Two Types of Ventricular Fibrillation in Isolated Rabbit Hearts

Importance of Excitability and Action Potential Duration Restitution

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Background—The combined effects of excitability and action potential duration (APD) restitution on wavefront dynamics remain unclear.

Methods and Results—We used optical mapping techniques to study Langendorff-perfused rabbit hearts. In protocol IA (n=10), D600 at increasing concentrations was infused during ventricular fibrillation (VF). With concentration increased to 0.5 mg/L, fast VF (dominant frequency, 19.1±1.8 Hz) was consistently converted to ventricular tachycardia (VT). However, increasing D600 further to 2.5 or 5.0 mg/L converted VT to slow VF (11.9±2.3 Hz, P=0.0011). In an additional 4 hearts (protocol IB), tetrodotoxin converted a preexisting VT to slow VF (11.0±1.4 Hz). Optical maps show wandering wavelets in fast VF, organized reentry in VT, and spatiotemporal periodicity in slow VF. In protocol II, we determined APD and conduction time 

Conclusions—Two types of VF exist in isolated rabbit hearts. Fast (type I) VF is associated with a steep APD restitution, and wandering wavelets. Slow (type II) VF is associated with a flat APD restitution, a steep CT−1 restitution, and spatiotemporal periodicity. Both excitability and APD restitution are important in VF maintenance. (Circulation. 2002;106:1859-1866.)

Key Words: arrhythmia • fibrillation • mapping • ventricles

It is hypothesized that both action potential duration (APD) and conduction velocity (CV) restitution characteristics are sources of wavelength (WL) oscillations that lead to wave break. Because APD and CV oscillations are both associated with short diastolic intervals, it is difficult to test separately the relative importance of APD and CV restitutions in ventricular fibrillation (VF) maintenance. Methoxyverapamil (D600), an excitation-contraction uncoupler, not only inhibits slow Ca2+ inward current at low concentrations (1 μmol/L, equivalent to 0.52 mg/L) but also depresses fast Na+ inward current at higher concentrations (5 to 50 μmol/L, equivalent to 2.6 to 26 mg/L). The latter effect reduces excitability and CV. We hypothesize that low D600 concentrations flatten APD restitution by calcium channel blockade, whereas high D600 concentrations reduce excitability and steepen CV restitution by sodium channel blockade.

To estimate CV and excitability, we measured the inverse of conduction time (CT−1) between 2 epicardial points. Optical mapping techniques in Langendorff-perfused rabbit hearts were used to study the effects of different D600 concentrations on APD and CT−1 restitutions and on wavefront dynamics during VF. We also used tetrodotoxin (TTX), a sodium channel blocker, to determine the role of decreased excitability on VF/ventricular tachycardia (VT) transitions. The purpose of this study was to test the hypotheses that both excitability and APD restitution are important in VF maintenance.

Methods

Langendorff Preparation and Pseudo-ECG Recordings
The hearts of adult rabbits (3.4 to 4.8 kg) were excised under general anesthesia. The ascending aorta was immediately cannulated and perfused at 20 to 30 mL/min with oxygenated and warmed (36.5°C) Tyrode’s solution with a pH of 7.4. Then the heart was both perfused and superfused in a tissue bath made with transparent glass.
A pseudo-ECG was registered throughout the experiment with widely spaced bipoles, one at the left ventricular apex and the other at the high lateral wall of the right ventricle.

Optical Mapping
The optical mapping system has been described previously. The hearts were stained with di-4-ANEPPS. They were then excited with quasi-monochromatic light (500±40 nm) from a 250-W tungsten-halogen lamp. Fluorescent and scattered light was collected by an image-intensified charge-coupled device camera. The data were gathered at 3.75-ms sampling intervals, acquiring from 100×100 sites simultaneously over a 40×40-mm² area. The mapped area included parts of the right and left ventricular free walls. A pair of hook bipolar electrodes was inserted into the right ventricular outflow tract for pacing or the determination of effective refractory period (ERP).

Protocol I: Effects of D600 and TTX on VF/VT Activations

Protocol IA (n=10)
We used burst pacing (cycle lengths, 75 to 100 ms; currents, 5 to 10 mA) to induce baseline VF. Increasing concentrations of D600 (0.1, 0.5, 2.5, and 5.0 mg/L) were then infused sequentially (15 minutes for each) during VF to observe the change of rhythm. D600 was then washed out with drug-free Tyrode’s solution (washout period).

Protocol IB (n=4)
D600 (0.5 to 1.0 mg/L) was infused to convert baseline VF to VT. TTX (3 μmol/L) was then infused to observe the change of rhythm. After a 10-minute infusion, TTX was washed out with drug-free Tyrode’s solution.

Protocol II: Restitution Curves

Protocol IIA (n=7)
We used extrastimulus (S2) at twice diastolic threshold current to determine ERP at baseline and at the end of 15-minute infusion of different D600 concentrations (0.1, 0.5, 2.5, and 5.0 mg/L). APD and CT restitution were then determined by use of 12 different S1 pacing cycle lengths (500, 400, 300, 250, 200, 180, 160, 150, 140, 130, 120, and 110 ms) in all hearts (S1 pacing method).

In hearts 3 through 7, to minimize motion artifacts and to obtain baseline restitution data, an adjustable glass wall was used to compress and restrain the hearts during pacing. In these 5 hearts, we also determined APD restitution by using the S1-S2 method in addition to the above S1 pacing method.

Protocol IIB (n=3)
We first determined APD and CT restitution by the S1 pacing method at baseline, 15-minute 0.1 mg/L, and 15-minute 5.0 mg/L D600 infusion sequentially. We then induced VF if it did not occur during the previous S1 pacing. D600 was then washed out with drug-free Tyrode’s solution to obtain washout VT. After direct current cardioversion, APD and CT restitution were again determined immediately by the S1 pacing method.

Protocol III: Control (n=3)
To evaluate whether spontaneous VF/VT transition can occur without the presence of D600, we used drug-free Tyrode’s solution to

Figure 1. A through E, APD and CT restitution (data from heart 1 of protocol IIA). CT at ventricular walls was inhomogeneous during S1 pacing (A). Mean value of CT along lines 1 to 4 was used to estimate CT restitution (B). Recordings from sites a through d were used for APD analyses (C). D and E, Examples of CT (line 2) and APD15 (site a) determinations at different D600 concentrations and different S1 pacing cycle lengths. F through H, Isochronal maps showing effects of different D600 concentrations on CT (data from heart 7 of protocol IIA). Asterisks in B, C, and F through H mark pacing site. LAD indicates left anterior descending artery; PCL, pacing cycle length.
perfuse 3 hearts continuously for 60 minutes. A pseudo-ECG was recorded at 5, 30, and 60 minutes, respectively, to document the rhythm.

Data Analysis
Optical mapping data were processed through several image-processing algorithms. After data processing, pixels at several sites were chosen for APD and CT\(^{-1}\) determinations (Figure 1).

Construction of APD and CT\(^{-1}\) Restitution Curves

\(S_1\) Pacing Method
As shown in Figure 1A, CT at the ventricular walls was inhomogeneous during \(S_1\) pacing. Therefore, we used the mean value of CT\(^{-1}\) along 4 different lines to construct CT\(^{-1}\) restitution (Figure 1B). For APD determination, pixels at 4 sites (sites a through d) of the mapped area were used (Figure 1C). APD was measured at 70% repolarization (APD\(_{70}\)). Similarly, the mean value of APD\(_{70}\) at these 4 sites was used to estimate APD restitution. Figure 1, D and E, shows examples of CT\(^{-1}\) and APD\(_{70}\) determinations. APD and CT\(^{-1}\) restitution curves were then constructed by plotting means of APD\(_{70}\) (ms) and means of CT\(^{-1}\) (cm/s) against different \(S_1\) pacing cycle lengths. By use of the formula APD\(_{70}\)\(\times\)CT\(^{-1}\)=WL (cm), WL restitution curves were also constructed.

\(S_1\cdot S_2\) Method
When APD restitution was tested with the \(S_1\cdot S_2\) method, the APD\(_{70}\) associated with \(S_2\) was used. An APD restitution curve was created by plotting the \(S_1\) APD\(_{70}\) against its diastolic interval. A restitution curve was then generated by exponential fit. This curve was also obtained at sites a through d in each heart.

Determination of APD Dispersion
APD dispersion (ms) was defined as the difference between maximum and minimum APD\(_{70}\) obtained from 100 pixels evenly distributed over the mapped area during \(S_1\) pacing.

Fast Fourier Transform Analysis
Fast Fourier transforms (FFTs) of pseudo-ECGs (4 seconds in duration) were used to determine the dominant frequencies at different stages of ventricular arrhythmias. In protocol IA, 4 stages of VF were defined: (1) baseline VF (no D600), the stable VF 5 minutes after the successful induction by burst pacing; (2) fast (type 1) VF, the VF with 15-minute 0.1 mg/L D600 infusion. In hearts 6, 9, and 10 (Figure 2A), however, VF-to-VT transition occurred during 0.1 mg/L infusion. Fast VF was defined as the period of VF immediately preceding VF-to-VT transition in these 3 hearts; (3) slow (type II) VF, the VF at 3 minutes after the transition from VT to an irregular and slow rhythm; and (4) washout VF, the VF during the washout period.

Statistical Analysis
Paired t tests and ANOVA with repeated measures were used for statistical comparisons. A probability value of \(P\leq0.05\) was considered significant. In case of multiple comparisons, Bonferroni-adjusted probability values were used to determine the significance.

Results

Protocol IA

VF/VT Transitions During D600 Infusion
As in Figure 2A, baseline VF was successfully induced by burst pacing in all 10 hearts. After 0.1 mg/L D600 infusion, the irregular rhythm was converted to VT within 12 minutes in 3 hearts (hearts 6, 9, and 10). In the remaining 7, fast VF was consistently converted to VT within 8-minute 0.5 mg/L infusion. Subsequently, during 2.5 (n=3) or 5.0 (n=4) mg/L infusion, VT was again converted to an irregular and slow rhythm (slow VF). Finally, washout VT (6 of 10 hearts) and VF (10 of 10 hearts) were obtained sequentially within 25-minute washout. Figure 3, A through I, shows examples of pseudo-ECG during VF/VT transitions. Note that as in Figure 3, C and F, VF/VT transitions always occurred abruptly.

FFT analyses of pseudo-ECG (Figure 3, A’ through I’) show that there was a significant difference of the mean dominant frequency when baseline VF, fast VF, and washout VF occurred (17.9±1.9, 19.1±1.8, and 17.7±1.7 Hz, \(P=0.001\)). In the 7 hearts with transition to slow VF, the mean dominant frequency during fast VF was much higher than during slow VF (19.8±1.5 versus 11.9±2.3 Hz, \(P=0.001\)).

Wavefront Characteristics During VF and VT
Optical mapping data showed that multiple wavefronts were present during both fast VF (Figure 4B) and slow VF (Figure 4D). However, wavefront characteristics in these 2 periods were distinctly different. Both wandering wavelets and organized reentry with a drifting core were present during fast VF. As observed previously for Wiggers’ stage II VF in vivo, wave-wave interaction, wave break, and generation of new
reentry occurred continuously. During slow VF, however, wave-wave interaction and generation of new reentry were rarely observed. In contrast, the mapped area always showed the presence of a single long wavefront or a single epicardial breakthrough, activating repetitively in a similar pattern (i.e., spatiotemporal periodicity). These wavefronts propagated slowly and usually spontaneously ceased to propagate in segments, leading to wave break (Figure 4D and D').

After the transition from fast VF to VT, activation patterns were characterized by either stationary spiral waves (n=7, Figure 4C) or epicardial breakthroughs (n=3). The mean dominant frequency was 17.5±2.2 Hz after 15-minute 0.5 mg/L D600 infusion.

Protocol IB
Effects of TTX on VT
Baseline VF was first induced by burst pacing in all 4 hearts (Figure 5A). After the infusion of 0.5 to 1.0 mg/L D600, the irregular rhythm was consistently converted to VT within 25 minutes (Figure 5B). After TTX (3 μmol/L) infusion, the VT was again converted to an irregular and slow rhythm (TTX-induced slow VF) within 2 minutes (Figure 5C and D). Washout VT and/or VF occurred within 10-minute washout (Figures 2B and 5E). There was a significant difference of the mean dominant frequency between baseline VF and TTX-induced slow VF (18.6±1.0 versus 11.0±1.4 Hz, P=0.0011). Figure 5A' through E', shows typical examples. On the basis of the above findings, slow VF was a result of combined calcium and sodium channel blockades.

Wavefront Characteristics During TTX-Induced Slow VF
Wave-wave interaction and reentry formation were rarely observed. The mapped area always showed the presence of a
single long wavefront, activating repetitively in a similar pattern. These wavefronts also propagated slowly, leading to spontaneous wave break (Figure 5, F and F'). Figure 5, G and G', shows washout VT. There was a stable activation pattern with 2:1 conduction at site a, causing electrogram alternans.

Protocol IIA

Effects of D600 on ERP and APD Dispersion
In all 7 hearts, ERP shortened progressively ($P<0.0001$) with increasing D600 concentrations. At an $S_1$ pacing cycle length of 500 ms, ERPs were 147±14 (baseline), 124±14 (0.1 mg/L), 111±10 (0.5 mg/L), 94±11 (2.5 mg/L), and 91±11 ms (5.0 mg/L). However, D600 had no significant effect on APD dispersion ($P=0.25$, data from hearts 3 through 7). Dispersions of APD$_{90}$ at an $S_1$ pacing cycle length of 160 ms were 19±3 (baseline), 16±2 (0.1 mg/L), 16±3 (0.5 mg/L), 17±2 (2.5 mg/L), and 16±2 ms (5.0 mg/L).

Effects of D600 on APD, CT$^{-1}$, and WL Restitutions
$S_1$ pacing method. Effects of D600 on APD, CT$^{-1}$, and WL restitutions were similar among all 7 hearts. Figure 6, A through C, shows an example. At baseline and 0.1 mg/L, APD restitution was steep but CV estimated from CT$^{-1}$ was fast with flat restitution (Figure 6, A and B). Increasing D600 to 0.5 mg/L flattened APD restitution (Figure 6A). These changes are associated with fast VF-to-VT transition. Further increase of D600 to 2.5 and 5.0 mg/L slowed CV (estimated from CT$^{-1}$) and steepened CT$^{-1}$ restitution. The range of $S_1$ pacing cycle lengths over which CT$^{-1}$ decreased was wider for 5.0 mg/L than for 2.5 mg/L (Figure 6B). These changes were associated with VT-to-slow VF transition. In addition, WL restitution curves continuously shifted downward with infusions of 0.1, 0.5, 2.5, and 5.0 mg/L (Figure 6C). This finding indicates the progressive shortening of WL at increasing D600 concentrations. However, VF occurred both at long WL (low D600 concentration) and short WL (high D600 concentration). Therefore, the absolute value of WL did not determine whether the rhythm was VF or VT. The Table summaries the mean APD$_{90}$ and CT$^{-1}$ in these 7 hearts at different D600 concentrations (including baseline data in hearts 3 through 7) and different $S_1$ pacing cycle lengths.
Effects of D600 on Spatial Heterogeneity of Restitutions

APD Restitution

At baseline, the maximum slope of APD restitution was different among the 4 recording sites (site a, 2.60±0.50; b, 3.08±0.60; c, 1.66±0.34; and d, 2.51±1.10; P=0.040). However, this heterogeneity became insignificant after D600 infusion.

CT⁻¹ Restitution

Although there was no conduction block during S₁ pacing in all hearts studied, CT⁻¹ decreased inhomogeneously at increasing D600 concentrations (Figure 1, F through H). “Maximum CT⁻¹ reduction” was used to estimate the heterogeneity of CT⁻¹ restitution. It was defined as the difference of CT⁻¹ at the longest and the shortest S₁ pacing cycle lengths (see Figure 6B). There was no significant difference of maximum CT⁻¹ reduction along the 4 different lines at baseline, 0.1, and 0.5 mg/L. However, significant heterogeneity occurred at 2.5 mg/L (line 1, 22±8; line 2, 18±5; line

APD₇₀ and CT⁻¹ (Protocol IIA)

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PCL indicates pacing cycle length.
*Baseline data from hearts 3 to 7.
†P<0.05, ‡P<0.01, §P<0.001 by paired t test when compared with the data during 0.1-mg/L infusion.
∥Data from 2 to 6 hearts without statistical comparison (missing data caused by VF induction).

S₁-S₂ method. In the 5 hearts with the S₁-S₂ method for APD restitution determination (as in Figure 6, D through F, D’ through F’), the slope of APD restitution was >1 with short diastolic intervals at baseline (range, 32±6 to 17±7 ms) and 0.1 mg/L infusion (range, 24±4 to 12±6 ms). Furthermore, maximum slope of APD restitution decreased progressively (P<0.0001) with increasing D600 concentrations. Maximum slopes were 2.46±0.83 (baseline), 1.49±0.42 (0.1 mg/L), 0.64±0.24 (0.5 mg/L), 0.27±0.17 (2.5 mg/L), and 0.22±0.12 (5.0 mg/L).

Figure 6. Restitution curves. A through C, APD, CT⁻¹, and WL restitutions determined by S₁ pacing method. Data from heart 6 of protocol IIA. D through F and D’ through F’, APD restitutions determined by S₁-S₂ method. Data from heart 3 of protocol IIA. Note that maximum slope of APD restitution was >1 at baseline and 0.1 mg/L D600 infusion.
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3, 16±3; line 4, 15±4 cm/s; P=0.035) and 5.0 mg/L (line 1, 31±8; line 2, 30±3; line 3, 22±6; line 4, 19±9 cm/s, P=0.020) D600 infusions.

Protocol II B
In all 3 hearts studied, VF (dominant frequency: 10.6, 11.0, and 11.4 Hz) was induced after 15-minute 5.0 mg/L infusion. Washout VT (13.4, 15.3, and 15.5 Hz) was then consistently obtained within 15-minute washout. Immediately after cardioversion of washout VT, neither APD nor CT-1 restitution was steep. They were consistently located at the position between the restitutions obtained at low (0.1 mg/L) and high (5.0 mg/L) D600 concentrations.

Protocol III
None of the 3 drug-free hearts showed spontaneous VF/VT transitions or VF termination during 60-minute perfusion. FFT analyses of pseudo-ECG showed no significant change (P=0.19) of the dominant frequency when baseline VF persisted for 5, 30, and 60 minutes (16.7±0.6, 17.1±0.5, and 16.6±1.0 Hz).

Discussion
This study has the following major findings. (1) Increasing D600 from 0.1 to 0.5 mg/L resulted in flattening of APD restitution and conversion of VF into VT. Further increase of D600 to >0.5 mg/L reduced excitability, decreased CT-1, steepened CT-1 restitution, and converted VT back into VF. (2) VF/VT transitions did not correlate with the absolute value of WL or APD dispersion but correlated well with the steepness of APD and CT-1 restitutions. The presence of spatially heterogeneous restitutions was also associated with VF maintenance. (3) During washout VT, neither APD nor CT-1 restitution is steep. On the basis of these results, we propose that there are 2 types of VF. Fast (type I) VF is associated with a steep APD restitution, normal excitability with a flat CT-1 restitution, and wandering wavelets. Slow (type II) VF is associated with a flat APD restitution, low excitability with a steep CT-1 restitution, and spatiotemporal periodicity. When neither APD nor CT-1 restitution is steep, VF is converted to VT.

VF/VT Transitions: Importance of APD Restitution and Excitability
It is known that APD restitution is important in VF maintenance.1-3 In addition to APD restitution, variations of excitability may also create spatial cycle length variations, causing wave break and VF formation.1 When APD restitution was flattened by D600 without depressing excitability or steepening CT-1 restitution, fast VF converted to VT. However, when excitability was depressed such that CT-1 restitution became steep with higher D600 concentrations, VT again converted back to slow VF. Pseudo-ECG of slow VF demonstrated a highly irregular and polymorphic rhythm diagnostic of fibrillation (Figure 3G). More importantly, this VT-to-VF transition occurred while APD restitution remained relatively flat. These results suggest that reduced excitability leading to steep CT-1 restitution contributes to VF maintenance. Compatible with this notion, TTX depressed fast Na+ inward current and reduced excitability, converting a preexisting VT into an irregular and slow rhythm (Figure 5, C and D).

Indicators of CT-1 Restitution for VF Maintenance
In Figure 6B, the steepness of CT-1 restitution is slightly greater for 2.5 mg/L than for 5.0 mg/L. The range of S1 pacing cycle lengths over which this curve descends, however, is wider for 5.0 mg/L. These findings suggest that the range over which this curve descends might be a better indicator than the steepness for VF maintenance.

Two Types of VF
In this study, activation patterns of slow VF were very different from those of fast VF. Fast VF (dominant frequency: 19.1±1.8 Hz) was characterized by wandering wavelets and organized reentry with short life spans. Slow VF (11.9±2.3 Hz), however, rarely showed wave-wave interaction or epicardial reentry. Rather, the mapped area always showed a single long wavefront or a single epicardial breakthrough emerging from the same region repetitively. As this wavefront propagated outward, it frequently developed wave breaks at some locations, suggesting fibrillatory conduction block. Chen et al previously reported that VF in rabbit hearts had a wide range of activation rates (dominant frequency, 7.0 to 20.1 Hz). Like us, they also observed significant spatiotemporal periodicity during slow VF (9.9 Hz).

Implications for Mechanisms of VF
Two major hypotheses have been proposed to explain cardiac fibrillation. One is the multiple-wavelet hypothesis,8 and the other is the focal-source hypothesis.9 In support of the multiple-wavelet hypothesis, computerized mapping studies have documented that VF is characterized by the presence of multiple wandering wavelets in the hearts of large animals.5,6,10 Both steep APD restitution and preexisting heterogeneities play synergistic roles in creating wave breaks that maintain VF.1,5,11 Organized reentrant wavefronts (rotors) have short life spans because of their intrinsic dynamic instability as well as outside interference. In support of the focal-source hypothesis, Jalife et al12 hypothesized that a fairly stable mother rotor may serve as a source of fast focal activation. Because of its fast rate, wavefronts emerging from the mother rotor develop conduction block. Unlike the multiple-wavelet mechanism, however, wave breaks are epi-phenomena and are not essential for VF maintenance. These 2 hypotheses are thought to be competing rather than complimentary mechanisms of VF.13,14

On the basis of the results of this study, we propose that these 2 mechanisms are both important in understanding VF maintenance. At baseline, with a steep APD restitution and normal excitability, the mechanism of VF is compatible with the multiple-wavelet hypothesis. However, when excitability is depressed and CT-1 restitution steepens, because of either drugs or ischemia,15,16 the focal-source (mother-rotor) mechanism may gain increasing importance. Under these conditions, complex patterns of electrical activation associated with fibrillatory conduction block promote the electrocardiographic appearance of VF.
Clinical Implications
Our findings may partially explain Wiggers’ 4 stages of VF. Wiggers’ stage I VF resembles VT. Because of a steep APD restitution, VT degenerates into multiple-wavelet (Wiggers’ stage II) VF. Drugs that flatten APD restitution may prevent this degeneration. As ischemia progresses, reduced excitability may convert fast (Wiggers’ stage II) VF into slow (Wiggers’ stages III and IV) VF. For the latter 2 stages of VF, flattening APD restitution alone might not be a useful intervention.

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