0.9±1.2%, with 3.6±0.9 PVC morphologies. Figure 2 shows examples of different PVC morphologies initiating sustained VF. Triggering PVCs occurred at an average QT index of 0.92±0.05, consistent with prior work.[29]

Substrate Characterization

Figure 3 illustrates the myocardial substrate for patients with ischemic cardiomyopathy based upon bipolar (top row) and unipolar mapping (middle row). Figure 4 shows the myocardial substrate for patients with nonischemic cardiomyopathy utilizing bipolar (top row) and unipolar mapping (middle row). Voltage mapping included an average of 1050±779 bipolar and 1030±787 unipolar voltage samples per patient (table S2). Overall, bipolar voltage mapping classified 66±21% of the ventricular myocardium (LV and RV) as normal, 21±10% as borderzone, and 13±13% as scar (table S3). Unipolar mapping identified 68±33% as normal, 15±13% as borderzone, and 17±22% as scar (table S4). There were no significant differences in the proportions of normal, borderzone, and scar tissue between patients with ischemic and nonischemic cardiomyopathy.

VF Characteristics

Two episodes of VF (cycle length 203±21 msec, duration 15±3 seconds) were induced in all patients via the arrhythmia induction protocol (figure S5) with triple extrastimulus only in patients 1–3 (final extrastimulus cycle length (CL) 230±49 ms), a combination of triple extrastimulus and rapid pacing in patients 4 and 6, and rapid pacing only in patient 5 (average rapid pacing CL 280 ms, figure 1B). Ventricular activation was highly disorganized (figure 1B and S6), consistent with VF;[30] surface electrograms for all patients during VF are shown in the supplemental material section III. Table S7 details VF induction data for study patients.

Results of VF Mapping

An average of 3.3±0.5 VF electrical substrate sites were identified per individual. Supplemental videos 1–6 show arrhythmia activation and mapping data for all ablation patients (please see supplemental material, section I for video legends). Figure 1 panel D shows a functional reentry site in the posteroseptal LV in study patient 5. Of the 20 total sites, 15 (75%) were located in the LV. The majority (17 of 20, 85%) were associated with bipolar or unipolar voltage abnormalities, although 3 (15%) localized to tissue with “normal” voltage amplitude in the vicinity of the LV posteroseptal papillary muscle (patient 2), apical His-Purkinje system (patient 2) and RV posterior papillary muscle (patient 1). As noted in supplemental material table S6, a minority of sites (7 of 20, 35%) exhibited local abnormal ventricular activities (LAVA) or late potentials (figure 5 at rotor site 1). Notably, ablation patient 6 had no evidence of LAVA or late potentials at any targeted site. Data processing to identify target sites required 10.3±2.2 minutes.

VF Source Reproducibility and Stability

There was modest spatial conservation of the dominant VF electrical substrate sites; 11 of 20 sites (55%) exhibited spatial conservation between VF inductions and 12 of 20 sites (60%) exhibited spatial conservation between transient interruptions during a VF event (table S5). Targeted sites were stable for an average of 6.7±2.3 VF cycles (approximately 1.3 seconds) prior to interruption or migration.

VF Ablation and Noninducibility

An average of 38±11 minutes of radiofrequency ablation energy was delivered per procedure, about 11.4 minutes per target site. Figures 3 and 4 (bottom rows) illustrate targeted ablation lesions (circular markers). Following ablation, sustained VF was no longer inducible with pacing according to the study protocol (0 of 6 patients inducible, p=0.041 vs. pre-ablation, table S7). Supplemental material figure S8 shows inability to induce sustained VF in patient #6 following ablation (supplement section III illustrates reinduction attempts for all ablation patients).

Clinical Outcomes

Prior to enrollment or ablation, all patients experienced an average of 5.1±2.9 ICD shocks for VF over 7.1±5.7 months. The pre-procedure shock density for the VF ablation group was 1.37±1.05 shocks per month. Over a median follow up of 1.0 years (interquartile range 0.5–1.5 years), survival from the combined endpoint of all-cause mortality and ICD shocks was 83% in the VF ablation group. The post-ablation shock density was 0.05±0.12 shocks per month, (p=0.019 versus pre-ablation).

In comparison, the reference group shock density was 1.19±1.40 shocks per month over 7.0±6.6 months prior to enrollment. Following enrollment, the reference group survival from the combined endpoint was 17% (p=0.046, figure 6; table 2). Average shock density in the reference group after enrollment was 0.69±0.56 shocks per month (p=0.334 versus pre-enrollment).

In the VF ablation group, 1 patient experienced 2 ICD shocks for monomorphic VT at 7 months post-ablation, and subsequently died due to respiratory failure from metastatic lung cancer. In reference patients, 4 patients experienced ICD shocks, 1 patient experienced electrical storm from VF, and 3 patients died during follow-up from heart failure, electrical storm, and sepsis (table 2).

Procedural Duration and Safety

The average procedure time was 4.7±1.4 hours; the electrophysiology study and mapping portions of the procedure were 2.8±1.1 hours while ablation required 1.9±0.6 hours.

Following the procedure, 1 patient experienced groin hematoma, and 2 patients required hospitalization greater than 1 night after the procedure for fluid overload. No ablation patient experienced cardiac tamponade, electrical storm, disruption of ICD function, thromboembolism, or procedural death. Left ventricular ejection fraction was similar pre-ablation (37±19%) versus post-ablation (36±19%, p=0.92) as assessed by echocardiography at an average of 7.0±6.2 months after ablation (table S12).

Medical Management and ICD Programming

All study patients were on beta-adrenergic blockade medications at baseline (table S8). There was no increase in beta-blockade in the VF ablation group following ablation. In contrast, beta-blockade dosage was increased in 3 of 6 reference patients after study enrollment.

One patient in the VF ablation group was started on electrolyte supplementation after ablation, versus 3 patients in the reference arm. No antianginal medications were started after VF ablation, while 1 patient's isosorbide mononitrate dose was increased in the reference group. There were no changes to the ICD configuration (dual chamber versus biventricular ICD) or arrhythmia detection parameters in either group at 6 months (please see tables S8 and S9 for additional details).

Antiarrhythmic Drug Therapy

At six months follow-up in the VF ablation group, 4 of 6 patients were off antiarrhythmic drugs (table S10). Patient 5 remained on amiodarone for atrial fibrillation management and patient 6 refused to stop sotalol due to post-traumatic stress disorder from pre-ablation ICD shocks. At six months in the reference arm, 1 patient had died, 2 patients were on antiarrhythmic drugs (patient 2 taking dofetilide and patient 5 taking amiodarone). Patient 3 was intolerant of multiple antiarrhythmics, and patients 1 and 4 refused ongoing antiarrhythmic therapy.

Procedural Delays and Ongoing VF Risk

In 3 VF ablation patients, there was a delay (3.7±1.6 months) between the desired and actual procedure date due to several reasons (table S11). Notably, each patient with a significant delay experienced ICD shocks for VF (2±1 shocks) at an average rate of 0.55±0.09 shocks per month. The post-enrollment shock density in the delay group was similar to the post-enrollment shock density in the reference group (0.69±0.86 shocks/month, p=0.799).

Discussion

There are three findings from this study. First, in a cohort of patients with advanced structural heart disease, multiple ICD shocks for VF, and rare, polymorphic PVCs, VESA is associated with a 1-year survival from the composite endpoint of 83% compared to 17% in a reference population. Second, only a subset of borderzone and scar was found to participate in VF maintenance, and electrical substrate mapping allowed more precise identification of VF sources both within and outside of conventional definitions of diseased substrate. Third, targeted VF ablation is feasible, exhibited an acceptable safety profile, and did not significantly impact left ventricular function. This study provides motivation for larger, randomized studies using this approach.

The Current Population versus Prior VF Populations with Triggers

Our study population comprised patients with advanced structural heart disease and rare, polymorphic triggers for VF. This differs from patients with idiopathic VF in the context of no or minimal structural heart disease. While VF trigger ablation is a guideline-directed therapy for idiopathic VF,[2] trigger ablation was infeasible for our patients. In patients with idiopathic VF, Haissaguerre and colleagues demonstrated an ablation success rate of 83% guided by body surface mapping.[6] Ablation of PVC triggers has also been described for other VF subtypes[5] including idiopathic VF,[4, 31] long-QT syndrome,[32] Brugada syndrome,[32] and electrical storm.[33]

Prior work has noted the importance of Purkinje triggers to electrical storm after myocardial infarction.[8] Ablation targeting Purkinje extrasystoles in VF storm following myocardial infarction resulted in an 84% freedom from recurrent storm. In contrast, the presence of only rare, polymorphic PVCs in our population made it difficult to employ that approach.

VF Electrical Substrate Mapping and Ablation

In this feasibility study of high-risk individuals with advanced structural heart disease, recurrent VF, and rare polymorphic triggers, we found a significant reduction in the composite endpoint of ICD shocks, electrical storm, and all-cause mortality associated with VESA compared with the reference group. The occurrence of VF in ablation patients whose procedures were delayed and the ongoing VF risk in the reference group argue against arrhythmia episodes being part of a “cluster” which would have resolved without intervention, and emphasizes the ongoing risk for VF without intervention in the study group.

There was substantial VF organization in our study, in agreement with basic reports[34] and prior surgical VF mapping in patients.[35] In our study, the majority of potential VF-sustaining mechanisms exhibited spatial conservation within or between VF episodes. We acknowledge that we were unable to differentiate VF drivers from passive electrical rotational activity in this study, and that mapping specificity may be suboptimal. Future work using advanced temporal or vector analysis[36] may allow more accurate determination of the role of different electrical substrate sites to the maintenance of VF.

Larger controlled, randomized trials are required to confirm these results. However, this approach may be a therapeutic option for VF patients with ischemic and non-ischemic cardiomyopathy who have failed antiarrhythmic drug therapy and in whom trigger ablation is impractical.

VF Voltage Mapping to identify Structural Substrate

Multiple studies have demonstrated the importance of structural abnormalities and fibrosis to the formation of wavebreak,[37] initiation of functional reentry,[34] and perpetuation of VF.[38–40] Recent work has shown that VF from Brugada syndrome may be managed with ablation of pro-arrhythmic substrate.[41] Based on the notion that all borderzone tissue may participate in arrhythmia perpetuation, some strategies have advocated substrate homogenization[42] or core isolation[43] to eliminate VF.

In optical mapping studies of human hearts, Hansen and colleagues found that reentrant drivers in human atrial fibrillation anchored to tracts with specific characteristics of increased transmural fiber angle differences and interstitial fibrosis.[44] Ablation of these tracts terminated fibrillation and prevented subsequent arrhythmia induction. It is unclear whether such specifically abnormal ventricular tissue operates in VF, or could be successfully identified and ablated.

We identified VF electrical targets in areas of abnormal voltage, but also sites of preserved voltage (15% of sites) which could have been missed with a voltage-based ablation approach.[26] This is consistent with recent insights that identification of a single voltage cut-

off to identify areas of fibrosis in nonischemic cardiomyopathy may be challenging.[45] VF driver sites in our study were inconsistently associated with late potentials or LAVA, with no abnormal potentials in the targeted regions in patient 6. Although it may be argued that VF source ablation could be achieved without specific mapping, we have shown in a canine model that ablating control sites was ineffective in suppressing VF compared to the current approach to identify electrical targets.[11]

Future work is required to determine the precise relationship in VF between triggers and sustaining mechanisms; such insight may allow more accurate delivery of ablation or emerging regenerative therapies,[46, 47] or help to design preventative approaches designed to reduce fibrosis in high-risk patients.[48]

VF Ablation Feasibility and Safety

In this study, we found endocardial VF substrate mapping and ablation were highly feasible and no adverse events of thromboembolism, electrical storm, or tamponade were noted after the procedure. Fluid overload prolonged the hospital stay of 2 patients despite intra- and post-procedure diuresis, however, both had been admitted to the hospital for heart failure exacerbations in the months leading up to the ablation procedure.

Prior studies that localized VF substrate focused on limited regions, such as the epicardial RV in Brugada Syndrome.[49] In contrast, localizing biventricular sites in patients with ischemic or nonischemic cardiomyopathy using point-by-point mapping may be lengthy and introduce risks. Our approach was to use panoramic ventricular mapping to identify critical ventricular sites, complemented with detailed mapping. Body surface mapping has been reported in VF,[6, 50] with case studies showing promising results,[11, 12] but its limitations include resolution of the interventricular septum. We frequently found VF sources at the septum (supplemental material, table S6).

Limitations

The small study size is a limitation, and clinically meaningful differences may not be statistically significant. However, the robust endpoints (ICD shocks confirmed by device interrogation, admission for electrical storm, and all-cause mortality) support the association of a reduction in the primary endpoint with targeted substrate ablation in study patients with advanced cardiomyopathy, refractory VF, and rare, polymorphic PVCs. Second, this was not a randomized trial, which may have resulted in ascertainment bias, and comparisons between the ablation and reference groups should be interpreted with this in mind. However, the proportion of ICM and NICM was the same in the ablation and reference arms, and interestingly the major difference between groups was a greater number of pre-enrollment ICD shocks in the ablation arm which may have biased the study toward the null hypothesis. Furthermore, the ablation procedure was delayed for 3 patients in the ablation arm, and all 3 patients had ICD shocks for VF during the delay, also arguing against the active treatment limb being a lower VF-risk group. A third limitation is that our study protocol did not include patients with decompensated heart failure and significant volume overload, and the results should not be extrapolated to such patients. A fourth limitation is that the etiologies of the RV abnormalities in patients with ischemic cardiomyopathy were unable to be

determined precisely, although all patients had large right coronary artery infarctions and advanced COPD, which may have contributed to right ventricular ischemia and fibrosis. Notably all patients in the study tested negative for ARVC, sarcoidosis, and Brugada syndrome, which may result in RV scarring. Fifth, present mapping technology is unable to differentiate true VF-driving sites from passive electrical rotation, or provide high-resolution details of the VF circuits. Additionally, we did not attempt VF reinduction after ablating each site due to patient safety concerns and thus cannot comment on the relative importance of each targeted site. Future technologies are required to improve VF source detection and mapping. Sixth, we did not perform control ablation at non-VF-electrical-substrate sites in this study, although prior work in a canine model showed no impact of such sites on VF inducibility. Seventh, we were unable to provide the dimensions of targeted regions due to limitations of our mapping software, but in prior work the dimensions of VF source ablation were approximately 1.8 sq. cm.[11] Eighth, microarchitectural structure, which may impact arrhythmogenesis, was not assessed in this study. Finally, a limitation of the present mapping technique is an emphasis on endocardial activation patterns. Future studies combining endocardial mapping with epicardial invasive or non-invasive tools (e.g. CardioInsight) are required to determine whether the combination of these technologies improves VF electrical substrate localization.

Conclusions

VESA is feasible and is associated with a reduction in the composite endpoint of ICD shocks, electrical storm, and all-cause mortality compared to standard-of-care medical management. VF electrical mapping may enable targeting of regions which participate in arrhythmia maintenance, including sites with preserved electrogram voltage. This approach may represent a potential therapeutic option in patients with drug-refractory VF and rare, multifocal triggers, and thus motivate future randomized studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms:

VF	Ventricular Fibrillation
ICD	Implantable Cardioverter-Defibrillator
PVC	Premature Ventricular Complex
ECG	Electrocardiogram
VT	Ventricular Tachycardia
RV	Right Ventricle
LV	Left Ventricle
VESA	VF Electrical Substrate Ablation
LAVA	Local Abnormal Ventricular Activities

References:

1. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300:1423–31. [PubMed: 18812533]
2. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018;138:e272–e391. [PubMed: 29084731]
3. Hohnloser SH, Raeder EA, Podrid PJ, Graboys TB, Lown B. Predictors of antiarrhythmic drug efficacy in patients with malignant ventricular tachyarrhythmias. Am Heart J. 1987;114:1–7. [PubMed: 3604854]
4. Haissaguerre M, Shoda M, Jais P, Nogami A, Shah DC, Kautzner J, Arentz T, Kalushe D, Lamaison D, Griffith M, et al. Mapping and ablation of idiopathic ventricular fibrillation. Circulation. 2002;106:962–7. [PubMed: 12186801]
5. Van Herendael H, Zado ES, Haqqani H, Tschabrunn CM, Callans DJ, Frankel DS, Lin D, Garcia F, Hutchinson MD, Riley M, et al. Catheter ablation of ventricular fibrillation: importance of left ventricular outflow tract and papillary muscle triggers. Heart Rhythm. 2014;11:566–73. [PubMed: 24398086]
6. Haissaguerre M, Hocini M, Cheniti G, Duchateau J, Sacher F, Puyo S, Cochet H, Takigawa M, Denis A, Martin R, et al. Localized Structural Alterations Underlying a Subset of Unexplained Sudden Cardiac Death. Circ Arrhythm Electrophysiol. 2018;11:e006120. [PubMed: 30002064]
7. Nakamura T, Schaeffer B, Tanigawa S, Muthalaly RG, John RM, Michaud GF, Tedrow UB, Stevenson WG. Catheter ablation of polymorphic ventricular tachycardia/fibrillation in patients with and without structural heart disease. Heart Rhythm. 2019;16:1021–1027. [PubMed: 30710740]
8. Komatsu Y, Hocini M, Nogami A, Maury P, Peichl P, Iwasaki YK, Masuda K, Denis A, Voglimacci-Stephanopoli Q, Wichterle D, et al. Catheter Ablation of Refractory Ventricular Fibrillation Storm After Myocardial Infarction. Circulation. 2019;139:2315–2325. [PubMed: 30929474]
9. Hayase J, Vampola S, Ahadian F, Narayan SM, Krummen DE. Comparative efficacy of stellate ganglion block with bupivacaine vs pulsed radiofrequency in a patient with refractory ventricular arrhythmias. J Clin Anesth. 2016;31:162–5. [PubMed: 27185701]

10. Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. Circulation. 2010;122:173–83. [PubMed: 20625142]
11. Krummen DE, Hayase J, Vampola SP, Ho G, Schricker AA, Lalani GG, Baykaner T, Coe TM, Clopton P, Rappel WJ, et al. Modifying Ventricular Fibrillation by Targeted Rotor Substrate Ablation: Proof-of-Concept from Experimental Studies to Clinical VF. J Cardiovasc Electrophysiol. 2015;26:1117–26. [PubMed: 26179310]
12. Hayase J, Tung R, Narayan SM, Krummen DE. A case of a human ventricular fibrillation rotor localized to ablation sites for scar-mediated monomorphic ventricular tachycardia. Heart Rhythm. 2013;10:1913–6. [PubMed: 23911894]
13. Ho G, Hoffmayer KS, Villongco CT, Vidmar D, Rappel WJ, Krummen DE. Successful ventricular fibrillation functional substrate ablation via a single vascular access site. HeartRhythm Case Rep. 2018;4:173–176. [PubMed: 29915711]
14. Lee DC, Oz MC, Weinberg AD, Lin SX, Ting W. Optimal timing of revascularization: transmural versus nontransmural acute myocardial infarction. Ann Thorac Surg. 2001;71:1197–202; discussion 1202–4. [PubMed: 11308159]
15. Krummen DE, Hayase J, Morris DJ, Ho J, Smetak MR, Clopton P, Rappel WJ, Narayan SM. Rotor stability separates sustained ventricular fibrillation from self-terminating episodes in humans. J Am Coll Cardiol. 2014;63:2712–21. [PubMed: 24794115]
16. Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, Kralovec S, Sediva L, Ruskin JN, Josephson ME. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med. 2007;357:2657–65. [PubMed: 18160685]
17. Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation. 2000;101:1288–96. [PubMed: 10725289]
18. Bazan V, Frankel DS, Santangeli P, Garcia FC, Tschabrunn CM, Marchlinski FE. Three-dimensional myocardial scar characterization from the endocardium: Usefulness of endocardial unipolar electroanatomic mapping. J Cardiovasc Electrophysiol. 2019;30:427–437. [PubMed: 30614100]
19. Tokuda M, Tedrow UB, Inada K, Reichlin T, Michaud GF, John RM, Epstein LM, Stevenson WG. Direct comparison of adjacent endocardial and epicardial electrograms: implications for substrate mapping. J Am Heart Assoc. 2013;2:e000215. [PubMed: 24113324]
20. Komatsu Y, Cochet H, Jadidi A, Sacher F, Shah A, Derval N, Scherr D, Pascale P, Roten L, Denis A, et al. Regional myocardial wall thinning at multidetector computed tomography correlates to arrhythmogenic substrate in postinfarction ventricular tachycardia: assessment of structural and electrical substrate. Circ Arrhythm Electrophysiol. 2013;6:342–50. [PubMed: 23476043]
21. Dickfeld T, Lei P, Dilsizian V, Jeudy J, Dong J, Voudouris A, Peters R, Saba M, Shekhar R, Shorofsky S. Integration of three-dimensional scar maps for ventricular tachycardia ablation with positron emission tomography-computed tomography. JACC Cardiovasc Imaging. 2008;1:73–82. [PubMed: 19356409]
22. Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation. Circ Res. 2013;112:849–62. [PubMed: 23449547]
23. Avitall B, Mughal K, Hare J, Helms R, Krum D. The effects of electrode-tissue contact on radiofrequency lesion generation. Pacing Clin Electrophysiol. 1997;20:2899–910. [PubMed: 9455749]
24. Reichlin T, Lane C, Nagashima K, Nof E, Chopra N, Ng J, Barbhaiya C, Tadros T, John RM, Stevenson WG, et al. Feasibility, efficacy, and safety of radiofrequency ablation of atrial fibrillation guided by monitoring of the initial impedance decrease as a surrogate of catheter contact. J Cardiovasc Electrophysiol. 2015;26:390–396. [PubMed: 25588901]
25. Ariyarathna N, Kumar S, Thomas SP, Stevenson WG, Michaud GF. Role of Contact Force Sensing in Catheter Ablation of Cardiac Arrhythmias: Evolution or History Repeating Itself? JACC Clin Electrophysiol. 2018;4:707–723. [PubMed: 29929663]
26. Di Biase L, Burkhardt JD, Lakkireddy D, Carbucicchio C, Mohanty S, Mohanty P, Trivedi C, Santangeli P, Bai R, Forleo G, et al. Ablation of Stable VTs Versus Substrate Ablation in Ischemic

Cardiomyopathy: The VISTA Randomized Multicenter Trial. J Am Coll Cardiol. 2015;66:2872–2882. [PubMed: 26718674]

27. Sarrazin JF, Kuehne M, Wells D, Chalfoun N, Crawford T, Boonyapisit W, Good E, Chugh A, Oral H, Jongnarangsin K, et al. High-output pacing in mapping of postinfarction ventricular tachycardia. Heart Rhythm. 2008;5:1709–14. [PubMed: 19084809]
28. Sapp JL, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin JF, Thibault B, Rivard L, Gula L, Leong-Sit P, et al. Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs. N Engl J Med. 2016;375:111–21. [PubMed: 27149033]
29. Viskin S, Lesh MD, Eldar M, Fish R, Setbon I, Laniado S, Belhassen B. Mode of onset of malignant ventricular arrhythmias in idiopathic ventricular fibrillation. J Cardiovasc Electrophysiol. 1997;8:1115–20. [PubMed: 9363814]
30. Ho G, Villongco CT, Yousefian O, Bradshaw A, Nguyen A, Faiwiszewski Y, Hayase J, Rappel WJ, McCulloch AD, Krummen DE. Rotors exhibit greater surface ECG variation during ventricular fibrillation than focal sources due to wavebreak, secondary rotors, and meander. J Cardiovasc Electrophysiol. 2017;28:1158–1166. [PubMed: 28670858]
31. Knecht S, Sacher F, Wright M, Hocini M, Nogami A, Arentz T, Petit B, Franck R, De Chillou C, Lamaison D, et al. Long-term follow-up of idiopathic ventricular fibrillation ablation: a multicenter study. J Am Coll Cardiol. 2009;54:522–8. [PubMed: 19643313]
32. Haissaguerre M, Extramiana F, Hocini M, Cauchemez B, Jais P, Cabrera JA, Farre J, Leenhardt A, Sanders P, Scavee C, et al. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndromes. Circulation. 2003;108:925–8. [PubMed: 12925452]
33. Tilz RR, Lin T, Makimoto H, Ouyang F. Successful epicardial ablation of electrical storms due to recurrent ventricular fibrillation triggered by premature ventricular contractions. Heart Rhythm. 2014;11:146–9. [PubMed: 24103223]
34. Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. Nature. 1998;392:75–8. [PubMed: 9510249]
35. Nash MP, Mourad A, Clayton RH, Sutton PM, Bradley CP, Hayward M, Paterson DJ, Taggart P. Evidence for multiple mechanisms in human ventricular fibrillation. Circulation. 2006;114:536–42. [PubMed: 16880326]
36. Vidmar D, Krummen DE, Hayase J, Narayan SM, Ho G, Rappel WJ. Spatiotemporal Progression of Early Human Ventricular Fibrillation. JACC Clin Electrophysiol. 2017;3:1437–1446. [PubMed: 29238755]
37. Kim YH, Xie F, Yashima M, Wu TJ, Valderrabano M, Lee MH, Ohara T, Voroshilovsky O, Doshi RN, Fishbein MC, et al. Role of papillary muscle in the generation and maintenance of reentry during ventricular tachycardia and fibrillation in isolated swine right ventricle. Circulation. 1999;100:1450–9. [PubMed: 10500048]
38. Valderrabano M, Lee MH, Ohara T, Lai AC, Fishbein MC, Lin SF, Karagueuzian HS, Chen PS. Dynamics of intramural and transmural reentry during ventricular fibrillation in isolated swine ventricles. Circ Res. 2001;88:839–48. [PubMed: 11325877]
39. Nair K, Umapathy K, Farid T, Masse S, Mueller E, Sivanandan RV, Poku K, Rao V, Nair V, Butany J, et al. Intramural activation during early human ventricular fibrillation. Circ Arrhythm Electrophysiol. 2011;4:692–703. [PubMed: 21750274]
40. Everett THt Wilson EE, Foreman S Olgin JE. Mechanisms of ventricular fibrillation in canine models of congestive heart failure and ischemia assessed by in vivo noncontact mapping. Circulation. 2005;112:1532–41. [PubMed: 16145002]
41. Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, Likittanasombat K, Bhuripanyo K, Ngarmukos T. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation. 2011;123:1270–9. [PubMed: 21403098]
42. Di Biase L, Santangeli P, Burkhardt DJ, Bai R, Mohanty P, Carbucicchio C, Dello Russo A, Casella M, Mohanty S, Pump A, et al. Endo-epicardial homogenization of the scar versus limited substrate ablation for the treatment of electrical storms in patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2012;60:132–41. [PubMed: 22766340]

43. Tilz RR, Makimoto H, Lin T, Rillig A, Deiss S, Wissner E, Mathew S, Metzner A, Rausch P, Kuck KH, et al. Electrical isolation of a substrate after myocardial infarction: a novel ablation strategy for unmappable ventricular tachycardias--feasibility and clinical outcome. Europace. 2014;16:1040–52. [PubMed: 24574495]
44. Hansen BJ, Zhao J, Csepe TA, Moore BT, Li N, Jayne LA, Kalyanasundaram A, Lim P, Bratasz A, Powell KA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. Eur Heart J. 2015;36:2390–401. [PubMed: 26059724]
45. Glashan CA, Androulakis AFA, Tao Q, Glashan RN, Wisse LJ, Ebert M, de Ruiter MC, van Meer BJ, Brouwer C, Dekkers OM, et al. Whole human heart histology to validate electroanatomical voltage mapping in patients with non-ischaemic cardiomyopathy and ventricular tachycardia. Eur Heart J. 2018;39:2867–2875. [PubMed: 29617764]
46. Perlstein I, Burton DY, Ryan K, Defelice S, Simmers E, Campbell B, Connolly JM, Hoffman A, Levy RJ. Posttranslational control of a cardiac ion channel transgene in vivo: clarithromycin-hMiRP1-Q9E interactions. Hum Gene Ther. 2005;16:906–10. [PubMed: 16000071]
47. Igarashi T, Finet JE, Takeuchi A, Fujino Y, Strom M, Greener ID, Rosenbaum DS, Donahue JK. Connexin gene transfer preserves conduction velocity and prevents atrial fibrillation. Circulation. 2012;125:216–25. [PubMed: 22158756]
48. Trappe K, Thomas D, Bikou O, Kelemen K, Lugenbiel P, Voss F, Becker R, Katus HA, Bauer A. Suppression of persistent atrial fibrillation by genetic knockdown of caspase 3: a pre-clinical pilot study. Eur Heart J. 2013;34:147–57. [PubMed: 21785105]
49. Gonzalez-Melchor L, Brugada J, Martinez-Sande JL, Garcia-Seara J, Fernandez-Lopez JA, Pappone C, Gonzalez-Juanatey JR. Epicardial mapping and ablation of the right ventricle substrate during flecainide testing in Brugada syndrome. HeartRhythm Case Rep. 2016;2:52–56. [PubMed: 28491631]
50. Cochet H, Dubois R, Sacher F, Derval N, Sermesant M, Hocini M, Montaudon M, Haissaguerre M, Laurent F, Jais P. Cardiac arrythmias: multimodal assessment integrating body surface ECG mapping into cardiac imaging. Radiology. 2014;271:239–47. [PubMed: 24475841]

What is Known?

- Refractory ventricular fibrillation may result in painful implantable cardioverter-defibrillator shocks and mortality.
- Ablation of premature ventricular complex triggers is effective in suppressing arrhythmia episodes in patients with frequent, monomorphic ventricular ectopy.

What the Study Adds?

- For patients in whom trigger ablation is infeasible, sites of conduction slowing and rotation or rapid focal activation during VF may be identified.
- Ablation of 3–4 electrical substrate sites is associated with improved freedom from ICD shocks, ventricular arrhythmia storm, and mortality at a median follow-up of 1 year.
- Targeted ablation exhibits acceptable safety without adverse impact on left ventricular function.

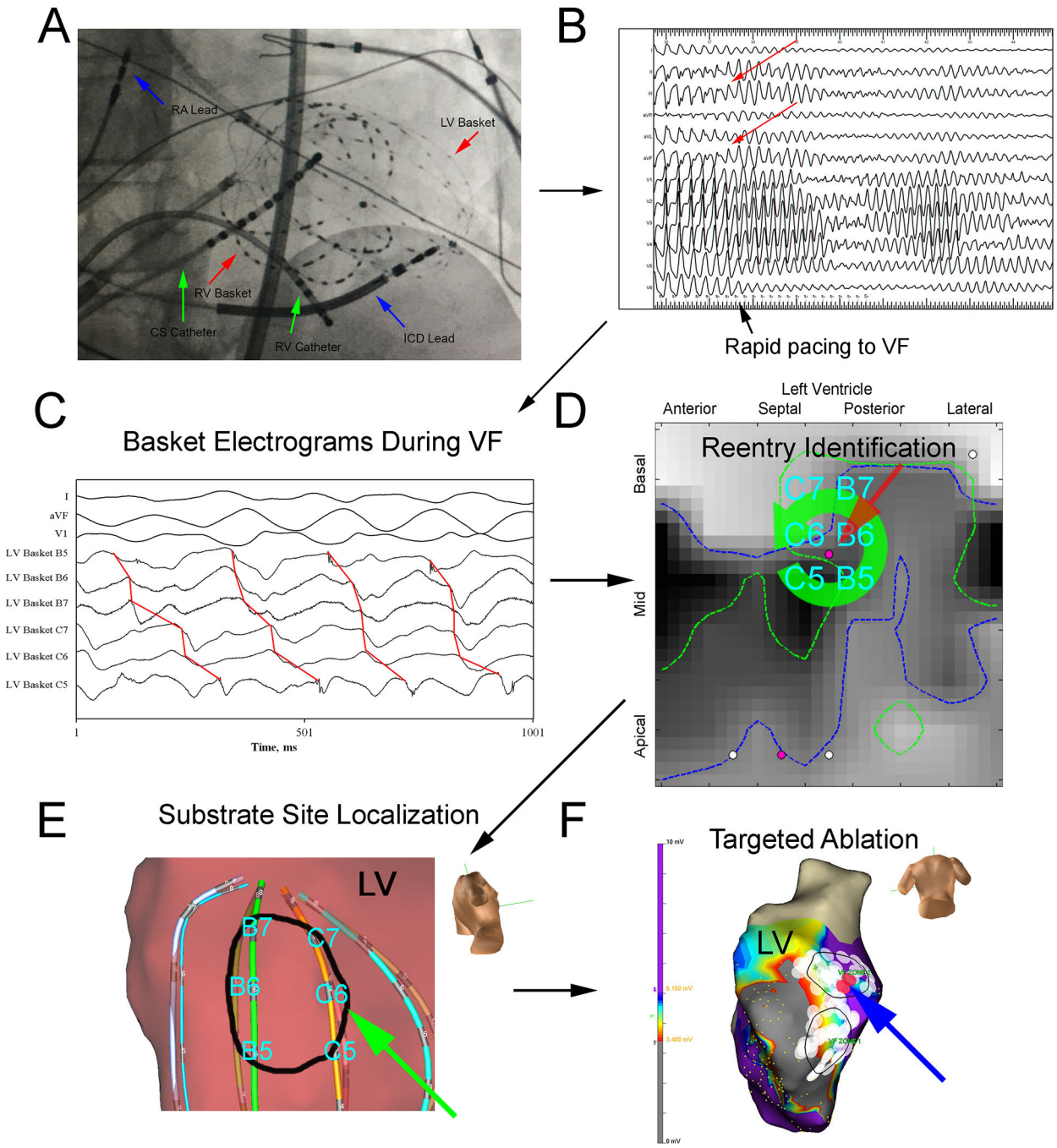

Figure 1.

VF Electrical Substrate Mapping and Ablation. Panel A shows biventricular basket placement (red arrows) in a 56-year-old male with ischemic cardiomyopathy. In this patient 60 mm basket catheters were placed in both the LV and the RV, based on enlarged ventricular sizes from pre-procedural transthoracic echocardiography. A RV quadripolar catheter (used for VF induction) and a CS catheter are also shown (green arrows) in addition to the patient's dual chamber ICD leads (blue arrows). Panel B shows induction of VF with rapid pacing. VF initiates at a pacing cycle length of 260 msec (see change in surface ECG

morphology, red arrows). Panel C shows sample basket catheter recordings from a localized reentrant circuit; the relationship of local activation between electrograms is shown with the red lines. Panel D illustrates a snapshot of the activation and phase analysis movie coinciding with the electrograms in C. The phase singularity (red arrow to pink dot) during this time period precesses in the region of the B5–7, C5–7 electrodes of the LV basket. Panel E shows the process of identifying the correct basket electrodes on the electroanatomic mapping system and marking an area of interest (green arrow to black circle) on the LV geometry. Panel F shows the ablation lesions (white and red circular markers) placed at the target site. Following ablation at the indicated location (blue arrow), VF was no longer induced with either ablation or rapid pacing.

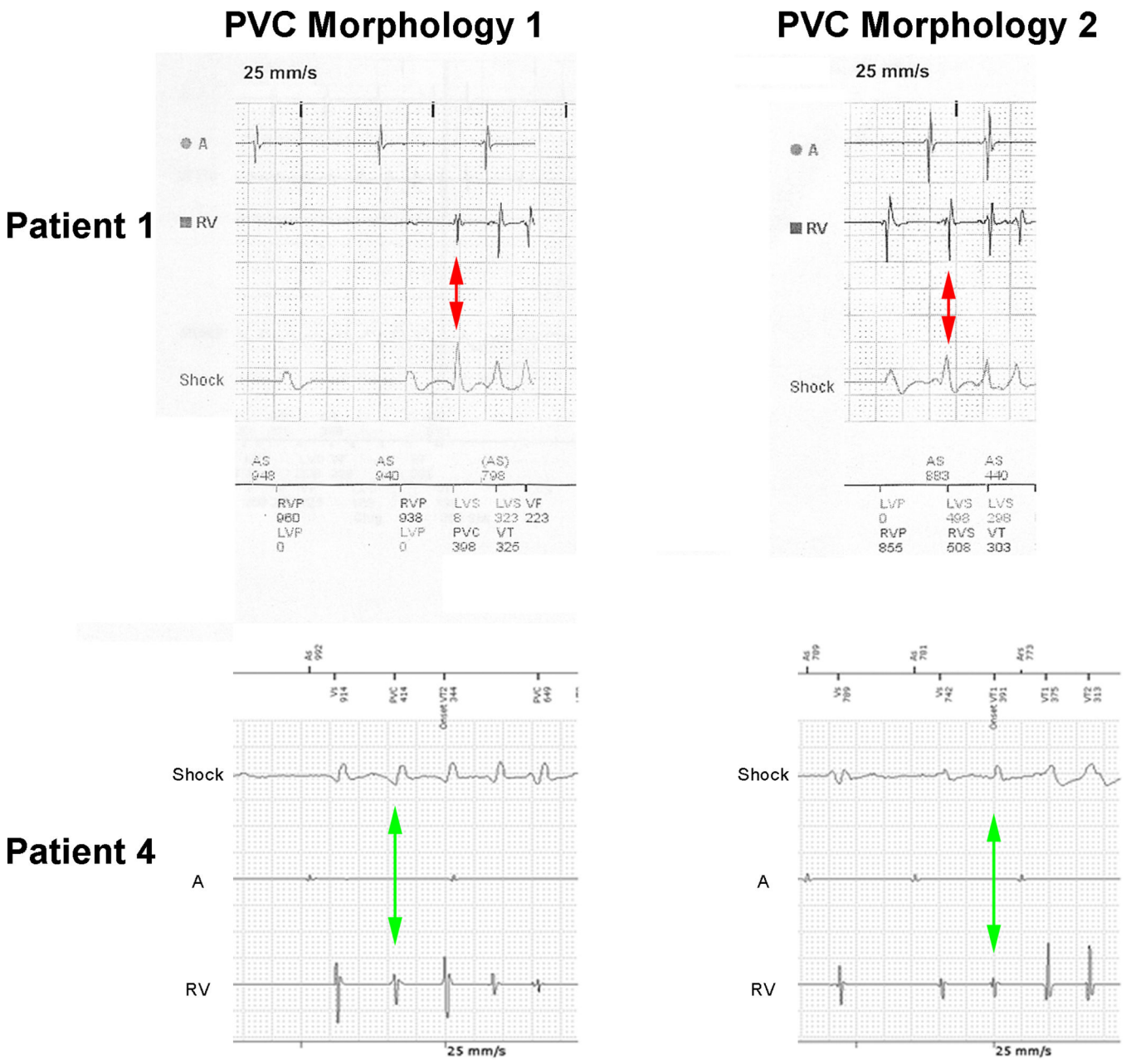

Figure 2.

Different PVC Morphologies Initiating VF. The top row shows ICD interrogation data illustrating distinct PVC morphologies (red arrows) which initiate VF in patient 1. Note the distinct morphologies on the RV electrogram recordings. The bottom row shows ICD interrogation data illustrating distinct PVC morphologies (green arrows) initiating VF in ablation patient 4. Note the dissimilar morphologies on both the shock and RV electrogram tracings.

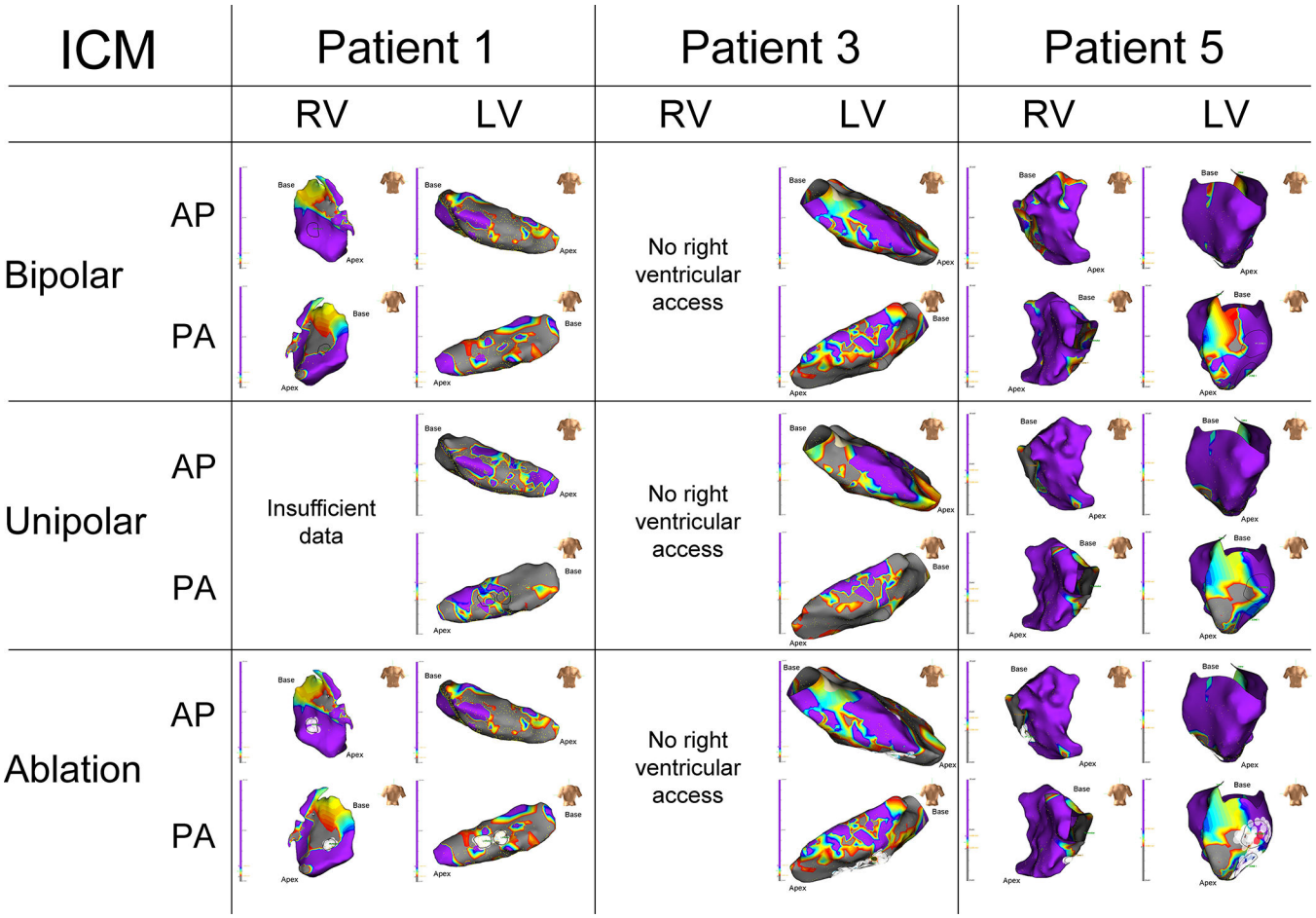

Figure 3.

Voltage Abnormalities in Patients with Ischemic Cardiomyopathy. The top row of images shows the RV and LV bipolar mapping results, the middle row shows the results from unipolar mapping, and the lower row illustrates ablation lesions applied after VF electrical substrate mapping. Voltage cutoffs for normal (purple), borderzone (red to blue), and scar (gray) are identified in the voltage scale to the left of each image. Images are presented in standard anteroposterior (AP) and posteroanterior (PA) views. Note that insufficient data were available for the unipolar RV map for ablation patient 1, and that RV access was not obtained due to severe vascular thromboembolic (inferior vena cava) and anatomic (superior vena cava) disease in patient 3.

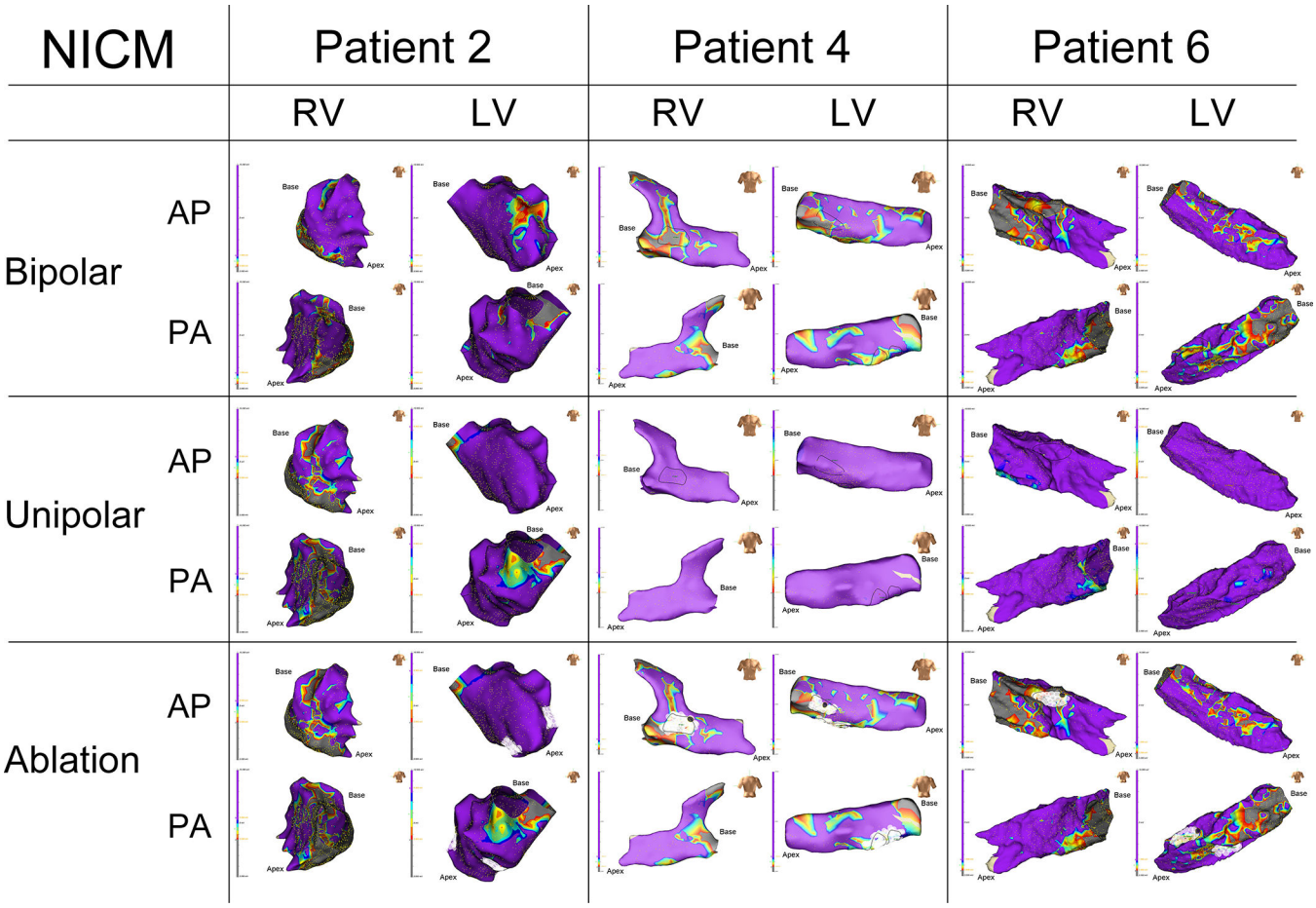

Figure 4.

Voltage Abnormalities in Patients with Nonischemic Cardiomyopathy. The top row of images shows the RV and LV bipolar mapping results, the middle row shows the results from unipolar mapping, and the lower row illustrates ablation lesions applied after VF source mapping. Voltage cutoffs for normal (purple), borderzone (red to blue), and scar (gray) are identified in the voltage scale to the left of each image. Images are presented in standard anteroposterior (AP) and posteroanterior (PA) views.

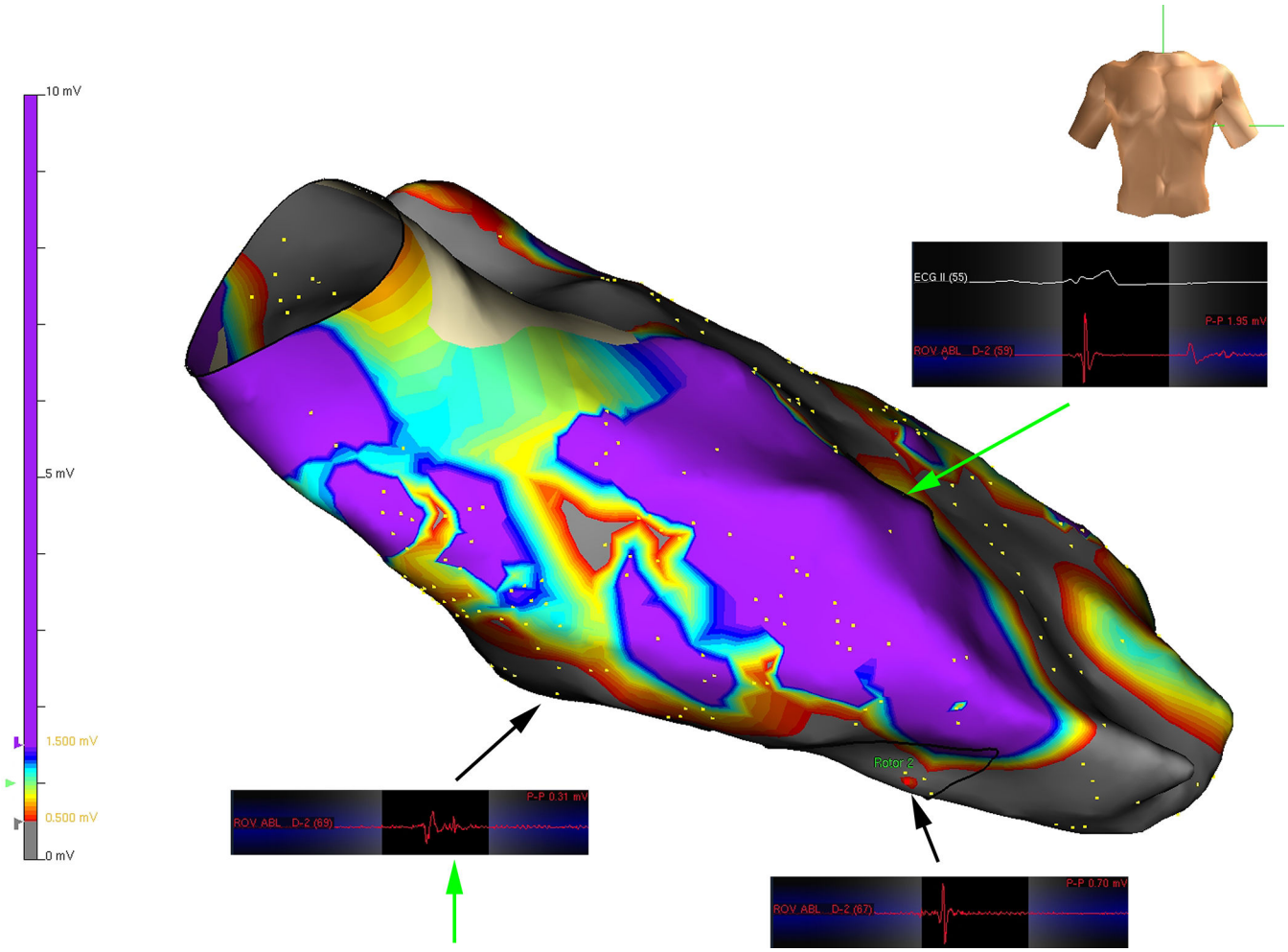

Figure 5.

Electrogram Characteristics of VF Electrical Substrate Sites in Ablation Patient 3. Sampled electrograms from the 3 targeted VF substrate sites are illustrated. Of note, a local abnormal ventricular activities (LAVA) potential was observed only in rotor site 1. No LAVA or late potentials were observed in any sampled electrogram at sites 2 or 3.

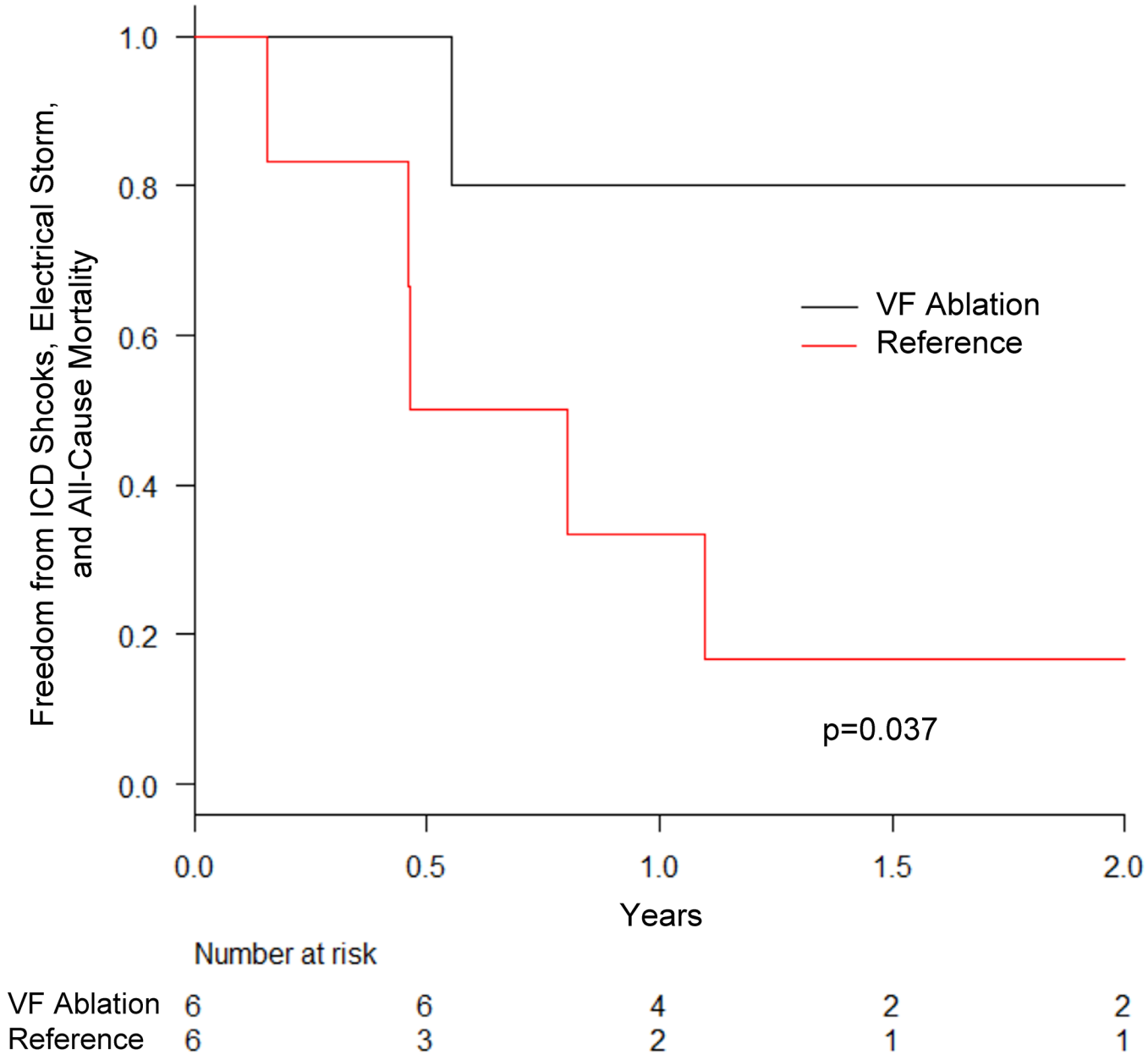

Figure 6.

Kaplan-Meier Survival Analysis: Freedom from ICD Shocks, Electrical Storm, or All-Cause Mortality in Ablation vs. Reference Patients. Survival from the combined endpoint was 83% in VF ablation patients compared with 17% in reference patients at a median follow-up of 1.0 years (interquartile range 0.5–1.5 years, p=0.037).

Table 1.

Patient Demographics

Characteristics	VF Ablation (n=6)	Non-ablation Reference (n=6)	p Value
Age, years	60±10	65±15	0.52
LVEF, %	38±20	28±6	0.30
Ischemic CMP	3	3	1
Etiologies of NICM (presumptive)	Hypertensive (patient 2) Valvular (patient 4) Viral (patient 6)	Valvular (patient 2) Valvular (patient 3) Idiopathic (patient 6)	--
NYHA Class	1.8±0.8	2.2±0.8	0.55
Atrial fibrillation	3	4	1
Hypertension	3	5	0.55
Diabetes mellitus	0	2	0.46
Hyperlipidemia	3	5	0.55
Prior CABG	2	1	1
Prior valve surgery	1	1	1
COPD	4	1	0.24
Medications			
Aspirin	2	4	0.57
Beta-blocker	6	6	1
ACEi/ARB/ARNI	4	5	1
Digoxin	1	1	1
Warfarin/DOAC	3	3	1
Statin	4	5	1
AAD Used/Failed			
Amiodarone	6	3	0.18
Mexiletine	2	2	1
Sotalol	3	5	0.55
Dofetilide	0	2	0.46

VF=ventricular fibrillation; LVEF=left ventricular ejection fraction; CMP=cardiomyopathy; NICM=non-ischemic cardiomyopathy; NYHA=New York Heart Association; CABG=coronary artery bypass graft surgery; COPD=chronic obstructive pulmonary disease; ACEi=ace inhibitor; ARB=angiotensin receptor blocker, ARNI= angiotensin receptor-neprilysin inhibitor; DOAC=direct oral anticoagulant; AAD=antiarrhythmic drug.

Table 2.

Individual Patient Characteristics and Outcomes

Patient Characteristic	Patient Number	Age (years), Sex	Cardiomyopathy type	LVEF, %	LVIDd, mm	NYHA Class	ICD shocks prior to ablation or enrollment	Time Duration of Shocks Prior to Ablation or Enrollment (Months)	Antiarrhythmic drugs used or failed	All-cause ICD Shocks in Follow-up	Electrical Storm and/or Mortality (Setting; Etiology)
VF Ablation Group	**1**	72, M	Ischemic	21%	72	II	7	3.6	Amiodarone, sotalol	0	0
	2	45, M	Nonischemic	59%	46	I	2	3.0	Amiodarone, mexiletine	0	0
	3	68, M	Ischemic	26%	55	II	9	2.8	Amiodarone, sotalol	2 (VT)	Mortality (Inpatient; Lung Cancer)
	4	64, M	Nonischemic	42%	63	II	9	7.6	Amiodarone, mexiletine	0	0
	5	56, M	Ischemic	16%	73	III	9	10.6	Amiodarone	0	0
	6	52, F	Nonischemic	61%	46	I	6	15.6	Amiodarone, sotalol	0	0
Summary		**60±10**	**Nonischemic=3**	**38±20**	**59±12**	**1.8±0.8**	**7.0±2.8**[†]	**7.2±5.2**	**1.8±0.4 antiarrhythmics**	**0.3±0.8 all cause shocks, p<0.001**[†]	**n=1**
Reference Patients	**1**	69, M	Ischemic	23	68	III	2	18.6	Sotalol	0	Mortality (Outpatient; Heart Failure)
	2	70, M	Nonischemic	29	59	II	6	5.2	Sotalol, dofetilide	0	0
	3	77, M	Nonischemic	22	70	III	4	1.0	Amiodarone, mexiletine	11 (VF)	Electrical Storm, Mortality (Hospice; Electrical Storm)
	4	60, M	Ischemic	25	69	II	2	1.5	Sotalol	1 (VF)	0
	5	74, M	Ischemic	36	60	I	2	5.2	Amiodarone, sotalol, dofetilide	3 (VF)	0
	6	37, M	Nonischemic	35	71	II	3	10.5	Amiodarone, mexiletine, sotalol	3 (VF)	Mortality (Inpatient; Sepsis)
Summary		**65±15**	**Nonischemic=3**	**28±6**	**66±5**	**2.2±0.8**	**3.2±1.6**	**7.0±6.6**	**2.0±0.9 antiarrhythmics**	**3.0±4.1**	**n=3**
p (VF Ablation vs. References)		0.52	1	0.30	0.22	0.55	**0.03**	0.96	0.57	0.10	0.55

LVEF=left ventricular ejection fraction; LVIDd=left ventricular internal dimension, diastolic; NYHA=New York Heart Association; ICD=implantable cardioverter-defibrillator; VF=ventricular fibrillation; M=male; F=female; VT=ventricular tachycardia; IQR=interquartile range

[*] =patient experienced combined endpoint of ICD shock, arrhythmia storm, or death

† denotes p=0.001 for the comparison of all-cause ICD shocks in 6 months pre-ablation with all-cause ICD shocks post ablation during 1.2 years (IQR 0.7 – 2.0 years) follow-up.