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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. (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

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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