Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 24, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.03.037

Rotor Stability Separates Sustained Ventricular Fibrillation From Self-Terminating Episodes in Humans

David E. Krummen, MD,*† Justin Hayase, MD,*† David J. Morris, MD,*† Jeffrey Ho, MD,*†
Miriam R. Smetak, BS,† Paul Clopton, MS,† Wouter-Jan Rappel, PHD,*
Sanjiv M. Narayan, MD, PHD*†
San Diego, California

Objectives This study mapped human ventricular fibrillation (VF) to define mechanistic differences between episodes requiring defibrillation versus those that spontaneously terminate.

Background VF is a leading cause of mortality; yet, episodes may also self-terminate. We hypothesized that the initial maintenance of human VF is dependent upon the formation and stability of VF rotors.

Methods We enrolled 26 consecutive patients (age 64 ± 10 years, n = 13 with left ventricular dysfunction) during ablation procedures for ventricular arrhythmias, using 64-electrode basket catheters in both ventricles to map VF prior to prompt defibrillation per the institutional review board–approved protocol. A total of 52 inductions were attempted, and 36 VF episodes were observed. Phase analysis was applied to identify biventricular rotors in the first 10 s or until VF terminated, whichever came first (11.4 ± 2.9 s to defibrillator charging).

Results Rotors were present in 16 of 19 patients with VF and in all patients with sustained VF. Sustained, but not self-limiting VF, was characterized by greater rotor stability: 1) rotors were present in 68 ± 17% of cycles in sustained VF versus 11 ± 18% of cycles in self-limiting VF ($p < 0.001$); and 2) maximum continuous rotations were greater in sustained (17 ± 11, range 7 to 48) versus self-limiting VF (1.1 ± 1.4, range 0 to 4, $p < 0.001$). Additionally, biventricular rotor locations in sustained VF were conserved across multiple inductions (7 of 7 patients, $p = 0.025$).

Conclusions In patients with and without structural heart disease, the formation of stable rotors identifies individuals whose VF requires defibrillation from those in whom VF spontaneously self-terminates. Future work should define the mechanisms that stabilize rotors and evaluate whether rotor modulation may reduce subsequent VF risk. (J Am Coll Cardiol 2014;63:2712–21) © 2014 by the American College of Cardiology Foundation

Ventricular fibrillation (VF) is a common, life-threatening arrhythmia and a major cause of the 700,000 cases of sudden cardiac death in the United States and Europe annually (1). Although our understanding of VF mechanisms continues to improve (2), we still do not fully understand the mechanistic differences between VF episodes that perpetuate and those that spontaneously terminate (3).

Superficially, VF appears to be random and disorganized. However, significant progress has been made to identify deterministic features within VF (4,5). Detailed epicardial mapping suggests the coexistence of electrical rotors and disorganized activity in induced VF in patients with preserved ventricular function during open heart surgery (6). However, the importance of rotors and other propagation patterns to the maintenance of human VF remains uncertain. VF rotors have been studied in the context of ischemia (7) and scar (8) using animal models and explanted human hearts; yet, these studies have not explained why some VF episodes require defibrillation whereas others self-terminate without consequence.

Prior work has shown the presence of rate gradients (9) in sustained VF, supporting the concept of spatial preferences

From the *University of California San Diego, San Diego, California; and the †Veterans Affairs San Diego Healthcare System, San Diego, California. Dr. Krummen has received grant support from the American Heart Association (10 BGIA 3500045) and National Institutes of Health (HL 83359); has served as a consultant to InsilicoMed; and has received fellowship program support from Biotronik, Boston Scientific, Medtronic, St. Jude Medical, and Biosense-Webster. Dr. Rappel has intellectual property interest and equity in Topera Medical. Dr. Narayan has received grant support from the National Institutes of Health (HL 83359, HL103800) and the Doris Duke Foundation; has intellectual property and ownership interest in Topera Medical; has served as a consultant to Biotronik, Medtronic, St. Jude Medical, and Topera; and has received fellowship program support from Biotronik, Boston Scientific, Medtronic, St. Jude Medical, and Biosense-Webster. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Hakan Oral, MD, served as Guest Editor for this paper.

Manuscript received December 29, 2013; revised manuscript received March 23, 2014, accepted March 29, 2014.

for VF drivers. Subsequent work evaluating surface electrocardiogram patterns found evidence for repetitive spatial paths of VF sources (10). More recent studies have shown evidence that electrical rotors predominantly associate with areas of scar (11). Based upon these data, we hypothesized that greater electrical rotor stability would predict the perpetuation of early human VF and its progression to sustained VF.

Methods

Patient enrollment. In this prospective study of the relationship between VF rotors and duration, we enrolled consecutive patients presenting for ventricular arrhythmia ablation at the University of California San Diego and Veterans Affairs San Diego Healthcare System. The protocol was approved by a joint University of California San Diego/Veterans Affairs institutional review board, and all patients provided written, informed consent after a full discussion of risks and potential benefits. Exclusion criteria included the presence of ventricular thrombus, hemodynamic instability precluding the safe induction of VF, and unrevascularized coronary ischemia.

Antiarrhythmic drugs (mexiletine [n = 2], amiodarone [n = 1], dronedarone [n = 1], and sotalol [n = 6]) were discontinued >5 half-lives (6 weeks for amiodarone) prior to the electrophysiology study. Left ventricular (LV) function was assessed by transthoracic echocardiography prior to the procedure.

Study protocol. The study protocol is summarized in Figure 1. Patients were intubated, ventilated, and maintained under a consistent general anesthetic protocol. A decapolar catheter was placed in the coronary sinus, and a quadripolar catheter was placed in the right ventricle (RV) for VF induction. Invasive arterial pressure and vital signs were monitored continuously throughout the case.

Basket catheters (64-electrode, Constellation, Boston Scientific, Natick, Massachusetts) were advanced for simultaneous recording into the RV and LV either by retrograde aortic (Figs. 2A and 2B) or transseptal (Fig. 2C) approaches to best suit the clinical procedure. Basket catheter contact was evaluated by: 1) evaluating fluoroscopic basket catheter morphology to ensure uniform deformation by cineangiography (Figs. 2A to 2C); 2) imaging with intracardiac ultrasound; and 3) ensuring that electrogram amplitude both at baseline and during VF was acceptable. Electrodes with noisy or low amplitude signals (<0.5 mV) were excluded from analysis, and the corresponding areas on phase mapping were left blank; on average, 10 ± 7 out of 128 electrodes (7.8%) were excluded in each case due to suboptimal contact or noise.

VF induction. Following baseline programmed ventricular stimulation, rapid pacing was performed for 15 s, followed by a 1-min recovery period, for each cycle length (CL) of 350, 300, and 250 ms; then, the pacing was decremented by 10 ms until VF induction (Fig. 2D) or 2:1 capture (minimum CL 170 ms) per protocol, similar to prior work (12). As soon as VF was induced, defibrillator charging commenced, and VF was recorded during this charging period. VF was defibrillated as soon as charging was complete (11.4 ± 2.9 s; range 8 to 15 s). After a 5-min waiting interval, a second episode of VF was induced in each patient either with a second burst pacing induction, or 3.2 s of rapid pacing followed by a 2-J T-wave shock (in patients with implantable cardioverter-defibrillators [ICDs]). VF was defined as varying electrocardiogram morphology with a rate >220 beats/min as previously described (8). Following the second attempted VF induction, the clinical procedure was commenced in routine fashion.

Abbreviations and Acronyms

- **CL** = cycle length
- **EF** = ejection fraction
- **ICD** = implantable cardioverter-defibrillator
- **LV** = left ventricle/ventricular
- **ROC** = receiver-operating characteristic
- **RV** = right ventricle/ventricular
- **VF** = ventricular fibrillation
- **VT** = ventricular tachycardia

Electrogram analysis. Unipolar basket electrograms were recorded at 1,000 Hz and filtered from 0.05 to 500 Hz (Bard Pro, Billerica, Massachusetts). Electrograms were analyzed offline using software (RhythmView, Topera Medical, Palo Alto, California) that we have described previously (13), incorporating phase analysis (14) of unipolar electrograms (6), within physiologic constraints (15,16). Data were analyzed for the first 10 s of VF or until termination, whichever came first.

Rotational activity was identified as a phase singularity formed at the intersection of depolarization and repolarization isolines (4) consisting of at least 1 rotation (Fig. 3). Rotors were defined as regions of rotational activity that controlled surrounding activation, and the criteria for numbers of rotations in human VF were derived in this study. Regions of centrifugal propagation without rotation were defined as focal activation (Figs. 4A and 4B). Continuous, disorganized ventricular activation without a clear rotational or focal activation ("fibrillatory conduction") (Figs. 4C and 4D) was also documented. Data were analyzed independently by D.E.K., J.H., and S.M.N.; the majority opinion was carried.

Measuring rotor prevalence and stability. We quantified the prevalence of rotational activity as the percent of VF cycles showing such activity, with stability quantified as the maximum number of consecutive revolutions of electrical activity within a region bounded by 2 electrodes in each axis. We performed receiver-operating characteristic (ROC) analysis to determine criteria for prevalence and stability that functionally separated sustained from self-limiting episodes of VF.

Modeling endocardial recording of nonendocardial VF sources. To explore the endocardial projection of nonendocardial VF sources, we created a 3-dimensional computational model of a hairpin-shaped rotor filament, with both ends terminating on the epicardium. The Barkley model (17) was implemented on a 200 × 100 × 100 grid, and the filament was initiated as previously

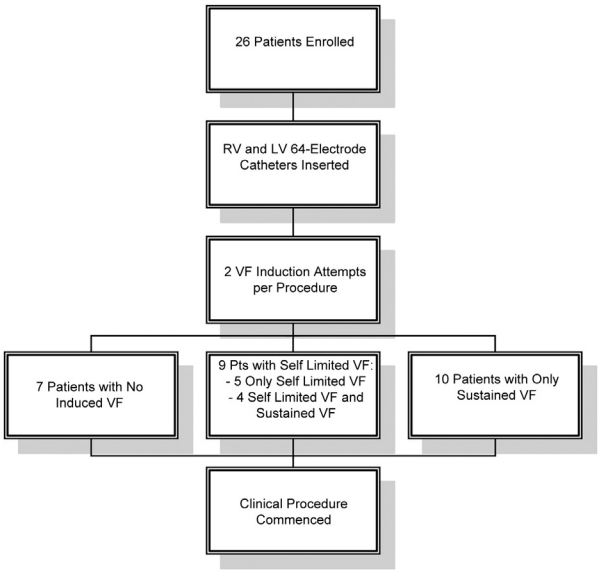

Figure 1 **Study Protocol**

LV = left ventricular; Pts = patients; RV = right ventricular; VF = ventricular fibrillation.

described (18). Additional details may be found in the Online Appendix, Section II, and Figure S1.

Statistical methods. Continuous variables are expressed as mean ± SD. The Student *t* test was used to compare continuous variables; the Fisher exact test was used to compare nominal variables. The ROC cutpoints were determined by optimization of the Youden index. The relationship between rotor stability and ejection fraction (EF) was calculated using Pearson correlation. Subject- and episode-wise statistics are indicated. For episode-wise comparisons, repeated measures analysis of variance was used to determine differences between self-limited and sustained VF episodes. The Bonferroni correction was applied for planned multiple comparisons. The paired *t* test was used in the analysis of patients with both sustained and self-limited VF. Statistics were calculated using SPSS version 19 (IBM, Somers, New York).

Results

We enrolled 26 patients (13 with LVEF <50%, age 64 ± 10 years); the demographics are shown in Table 1. There were no thromboembolic complications or other adverse events during the study.

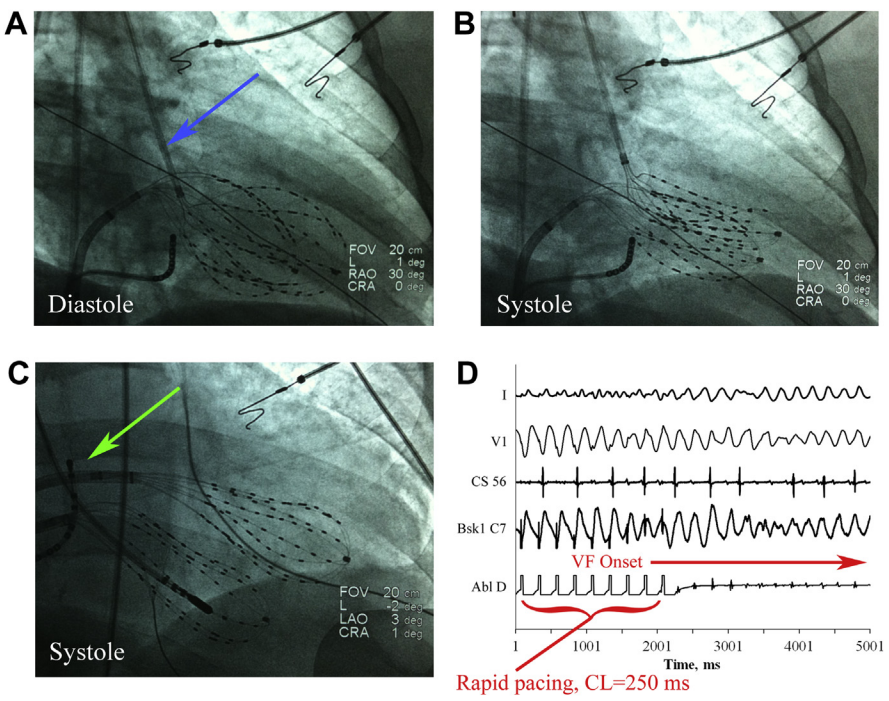

Figure 2 **Biventricular Mapping and VF Induction**

Right anterior oblique fluoroscopy of biventricular baskets during diastole **(A)** and systole **(B)** in a 51-year-old patient with a normal LV ejection fraction, mild RV dysfunction, and symptomatic ventricular tachycardia (VT) and premature ventricular contractions. The LV basket was advanced via the retrograde aortic approach **(blue arrow)**. **(C)** Anteroposterior fluoroscopy showing biventricular baskets in a 68-year-old patient during systole in which the LV basket was advanced via transseptal catheterization **(green arrow)**. **(D)** VF induction by protocol-driven rapid pacing (250 ms) showing surface electrocardiogram (I and V1) and intracardiac electrograms (CS56, LV basket [Bsk1] C7, and ablation distal [Abl D]). CL = cycle length; CRA = cranial; FOV = field of view; LAO = left anterior oblique; RAO = right anterior oblique; other abbreviations as in Figure 1.

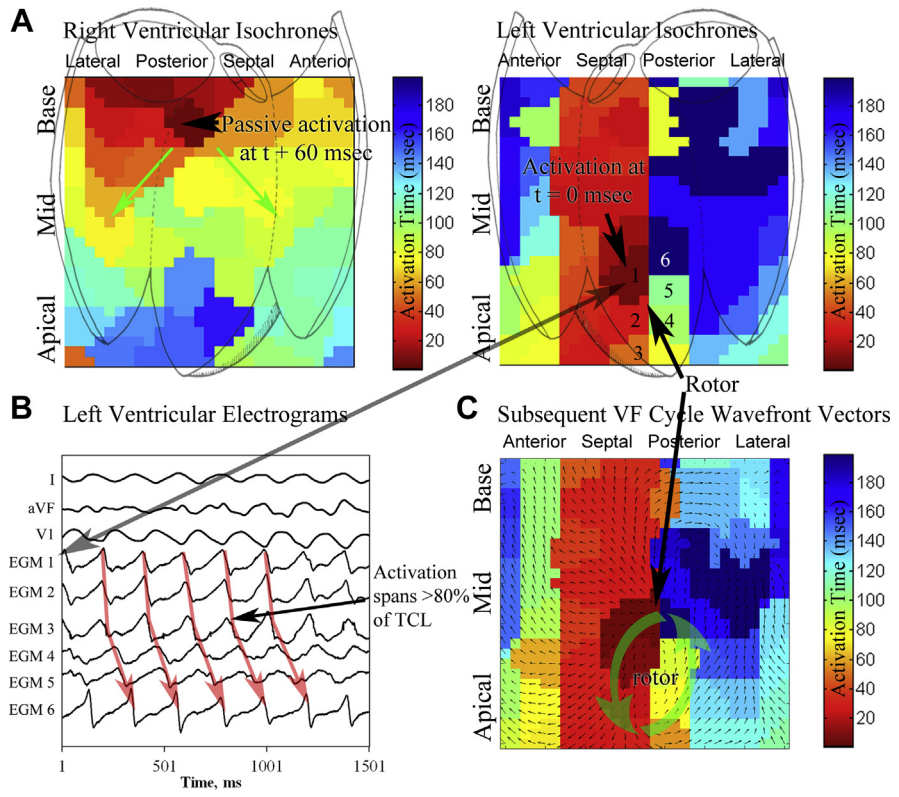

Figure 3 **Biventricular VF Analyses Showing Rotors**

(A) Isochronal analysis of the RV and LV during ventricular fibrillation in a 73-year-old patient, ejection fraction 25%, presenting for drug-refractory ventricular tachycardia. LV isochrones show a rotor (cycle length [CL] 220 ms) in the septal LV (Online Video 1). This rotor persisted for 15 continuous rotations (depicted ~5 seconds into VF); rotor activity was seen in 72% of all VF cycles in this patient. **(B)** Basket electrograms (EGMs) during VF, numbered (1 to 6) near the rotor core. Note that activation spans >80% of the VF cycle length. Artifact before cycles 3,4 of EGM3 is noise (absent on other EGMs). **(C)** Wave front vector analysis of the subsequent VF cycle, showing consistent rotation about the core with radial activation of distant tissue. Online Videos 2 and 3 illustrate spatially conserved RV rotors in 2 consecutive VF episodes in a 63-year-old patient with a left ventricular ejection fraction of 40%. TCL = tachycardia cycle length; other abbreviations as in Figure 1.

VF induction. A total of 52 VF induction attempts were performed per institutional review board–approved protocol, resulting in 36 episodes of VF (CL 210 ± 26 ms). Other VF induction attempts yielded monomorphic ventricular tachycardia (VT) (n = 8) or no ventricular arrhythmia (n = 8) and were excluded from analysis. There were no significant differences in CL between pacing-induced and shock-induced VF (see the Online Appendix, Section III, and Table S1, for additional details and results). Of VF episodes, 21 lasted ≥8 s ("sustained VF") and required defibrillation (duration 11.4 ± 2.9 s), and 15 were self-limited (duration 3.9 ± 1.4 s).

The demographics of patients with sustained and self-limited VF are shown in Table 2. The CL was similar for sustained VF (203 ± 25 ms) and self-limited VF (216 ± 21 ms, p = 0.08). Patients with self-limited VF had higher LVEF than those with sustained VF. Ischemic cardiomyopathy was more common in patients with sustained VF (50%) than without (0%, p = 0.03).

Rotors in VF. Localized sites of rotational activation were seen in 16 of 19 patients with VF (89%) and in all patients with sustained VF (10 of 10, 100%), in whom sustained rotors of longer prevalence and stability were found. Figure 3A and Online Video 1 show an LV counterclockwise rotor during induced VF in a 73-year-old patient with an EF of 25% who was presenting for first VT ablation. This rotor was mapped over 15 rotations; the VF required defibrillation to terminate. Electrograms showing sequential activation around a core, spanning >80% of the VF cycle, are shown in Figure 3B. Vector analysis of the subsequent VF cycle (Fig. 3C) shows stable activation around the core with wave front spread to more distant tissue, controlling ventricular activation. In Figure 3A, right ventricular activation is passive, consistent with transseptal conduction.

Spatial conservation of stable rotors over multiple VF inductions. Stable VF rotors in sustained VF were conserved over multiple inductions; there were 7 patients in whom 2 episodes of sustained VF were induced. In each, rotor sites were conserved within 1 electrode radius (7 of 7 patients, p = 0.023). Online Videos 2 and 3 show sequential VF episodes in a 63-year-old patient with recurrent VT in

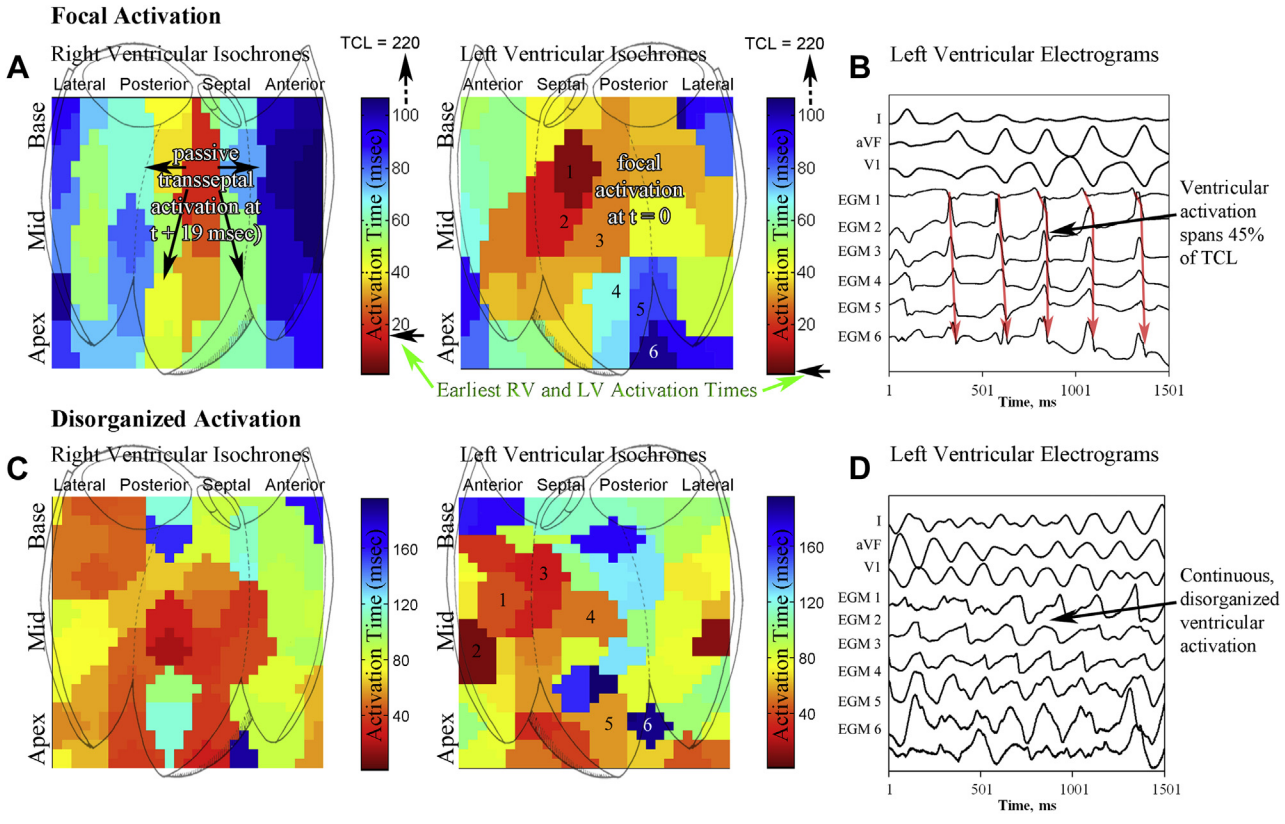

Figure 4 Focal and Disorganized Activation Patterns During VF

(A) Biventricular isochronal analysis of VF in a 68-year-old patient with idiopathic cardiomyopathy, an ejection fraction of 32%, showing a focal source in the anteroseptal LV with passive activation of the RV beginning 19 ms after LV activation (Online Video 4). **(B)** Electrograms at increasing distance from the focal source. Note that LV endocardial activation spans approximately 45% of the VF cycle length. **(C)** Disorganized biventricular activation without a stable rotor during VF in a 52-year-old patient with a normal ejection fraction (Online Video 5). **(D)** Intracardiac electrograms are varying and chaotic, spanning the VF cycle. Online Video 6 shows contrasting laminar activation during rapid pacing at a cycle length of 220 ms, prior to the onset of VF. Abbreviations as in Figures 1 and 3.

which the rotor recurs in the posteroseptal RV. In contrast, focal source locations were infrequently conserved (2 of 10 patients with conserved focal source sites, p = NS).

Differences in rotor prevalence between sustained and self-limited VF. Rotors were more prevalent in sustained VF; they were present for 68 ± 17% of VF cycles in sustained VF versus 11 ± 17% in self-limited VF ($p < 0.001$). ROC analysis for rotor prevalence and VF outcome demonstrate that a cutoff of ≥45% of VF cycles showing rotors separated sustained from self-limited VF with 100% sensitivity and 93% specificity (Fig. 5A).

Focal and disorganized activation patterns in VF. Figures 4A and 4B and Online Video 4 show an example of focal activation in a 68-year-old patient with idiopathic cardiomyopathy (LVEF 32%), located in the anteroseptal LV during VF (CL 222 ms). Figure 4B shows basket electrograms with activation spanning only 45% of the VF cycle. VF terminated spontaneously after 4 s. Figures 4C and 4D and Online Video 5 show disorganized activation in a 52-year-old patient with frequent, symptomatic premature ventricular contractions and an EF of 69% during VF. Basket electrograms show disorganized activation spanning each VF cycle. For comparison, rapid pacing prior to the onset of VF showed laminar activation without rotation (see Online Appendix, Section IV, Figure S2, and Online Video 6 for additional details).

Figure 5B shows the prevalence of rotors and alternative activation patterns for all VF episodes. Notably, focal activity comprised a greater proportion of VF cycles in self-limited VF (78 ± 29%) versus sustained VF (9 ± 9%, $p < 0.001$). Unlike rotors, focal sources were infrequently spatially conserved; 2 of 12 focal sources (17%, p = NS) were located within 1 electrode radius between VF episodes. Disorganized activation (fibrillatory conduction) was similarly prevalent between self-limited VF (23 ± 16%) and sustained VF (10 ± 15%, p = 0.1).

Differences in rotor stability between sustained and self-limited VF. Rotors in sustained VF persisted (and repeatedly re-emerged at stable locations) for more consecutive VF cycles (17 ± 11 cycles, range 7 to 48 cycles) than

Table 1 Study Demographics

	Preserved EF (n = 10)	LV Dysfunction (n = 12)	p Value
Age, yrs	62 ± 13	67 ± 7	0.27
Left atrial diameter, mm	36 ± 5	45 ± 12	0.08
LVEF, %	65 ± 8	33 ± 8	**0.001**
Hypertension	6 (60)	10 (83)	0.35
Diabetes mellitus	3 (30)	3 (25)	1.00
Hyperlipidemia	8 (80)	10 (83)	1.00
Coronary disease	6 (60)	6 (50)	0.69
Prior myocardial infarction	3 (30)	4 (33)	1.00
Prior PCI	3 (30)	4 (33)	1.00
CABG	1 (10)	3 (25)	0.59
COPD	1 (10)	1 (8.3)	1.00
Medications			
Beta-blocker	7 (70)	11 (92)	0.29
ACEI/ARB	4 (40)	10 (83)	0.07
Digoxin	1 (10)	4 (33)	0.32
Calcium-channel blockers	1 (10)	3 (25)	0.59
Mexiletine	0	1 (8)	1.00
Amiodarone	0	0	1.00
Sotalol	1 (10)	5 (42)	0.16
Dofetilide	0	0	1.00
Warfarin	2 (20)	5 (42)	0.38
Aspirin	5 (50)	4 (33)	0.67
Statin	7 (70)	7 (58)	0.68

Values are mean ± SD or n (%). **Bold** values indicate statistical significance.
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; LV = left ventricular; PCI = percutaneous coronary intervention.

rotors in self-limited VF (1.1 ± 1.4 cycles, range 0 to 4 cycles, $p < 0.001$). Figures 6A and 6B show a sustained VF episode in which the rotor completes 17 rotations, and was present for 91% of VF cycles. This VF episode required defibrillation (Fig. 6B). Figure 6C shows self-limited VF with focal activation and no rotor. A cutoff of 7 uninterrupted rotations (before transient interruption and re-emergence) separates sustained from self-limited VF (Fig. 5C). Figure 5D shows temporal rotor stability for sustained and self-limited VF.

Patients with both sustained and self-limited VF. There were 4 patients in whom sustained and self-limited VF were observed in separate episodes. Similar to the overall population, rotors were more prevalent (50 ± 14% vs. 8 ± 15% of rotations, $p = 0.032$) and more stable (15 ± 10 vs. 2 ± 2 consecutive rotations, $p = 0.04$) in sustained versus self-limited VF, respectively, for this subgroup.

Rotor stability, ventricular substrate, and location. We found that VF rotor duration was negatively correlated with LV function (correlation coefficient 0.58, $p = 0.037$). However, there was no significant relationship between rotor CL and temporal stability (see Online Appendix, Section V, and Figure S3).

Although the majority of rotors and focal sources were found in the left (67%) versus right ventricle (33%), the difference was not statistically significant. Similarly, no differences were found between apical and basal rotor

Table 2 Demographics of Patients With Sustained and Self-Limited VF

	Self-Limited VF (n = 9)	Sustained VF (n = 10)	p Value
Age, yrs	64 ± 8	67 ± 7	0.37
Left atrial diameter, mm	39 ± 9	44 ± 13	0.45
LVEF, %	52 ± 14	32 ± 9	**0.002**
Hypertension	8 (89)	8 (80)	1.00
Diabetes mellitus	3 (33)	2 (20)	0.63
Hyperlipidemia	7 (78)	9 (90)	0.58
Coronary disease	5 (56)	6 (60)	1.00
Prior myocardial infarction	2 (22)	5 (50)	0.35
Prior PCI	5 (56)	2 (20)	0.17
CABG	2 (22)	4 (40)	0.63
COPD	0	2 (20)	0.47
Cardiomyopathy, EF <50%	3 (33)	10 (100)	**0.003**
Etiology: ischemic CMP	0	5 (50)	**0.03**
Etiology: nonischemic CMP	3 (33)	5 (50)	0.65
Medications			
Beta-blocker	7 (78)	9 (90)	0.58
ACEI/ARB	6 (67)	8 (80)	0.63
Digoxin	0	4 (40)	0.09
Calcium-channel blockers	1 (11)	2 (20)	1.00
Mexiletine	0	2 (20)	0.47
Amiodarone	0	1 (10)	1.00
Dronedarone	0	0	1.00
Sotalol	0	5 (50)	**0.03**
Dofetilide	0	0	1.00
Warfarin	1 (11)	5 (50)	0.14
Aspirin	5 (56)	4 (40)	0.66
Statin	7 (78)	6 (60)	0.63

Values are mean ± SD or n (%). **Bold** values indicate statistical significance.
CMP = cardiomyopathy; other abbreviations as in Table 1.

characteristics (see Online Appendix, Section VI, and Table S2 for additional details).

Endocardial mapping of nonendocardial VF sources. In our simulations, nonendocardial rotors presented endocardially as focal activation. Additional details may be found in the Online Appendix, Section II, and Figure S1.

Discussion

There are 3 main findings of the present study. First, rotational activation is common in human VF, and stable rotors are common in sustained VF requiring defibrillation, which is most likely to result in clinical sequelae. Second, rotors lie in conserved areas for successive VF inductions, suggesting that rotors form in specific regions of pathologic structural and functional substrate. Third, focal activation without stable rotors is more prevalent in self-limiting VF, and may thus reflect the absence of this substrate. Importantly, these differences are seen in the subset of patients in whom both sustained and self-limited VF episodes were induced, and thus these findings are independent of structure. These findings motivate studies to define the mechanisms underlying rotor formation to explore the feasibility of localized therapies such as ablation, pre-emptive pacing, or cellular therapy to prevent VF.

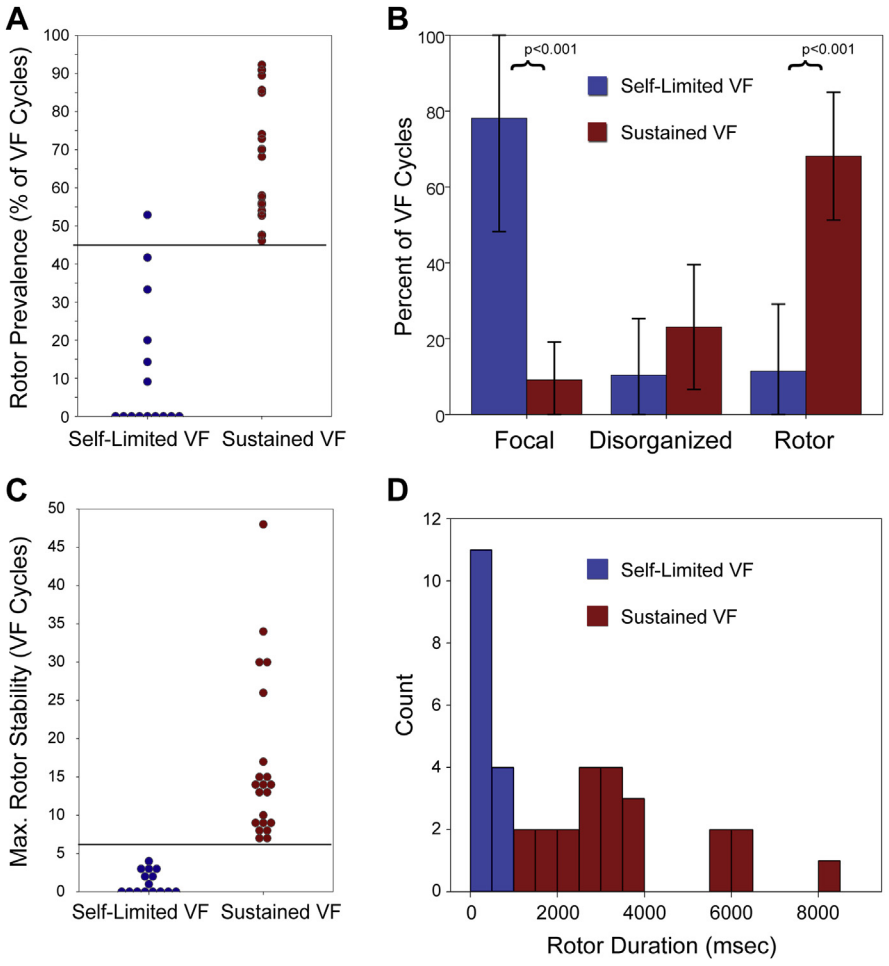

Figure 5 **Activation Patterns in Sustained Versus Self-Limited VF**

(A) Rotor prevalence for each ventricular fibrillation (VF) episode; prevalence ≥45% separates sustained from self-limited VF with 100% sensitivity and 93% specificity. **(B)** Rotor, disorganized, and focal activation prevalence for the study. Rotor and focal activation prevalence were different between sustained and self-limited VF. **(C)** Maximum rotor stability (consecutive rotations) for each episode: sustained and self-limited VF populations do not overlap. **(D)** Histogram of temporal rotor stability (ms) for sustained and self-limited VF. When rotors persisted <1 s, VF perpetuated and required defibrillation.

The importance of rotors to VF perpetuation. Multiple mechanisms have been observed in ongoing VF: sustained rotors (4,5) and focal sources (2) in canine ventricles, and transient rotors and multiple wavelets in human ventricles (6). A central question is whether these mechanisms differ between VF that terminates spontaneously and episodes that progress to sustained VF and result in symptoms, syncope, and sudden death.

In this work, we studied a spectrum of patients with ventricular arrhythmias. We found that rotor prevalence ≥45% of mapped cycles and stability ≥7 cycles identified VF that was sustained and required defibrillation from episodes that terminated spontaneously. Although such cutoffs will vary with the population because the mechanisms for and risk of VF may form a spectrum, they re-emphasize that the formation of stable rotors is important to VF maintenance. Perhaps the most compelling support for the importance of stable rotor formation comes from the subgroup with both sustained and self-limited episodes. Despite identical ventricular structure, significant differences in rotor stability were observed between the episode that required cardioversion and the episode that spontaneously terminated. Thus rotor stabilization is at least a hallmark of, and possibly a critical step in the transition of early VF to sustained VF.

Notably, the average rotor prevalence and stability in sustained VF were ~70% and 17 rotations, respectively. These values are substantially higher than prior work, but important differences must be considered. First, many prior studies used animal models (4,9,19), explanted human hearts supported by Langendorf-perfusion (8,11), or subjects undergoing open heart surgery (6,7). As shown by Qin et al. (20), such techniques may alter VF mechanisms. Our study employed multielectrode mapping via a percutaneous

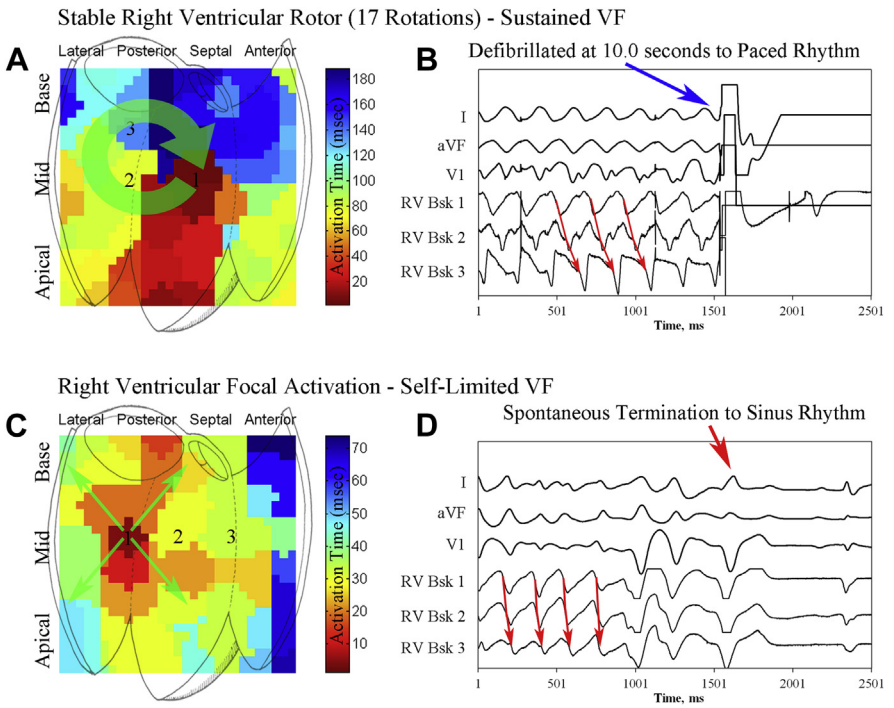

Figure 6 RV Rotor and Focal Activation During VF

(A) Isochronal analysis of VF showing an RV rotor in a 79-year-old patient with ischemic cardiomyopathy. Maximum rotor stability was 17 rotations, and rotor prevalence was 91%. **(B)** This VF episode was defibrillated (right side) 10 s after induction. **(C)** VF isochronal analysis demonstrating an RV focal source in a 68-year-old patient with preserved LV function. **(D)** VF terminated spontaneously. Abbreviations as in Figure 1.

approach in patients, more closely approximating physiologic conditions. Additionally, we sampled a large proportion of the endocardium of both ventricles, including both sides of the interventricular septum, using biventricular basket catheters. Such catheters have previously been used to study VF in animal models (21–23), and patients (24). Second, we quantified ventricular activation patterns in early VF. Different mechanisms may predominate later in VF due to progression of ischemia and electrical remodeling.

Structural determinants of VF rotor sites. Prior work has shown the dependence of rotors upon myocardial scar (8). A subsequent study supports the observation that rotors tend to more frequently localize at diseased substrate (11). Our work is in agreement with these findings, noting that the majority of sustained VF episodes, with more stable rotors, were found in patients with LV dysfunction. Ischemic cardiomyopathy, in particular, was more common in patients with sustained VF. However, the presence of structural heart disease or EF alone was an imperfect predictor of sustained VF; several patients without LV dysfunction had VF progress to sustained, clinically-significant episodes.

Importantly, we found that sustained VF rotor locations were conserved between episodes. Such spatial conservation implies that structural factors or fixed spatial distributions of functional gradients determine rotor locations. In a separate case report (25), we have previously described a patient in whom VT ablation incidentally coincided with the primary VF rotor site. He then presented with recurrence of VT several months later, and again consented to the study protocol, which was then unable to induce VF, only monomorphic VT. Based on these findings, future studies should examine if targeted intervention may reduce the probability of sustained VF (19).

Future directions: rotor sites as therapeutic targets. As with other arrhythmias, intervention in VF is possible at multiple points, including initiating triggers and sustaining sites. Previously, ablation of Purkinje-related premature ventricular contraction triggers has been shown to decrease VF episodes in studies of patients without structural heart disease (26). However, the role of triggers in initiating VF in patients with structural heart disease is less clear (27), whereas sustaining mechanisms for VF are acknowledged as the predominant driver for sudden death in all patients. Inspired by animal models showing stable VF rotors (4), and by recent work in which stable atrial fibrillation rotor sites were successfully identified and ablated in real time (28), we hypothesize that VF rotors may be suitable targets for ablation to decrease ICD shocks for patients with recurrent VF.

Study limitations. First, this study was limited by the spatial resolution of the electrode spacing (4 to 5 mm

interelectrode, 10 mm interspline) of the basket catheters. However, from wavelength considerations, the minimum action potential duration in the human ventricle is ~140 ms (15), and the minimum conduction velocity is approximately 40 cm/s (16), providing a minimum circumference of approximately 7 cm (2 cm diameter). Thus, the resolution should be sufficient to resolve such rotors. Second, only the endocardium was mapped. Based upon our simulation studies and others (29), endocardial mapping may misclassify nonendocardial rotors as focal sources, and thus underestimate the true prevalence of VF rotors. However, only a minority (17%) of mapped focal sources in this study displayed characteristics consistent with rotors. Transmural recordings are required to determine whether such cycles explain transient breaks in continuity observed in otherwise stable VF rotors. Furthermore, prior work in explanted human hearts has shown that the prevalence of intramyocardial rotors is low (8), and animal models of VF have shown that endocardial intervention altered VF inducibility (19), consistent with the hypothesis that the endocardium is important for early VF maintenance. As a result, we believe that endocardial mapping in this study will under detect <20% of rotors in early VF. Third, we enrolled a heterogeneous group of patients by design, using protocol-driven VF inductions to examine mechanistic differences in outcome. That the differences between sustained and self-limited VF were consistent across patients regardless of LV function and induction type supports the generalizability of our findings. Fourth, VF was induced by rapid pacing and T-wave shock, and differences in ischemic time may have influenced VF mechanisms. However, the total difference in ischemic time (~11 s) was significantly below the 30-s threshold for ischemia to significantly alter VF (7). Furthermore, we were unable to identify differences in VF rate, regularity, number of rotors, or rotor duration between these induction methods. Fifth, for practical reasons we could study only early VF in this procedural model. However, early VF is of critical importance because patients may become symptomatic and experience syncope or ICD shocks during early VF and because early VF initiates the cascade leading to sustained VF. Sixth, we did not routinely ablate rotor sites and retest VF inducibility to prove that such sites are critical for the maintenance of VF as we have for atrial rotor sites (30), although we have reported a case (25) in which that did occur, and VF was subsequently not inducible with the study pacing protocol. Future studies of VF rotor ablation are planned. Seventh, artifact during VF may have created the appearance of rotors. However, such an artifact was not seen during rapid pacing prior to VF. Finally, the sample size of the study is small, which may limit the generalizability of our findings.

Conclusions

Rotor prevalence and stability separate sustained and self-limited VF. Rotor sites in sustained VF are conserved, and rotor stability is inversely correlated with LV function, indicating that there is a dependence on a localized pro-arrhythmic substrate. Future studies should determine the conditions under which stable rotors form, and whether such sites may be safely modulated in humans to reduce subsequent VF risk.

Acknowledgments

The authors are indebted to Kathleen Mills, BA for coordinating this study. They also wish to thank Donna Cooper, RN, Elizabeth Greer, RN, Stephanie Yoakum, RNP, Ken Hopper, CVT, Tony Moyeda, CVT, Judy Hildreth, RN, and Cherie Jaynes, RN, for their assistance with the clinical portion of this study.

Reprint requests and correspondence: Dr. David E. Krummen, 3350 La Jolla Village Drive, University of California San Diego, Cardiology Section 111A, San Diego, California 92161. E-mail: dkrummen@ucsd.edu.

REFERENCES

1. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008;300:1423–31.
2. Li L, Zheng X, Dosdall DJ, Huang J, Ideker RE. Different types of long-duration ventricular fibrillation: can they be identified by electrocardiography. J Electrocardiol 2012;45:658–9.
3. Nair K, Umapathy K, Downar E, Nanthakumar K. Aborted sudden death from sustained ventricular fibrillation. Heart Rhythm 2008;5:1198–200.
4. Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. Nature 1998;392:75–8.
5. Davidenko JM, Pertsov AV, Salomonsz R, Baxter W, Jalife J. Stationary and drifting spiral waves of excitation in isolated cardiac muscle. Nature 1992;355:349–51.
6. Nash MP, Mourad A, Clayton RH, et al. Evidence for multiple mechanisms in human ventricular fibrillation. Circulation 2006;114:536–42.
7. Bradley CP, Clayton RH, Nash MP, et al. Human ventricular fibrillation during global ischemia and reperfusion: paradoxical changes in activation rate and wavefront complexity. Circ Arrhythm Electrophysiol 2011;4:684–91.
8. Nair K, Umapathy K, Farid T, et al. Intramural activation during early human ventricular fibrillation. Circ Arrhythm Electrophysiol 2011;4:692–703.
9. Zaitsev AV, Guha PK, Sarmast F, et al. Wavebreak formation during ventricular fibrillation in the isolated, regionally ischemic pig heart. Circ Res 2003;92:546–53.
10. Narayan SM, Bhargava V. Temporal and spatial phase analyses of the electrocardiogram stratify intra-atrial and intra-ventricular organization. IEEE Trans Biomed Eng 2004;51:1749–64.
11. Jeyaratnam J, Umapathy K, Masse S, et al. Relating spatial heterogeneities to rotor formation in studying human ventricular fibrillation. Conf Proc IEEE Eng Med Biol Soc 2011;2011:231–4.
12. Cao JM, Qu Z, Kim YH, et al. Spatiotemporal heterogeneity in the induction of ventricular fibrillation by rapid pacing: importance of cardiac restitution properties. Circ Res 1999;84:1318–31.
13. Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol 2012;23:447–54.
14. Bray MA, Wikswo JP. Considerations in phase plane analysis for nonstationary reentrant cardiac behavior. Phys Rev E Stat Nonlin Soft Matter Phys 2002;65:051902.
15. Narayan SM, Franz MR, Lalani G, Kim J, Sastry A. T-wave alternans, restitution of human action potential duration, and outcome. J Am Coll Cardiol 2007;50:2385–92.

16. Narayan SM, Bayer JD, Lalani G, Trayanova NA. Action potential dynamics explain arrhythmic vulnerability in human heart failure: a clinical and modeling study implicating abnormal calcium handling. J Am Coll Cardiol 2008;52:1782–92.
17. Barkley D. A model for fast computer-simulation of waves in excitable media. Physica D 1991;49:61–70.
18. Dutta S, Steinbock O. Steady motion of hairpin-shaped vortex filaments in excitable systems. Physical Review E 2010:81.
19. Pak HN, Kim GI, Lim HE, et al. Both Purkinje cells and left ventricular posteroseptal reentry contribute to the maintenance of ventricular fibrillation in open-chest dogs and swine: effects of catheter ablation and the ventricular cut-and-sew operation. Circ J 2008;72:1185–92.
20. Qin H, Kay MW, Chattipakorn N, Redden DT, Ideker RE, Rogers JM. Effects of heart isolation, voltage-sensitive dye, and electromechanical uncoupling agents on ventricular fibrillation. Am J Physiol Heart Circ Physiol 2003;284:H1818–26.
21. Eldar M, Ohad DG, Goldberger JJ, et al. Transcutaneous multielectrode basket catheter for endocardial mapping and ablation of ventricular tachycardia in the pig. Circulation 1997;96:2430–7.
22. Everett TH, 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.
23. Dosdall DJ, Osorio J, Robichaux RP, Huang J, Li L, Ideker RE. Purkinje activation precedes myocardial activation following defibrillation after long-duration ventricular fibrillation. Heart Rhythm 2010;7:405–12.
24. Shimizu W, Aiba T, Kurita T, Kamakura S. Paradoxic abbreviation of repolarization in epicardium of the right ventricular outflow tract during augmentation of Brugada-type ST segment elevation. J Cardiovasc Electrophysiol 2001;12:1418–21.
25. 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.
26. Knecht S, Sacher F, Wright M, et al. Long-term follow-up of idiopathic ventricular fibrillation ablation: a multicenter study. J Am Coll Cardiol 2009;54:522–8.
27. Sacher F, Victor J, Hocini M, et al. [Characterization of premature ventricular contraction initiating ventricular fibrillation]. Arch Mal Coeur Vaiss 2005;98:867–73.
28. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012;60:628–36.
29. Berenfeld O, Jalife J. Purkinje-muscle reentry as a mechanism of polymorphic ventricular arrhythmias in a 3-dimensional model of the ventricles. Circ Res 1998;82:1063–77.
30. Narayan SM, Krummen DE, Clopton P, Shivkumar K, Miller JM. Direct or coincidental elimination of stable rotors or focal sources may explain successful atrial fibrillation ablation: on-treatment analysis of the CONFIRM trial (Conventional Ablation for AF With or Without Focal Impulse and Rotor Modulation). J Am Coll Cardiol 2013;62:138–47.

Key Words: arrhythmia mechanisms ■ electrical rotors ■ electrophysiology ■ ventricular fibrillation.

APPENDIX

For supplemental figures and videos, please see the online version of this article.