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

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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.

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...
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 ofVF, 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.

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 defined.
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.

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**Figure 1** Study Protocol

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

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**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 [Ab1 D]). CL = cycle length; CRA = cranial; FOV = field of view; LAO = left anterior oblique; RAO = right anterior oblique; 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 length, are shown in Figure 3B. Vector analysis of the subsequent VF cycle (Fig. 3C) shows stable activation around 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.
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...
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 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.
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 (consecutive rotations) 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
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 recurrentVF.

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

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REFERENCES


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APPENDIX

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