Mother Rotors and the Mechanisms of D600-Induced Type 2 Ventricular Fibrillation

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Background—Two types of ventricular fibrillation (VF) have been demonstrated in isolated rabbit hearts during D600 infusion. Type 1 VF is characterized by the presence of multiple, wandering wavelets, whereas type 2 VF shows local spatiotemporal periodicity. We hypothesized that a single mother rotor underlies type 2 VF.

Methods and Results—One (protocol I) or 2 (protocol II) cameras were used to map the epicardial ventricular activations in Langendorff-perfused rabbit hearts. Multiple episodes of type 2 VF were induced in 22 hearts by high-concentration (≥2.5 mg/L) D600 (protocol I). During type 2 VF, a single spiral wave (n = 19) and/or an epicardial breakthrough pattern (n = 11) was present in 14 hearts. These spiral waves either slowly drifted or intermittently anchored on the papillary muscle (PM) of the left ventricle. Dominant-frequency (DF) analyses showed that the highest local DF was near the PM (12.5 ± 1.1 Hz). There was an excellent correlation between the highest local DF of these spiral waves and breakthroughs (11.8 ± 1.7 Hz) and the DF of simultaneously obtained global pseudo-ECG (11.2 ± 1.8 Hz, r = 0.97, P < 0.0001) during type 2 VF. We also successfully reproduced the major features of type 2 VF by using the Luo-Rudy action-potential model in a simulated, 3-dimensional tissue slab, under conditions of reduced excitability and flat action-potential duration restitution.

Conclusions—Either a stationary or a slowly drifting mother rotor can result in type 2 VF. Colocalization of the stationary mother rotors with the PM suggests the importance of underlying anatomic structures in mother rotor formation.

Keywords: arrhythmia • fibrillation • mapping • ventricles

We recently observed 2 different types of ventricular fibrillation (VF) coexisting in the same rabbit hearts. Type 1 (fast) VF is associated with a steep action-potential duration (APD) restitution, normal excitability, and multiple wandering wavelets. In contrast, type 2 (slow) VF is associated with a flat APD restitution, reduced excitability, and local spatiotemporal periodicity, compatible with VF due to a focal source. However, the nature of this focal source during type 2 VF remains unclear. We previously demonstrated that the papillary muscle (PM) can serve as an anchoring site for this mother rotor. An anchored stationary scroll wave can have a longer life span and can function as a mother rotor. We hypothesized that a triologically stable, single, mother rotor can result in type 2 VF. To test the hypothesis, we developed a mapping system capable of simultaneously mapping both the anterior and posterior aspects of the rabbit heart to locate the mother rotor. We also used computer modeling to simulate 2 different types of VF in a 3-dimensional tissue slab. The purposes of the present study were to (1) determine whether or not a mother rotor underlies type 2 VF and (2) test the hypothesis that anatomic structures, such as the PM, serve as an anchoring site for this mother rotor.

Methods

This research protocol was approved by the Institutional Animal Care and Use Committee of Taichung Veterans General Hospital and followed the guidelines of the American Heart Association. We used optical mapping techniques to study the epicardial ventricular activation patterns in 30 Langendorff-perfused rabbit hearts. New Zealand white rabbits (3.2 to 4.6 kg) were used. The hearts were excised under general anesthesia. The ascending aorta was immediately cannulated and perfused at 25 to 30 mL/min with oxygenated and warmed (36.5°C) Tyrode’s solution with a pH of 7.4. Afterward the hearts were both perfused and superfused in a tissue bath made of transparent glass.

Optical Mapping

Protocol I (n = 25): With a Single Camera

The single-camera mapping system and the methods for fast Fourier transform (FFT) analysis of pseudo-ECG have been
described previously. The pseudo-ECG was obtained with widely spaced bipoles, one at the apex of the left ventricle (LV) and the other at the high lateral wall of the right ventricle (RV). The signals were filtered from 0.05 to 100 Hz and were digitized by use of an AxoScope at 1 kHz. The pseudo-ECG (a true electrical recording) was used to determine the rhythm of the optical recordings. In our previous study, the mapped field focused on the RV, the interventricular septum, and a limited portion of the LV. Among the 10 hearts infused with increasing concentrations of D600, we observed large wavefronts with local spatiotemporal periodicity during type 2 VF. However, the possible sources of these wavefronts were not elucidated. In the present study, we modified the protocol by including the PM region of the LV in 15 hearts to determine whether the source of the wavefront might be a spiral wave in the LV. Results from all 25 hearts are included in the present report. The optical mapping data were gathered at 3.75-ms sampling intervals (267 frames/s), acquired from 100×100 sites simultaneously over a 40×40-mm² area. Optically recorded voltage signals were spatiotemporally filtered to reduce noise. Phase mapping was performed to evaluate the location and evolution of phase singularities (PSs) in VF. For cumulative PS display (ie, a PS map) over long acquisition intervals (typically 600 frames), PSs were identified by an automated PS tracking algorithm.

Type 2 VF was induced either by progressively increasing D600 concentrations (0.1, 0.5, 2.5, and 5.0 mg/L) during baseline VF (protocol IA, n=15) or by giving a high concentration (2.5 or 5.0 mg/L) of D600 from the beginning of the experiments (protocol IB, n=10). In both protocols IA and IB, D600 was washed out with drug-free Tyrode’s solution to induce washout ventricular tachycardia (VT).

Protocol II (n=5): With a Dual-Camera Mapping System
A dual-camera mapping system was used to simultaneously map the anterior and posterior aspects of the heart in an additional 5 hearts. Type 2 VF was induced by perfusing the heart with a high dose (5.0 mg/L) of D600 from the beginning of the experiments. The optical signals were gathered at 3.85-ms sampling intervals.
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Conduction anisotropy was included in the model, with the fast axis rotating by 13°, similar to that reported before.1 In hearts, there was a single, large wavefront activating episodes) was present in 14 hearts. In the remaining 8 hearts, there was a single spiral wave (Figures 3 and 4, 19 episodes) or a persistent epicardial breakthrough pattern in 10 episodes and a single spiral wave in 2 episodes. Figure 6 shows an example of persistent epicardial breakthroughs in the posterior wall. The anterior wall simultaneously showed a repetitive, single, large wavefront that either activated the entire ventricles (Figure 6C). Additionally, the posterior aspect of the heart displayed a persistent epicardial breakthrough pattern in 10 episodes and a single spiral wave in 2 episodes. Figure 6 shows an example of persistent epicardial breakthroughs in the posterior wall. The anterior wall simultaneously showed a single, large wavefront that either activated the entire anterior wall of the heart (frame 3550 ms) or propagated with wave breaks in the LV (not shown) and the RV (the remaining frames). The PSs were distributed in both ventricles (Figure 6C).

Results

Protocol I

Type 1 VF
As shown in Figure 1, baseline (type 1) VF was successfully induced by burst pacing in all 15 hearts for protocol IA. During type 1 VF, PSs occurred throughout both ventricles (Figure 1Aa–1Ac). However, consistent with previous reports,5 11,12 cumulative PS display during type 1 VF showed a clustering of PSs at the anterior PM, the epicardial coronary arteries, and the interventricular septum (arrowheads in Figure 1C).

Type 2 VF
With 2.5 or 5.0 mg/L D600 infusion, type 2 VF was successfully induced in 12 hearts for protocol IA and in all 10 hearts for protocol IB (Figure 2). During type 2 VF, a single spiral wave (Figures 3 and 4, 19 episodes) or a persistent epicardial breakthrough pattern (Figure 5, 11 episodes) was present in 14 hearts. In the remaining 8 hearts, there was a single, large wavefront activating repetitively, similar to that reported before.1

When single spiral waves were present, they either slowly drifted in and out of the mapped area (Figure 3) or intermittently anchored on the region overlying the PM roots in the LV (Figure 4). During anchoring, the PSs (as shown in Figure 4B) always clustered at the PMs (marked by a downward yellow arrow) in the LV, distributed along the interventricular septum, and scattered widely throughout the RV. The highest local DF was observed overlying the PMs (12.5±1.1 Hz; range, 10.4 to 14.3 Hz), followed by those overlying the interventricular septum and the RV. Figure 4C shows an example.

Among the 30 episodes of type 2 VF with either a single spiral wave or an epicardial breakthrough pattern, 19 had simultaneous pseudo-ECG recordings. The highest local DF of these spiral waves (10 episodes) and epicardial breakthroughs (9 episodes, 11.8±1.7 Hz) was correlated well with the DF of the simultaneously obtained, global pseudo-ECG (11.2±1.8 Hz, r=0.97, P<0.0001).

Protocol II In all 5 hearts studied, type 2 VF was successfully induced after a 15-minute, high-dose D600 infusion (5.0 mg/L). In a total of 12 episodes of type 2 VF (1 to 3 episodes from each heart), a repetitive, single, large wavefront was observed in the anterior aspect of the heart. Simultaneously, the posterior aspect of the heart displayed a persistent epicardial breakthrough pattern in 10 episodes and a single spiral wave in 2 episodes. Figure 6 shows an example of persistent epicardial breakthroughs in the posterior wall. The anterior wall simultaneously showed a single, large wavefront that either activated the entire anterior wall of the heart (frame 3550 ms) or propagated with wave breaks in the LV (not shown) and the RV (the remaining frames). The PSs were distributed in both ventricles (Figure 6C).

In hearts 1 and 3, type 2 VF terminated immediately after the abrupt termination of the persistent epicardial break-
throughs recorded in the posterior aspect of the heart. This finding indicates an association between these breakthroughs and type 2 VF maintenance.

Computer Simulation of D600-Induced VTs

Data from voltage maps of the heart showed that conduction velocity (CV) was slower in the RV than the LV. We simulated this tissue heterogeneity by changing the Na⁺ channel density from the LV to the RV. \( G_{Na} \) was reduced sigmoidally from the LV to the RV, and spatial heterogeneities of \( I_{Na} \) density were introduced as sinusoidal functions of space in the RV. Figure 7A shows how \( G_{Na} \), the maximum conductance of the Na⁺ channel, was changed from the LV to the RV. Figure 7B shows the pseudo-ECGs and DFs for type 1 VF, VT, and type 2 VF. Type 1 VF occurs at a \( G_{Na} \) of 0.045, which results in a steep slope of APD restitution. Infusion of low-dose D600 was modeled by decreasing \( G_{Na} \) to 0.02, which creates a restitution curve with a slope of <1 everywhere. Preexisting Na⁺ current density heterogeneities were not significant enough to cause a wave break in this tissue model with normal excitability. However, when \( I_{Na} \) density was decreased to reduce excitability proportionately throughout the tissue by shifting down the \( G_{Na} \) curve in Figure 7A and increasing \( \tau_s \) by a factor of 2, a stable, single, mother rotor anchored in the region with the highest excitability (ie, the LV). The surrounding heterogeneities now caused a wave break resembling in a fibrillatory conduction block, mostly near the boundaries of the regions with a low \( I_{Na} \) density in the RV. Figure 7C shows the snapshots of type 1 VF, VT, and type 2 VF in 3-dimensional tissue slabs.

Discussion

In this study, we have demonstrated that a single, stationary or a slowly drifting mother rotor underlies type 2 VF. The colocalization of a mother rotor with the PM suggests the importance of the underlying anatomic structures in the formation of the mother rotor. Compatible with experimen-
tal results, computer simulation showed a single mother rotor when the APD restitution was flattened and when $\mathit{I}_{\mathit{Na}}$ density was decreased to reduce excitability. We also demonstrated that different types of VF are associated with drastically different spatial distribution of PSs. Type 1 VF is associated with a wide distribution of PSs throughout both ventricles. Type 2 VF is associated with highly concentrated PSs overlying the PM of the LV. These findings support the hypothesis that type 1 VF and type 2 VF have different underlying mechanisms.1,14

### Possible Mechanisms of Cardiac Fibrillation

Although the activation patterns during VF are complex, phase analysis of VF signals has documented that only a limited number of PSs are present.7 These PSs are thought to be the sources of reentry that sustain VF. Two major hypotheses have been proposed to explain the generation of these PSs. One is the multiple-wavelet hypothesis,15 which states that constant wave breaks occur because of electrophysiological heterogeneity. Continued regeneration of new wave breaks at multiple locations is the mechanism that sustains VF. In contrast, the focal-source hypothesis16 states that a rapidly activating focal source drives the ventricle into fibrillation through fibrillatory conduction. This rapidly activating focal source could be a mother rotor17 associated with a single PS. The interaction between a sustained mother rotor and underlying heterogeneity could result in conduction blocks and a complex spatial distribution of excitation frequencies, leading to VF.2,18

### Wavelength Restitution Properties and 2 Types of VF

We1 have recently demonstrated that there are 2 different types of VF, depending on the wavelength restitution properties of the heart. We proposed that a steep APD restitution with normal CV restitution (ie, normal excitability) results in type 1 VF owing to a multiple-wavelet mechanism. On the other hand, a flat APD restitution with a broad CV restitution (ie, reduced excitability) results in type 2 VF owing to a focal source, most likely an anchored mother rotor. In the present study, we focused our effort to...
detect whether the focal source was a mother rotor by including the PM region of the LV in the mapped field. We also developed a dual-camera mapping system to simultaneously map the anterior and the posterior aspects of the heart. The results documented the presence of a sustained mother rotor during type 2 VF, but not in type 1 VF. In addition, we also observed a repetitive, epicardial breakthrough pattern in type 2 VF, compatible with an underlying focal source. A weakness of these mapping studies is that only the epicardial surface was mapped. It is possible that a mother rotor was present in the transmural myocardium during type 1 VF but failed to reveal itself on the epicardium. To partially overcome this problem, we used 3-dimensional computer simulation studies to document that a mother rotor with fibrillatory conduction can occur under conditions with reduced excitability and a flat APD restitution. However, when the APD restitution is steep and the excitability is normal, no mother rotor is present. These findings support the hypothesis that a mother rotor underlies type 2 VF but not type 1 VF. These data also support the idea that wavelength restitution properties determine the phenotypes of VF in normal rabbit ventricles.

Importance of the PM in the Formation of a Mother Rotor During Type 2 VF

The thickened tissue at the PM in the ventricle creates a source-sink mismatch. Mapping and computer simulation studies have shown that this source-sink mismatch facilitates the spiral wave anchoring at the PM. Furthermore, an abrupt change of fiber orientation or a specific spatial distribution of the Purkinje-muscle junction at the PM base can be associated with conduction delay and reentry formation. An important finding of the present study is that the mother rotors during type 2 VF were not randomly distributed throughout the ventricles. Rather, they clus-

Figure 5. Type 2 VF with persistent, epicardial breakthrough pattern. Aa–Ai, Selected phase maps with PSs marked with arrowheads. This epicardial breakthrough (asterisk in Aa, Ad, and Ag) was near interventricular septum. B, Local optical tracings and pseudo-ECG with FFT analysis. Letters x1, x2, and y indicate recording sites. C, PS map. With continuous wave breaks, PSs clustered at LV apex near anterior PM (arrows) and were distributed widely at RV. D, DF map. Note that highest local DF was in LV, near breakthrough site. Abbreviations are as defined in text.
tered around the PM region. These findings indicate that the PM is important in the maintenance of a single mother rotor during type 2 VF. Pak et al. used a β-adrenergic receptor blocker, propranolol, to convert a multiple-wavelet fibrillation (type 1 VF) into a slow fibrillation (type 2 VF) by flattening the APD restitution and reducing excitability. PM ablation terminated type 2 VF during propranolol infusion. This latter study further supports the hypothesis that the PM is the common anchoring site for the mother rotor during type 2 VF in isolated rabbit ventricles.

Epicardial Breakthrough Patterns During Type 2 VF

In the present study, we also observed the presence of a repetitive, epicardial breakthrough pattern during type 2 VF. The highest local DF at the epicardial breakthrough sites was correlated well with the DF of the simultaneous, global pseudo-ECG during type 2 VF. We also demonstrated in 2 hearts that termination of the epicardial breakthrough preceded the termination of VF. These findings suggest but do not prove that these breakthrough patterns were associated with an underlying anchored mother rotor. Other possibilities, including triggered activity and automaticity, cannot be ruled out by this mapping study.

Clinical Implications

We propose that there are 2 types of VF in humans. The initial VF in most situations is compatible with type 1 VF. Continued fibrillation induces acute global ischemia, which flattens APD restitution and decreases excitability, converting type 1 VF to type 2 VF. In certain clinical situations, acute or chronic regional ischemia preceding the onset of VF may depress excitability sufficiently to produce an immediate type 2 VF in the ischemic zone while type 1 VF is still present in the nonischemic zone. This is likely to be a particularly lethal situation because type 2 VF is unlikely to self-defibrillate. We propose that type 2 VF is important in the pathogenesis of sudden cardiac death and that understanding the basic mechanisms of type 2 VF is of significant clinical importance.
Limitations
A limitation of the study is that only the epicardial surface was mapped. This may be the reason why a mother rotor could not be documented in all episodes of type 2 VF. We cannot rule out the possibility that automaticity or triggered activity also played a role in type 2 VF. A second limitation is that rabbit hearts are small. Whether or not a mother rotor can result in VF in larger hearts is unclear. Also, because type 2 VF in this study was induced by D600 rather than by a disease process, it is unclear whether the data are applicable to VF in diseased ventricles. A third limitation is that dual mapping was performed in only 5 rabbits. The majority of the study was done with the single-camera system. In those rabbits, the movements of the rotors could not be fully determined.

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