A Mechanism of Transition From Ventricular Fibrillation to Tachycardia
Effect of Calcium Channel Blockade on the Dynamics of Rotating Waves

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Abstract—Abbreviation of the action potential duration and/or effective refractory period (ERP) is thought to decrease the cycle length of reentrant arrhythmias. Verapamil, however, paradoxically converts ventricular fibrillation (VF) to ventricular tachycardia (VT), despite reducing the ERP. This mechanism remains unclear. We hypothesize that the size and the dynamics of the core of rotating waves, in addition to the ERP, influence the arrhythmia manifestation (ie, VF or VT). The objectives of this study were (1) to demonstrate functional reentry as a mechanism of VF and VT in the isolated Langendorff-perfused rabbit heart in the absence of an electromechanical uncoupler and (2) to elucidate the mechanism of verapamil-induced conversion of VF to VT. We used high-resolution video imaging with a fluorescent dye, ECG, frequency and 2-dimensional phase analysis, and computer simulations. Activation patterns in 10 hearts were studied during control, verapamil perfusion (2×10^{-6} mol/L), and washout. The dominant frequency of VF decreased from 16.2±0.7 to 13.5±0.6 Hz at 20 minutes of verapamil perfusion (P<0.007). Concomitantly, phase analysis revealed that wavefront fragmentation was reduced, as demonstrated by a 3-fold reduction in the density of phase singularities (PSs) on the ventricular epicardial surface (PS density: control, 1.04±0.12 PSs/cm²; verapamil, 0.32±0.06 PSs/cm² [P=0.0008]). On washout, the dominant frequency and the PS density increased, and the arrhythmia reverted to VF. The core area of transiently appearing rotors significantly increased during verapamil perfusion (control, 4.5±0.6 mm²; verapamil, 9.2±0.5 mm² [P=0.0002]). In computer simulations, blockade of slow inward current also caused an increase in the core size. Rotating waves underlie VF and VT in the isolated rabbit heart. Verapamil-induced VF-to-VT conversion is most likely due to a reduction in the frequency of rotors and a decrease in wavefront fragmentation that lessens fibrillatory propagation away from the rotor. (Circ Res. 2000;86:684-691.)

Key Words: arrhythmia ■ fibrillation ■ tachycardia ■ verapamil ■ optical mapping

Recent, several studies addressed VF-to-VT transitions by studying the role of action potential duration (APD) and/or effective refractory period (ERP) on fibrillatory dynamics. Studies with potassium channel openers, cromakalim and acetylcholine respectively, showed that ERP shortening increases the vulnerability to reentry and accelerates its rate. In contrast, APD prolongation by tedisamil, an I_{Ca} and I_{K} blocker, increases both the spatial coherence and temporal regularity of VF. Similarly, dofetilide, an I_{K} blocker, increases the APD and ERP while slowing or suppressing VT.

Previously, Watanabe and Uchida and Watanabe et al reported that rapid ventricular stimulation in isolated rabbit hearts in the presence of verapamil, a calcium channel blocker, resulted in the induction of sustained monomorphic
VT (MVT). The induction of VT rather than fibrillation despite a reduction of ERP by verapamil seemed paradoxical, suggesting that parameters besides tissue refractoriness may play a role. We hypothesized that the size and dynamics of the core around which reentrant waves rotate, as well as refractoriness, may determine whether the arrhythmia manifests as VF or MVT. Our objectives were to (1) demonstrate functional reentry as a mechanism of VF and MVT in the isolated Langendorff-perfused rabbit heart in the absence of an electromechanical uncoupler and (2) elucidate the mechanism of verapamil-induced conversion of VF to MVT.

Materials and Methods

Langendorff-Perfused Rabbit Heart and Experimental Setup

Isolated rabbit hearts were immersed in a chamber and perfused via a cannula in the aorta with warm (36.5±1°C), oxygenated Tyrode’s solution (control) or Tyrode’s solution containing 2×10−6 mol/L verapamil. During VF, motion was eliminated by an adjustable glass wall, which gently restrained the heart against the chamber. Electromechanical uncouplers were not used. A volume-conducted ECG was recorded from 2 leads in the chamber. A bolus of 15 mL of the dye, di-4-ANEPPS (10 μg/mL), was injected into the aorta. Light (535 nm) was shone on the epicardial surface of the heart; the emitted fluorescence (590 nm) was acquired by a charge-coupled device camera at 120 frames per second. The background fluorescence was subtracted from each frame, and low-pass spatial filtering was applied. Optical recordings were 3 to 4 seconds in duration.

Phase Analysis and the Measurement of Core Area

Phase analysis was used to quantify the extent of wavefront fragmentation by determining the number of phase singularities (PSs). PSs are easily identified as sites where all phases converge, and the continuous spatial phase change reflects the processes of excitation, recovery, and diffusion.

Reentrant spiral waves were identified, and the sizes of their cores were measured by tracing the path of the “pivoting point” where the front and tail meet. The trajectory of this point is a closed loop, and the region within this loop is equivalent to the area of the core.

Experimental Protocols

VF and MVT

In 10 normal hearts, VF was induced by burst pacing of the left ventricular epicardium. Verapamil perfusion was initiated after 5 minutes of control recordings. After 30 minutes of verapamil, the heart was perfused and superfused with control solution once again (washout).

ERP and Conduction Velocity (CV)

The ERP was determined in 8 additional hearts via programmed stimulation (2 times diastolic threshold) at several cycle lengths (CLs) during control and verapamil perfusion. In 4 hearts, local CV was determined at pacing CL of 300 ms during control and verapamil perfusion.

VF and MVT Analysis

For PS analysis, 10 control VF recordings (obtained 5 minutes after induction) and 10 MVT recordings (obtained 20 minutes after verapamil perfusion) were identified. For determination of core areas, all recordings obtained during the first 5 minutes of VF and within 20 to 30 minutes of verapamil perfusion were analyzed, and all spirals were identified and their cores measured.

Results

Analysis of Frequency Changes

Verapamil perfusion during VF resulted in the rapid conversion of the arrhythmia to sustained MVT in all 10 hearts within 10 to 20 minutes. Figure 1A is an example of ECG recordings and their frequency spectra from an experiment. The ECGs during control and washout are irregular, with characteristic VF-like frequency spectra. Verapamil con-
verted VF to MVT, as indicated by the change in pattern of the ECG and the transformation of the frequency spectrum from multiple peaks (VF) to a single peak with its harmonic (MVT). Frequency analysis also demonstrated that VF-to-MVT transition was accompanied by a decrease in the dominant frequency (DF) (ie, the frequency at which maximum power occurred) from 17.01 Hz (control) to 11.64 Hz (verapamil) and an increase during washout to 16.08 Hz. Quantification of the frequency changes in the 10 hearts is illustrated in Figure 1B. With the VF-to-VT conversion, the DF in the power spectrum decreased from 16.2±0.7 to 13.5±0.6 Hz (P<0.007). Washout of verapamil resulted in the conversion of VT to VF and an increase in the DF to near control values (15.9±0.9 Hz after 10 minutes of washout, P=NS versus control).

Imaging of Verapamil-Induced Changes in Dynamics of VF

Video imaging of the anterior surface of the ventricles elucidated the effects of verapamil on wave dynamics during VF. Figure 2 shows ECGs, isochrone, and phase maps from 1 heart. The VF dynamics during both control and washout conditions were complex. Isochrone maps of VF (Figure 2B) show a short-lived high-frequency rotor during control (rotation period, 54.6 ms, corresponding to 18.3 Hz) and washout (rotation period, 65.4 ms, corresponding to 15.3 Hz). Propagation during VF was inhomogeneous, suggesting that breakup of waves propagating away from the rotors resulted in disorganized activity that is characteristic of VF. During verapamil, a slower rotor (rotation period, 84.0 ms, corresponding to 11.9 Hz) is present at the base of the heart. In contrast to VF, propagation during MVT was less fragmented and more repetitive. These data strongly suggest that with the reduction of the rotor frequency, propagation becomes less fragmented, thus manifesting as MVT.

This notion is further supported through the quantification of PSs. Figure 2C shows phase maps depicting the phase at an instant in time during the rotation of the rotors in Figure 2B. The asterisks represent PSs that are formed when breaks occur in the propagating waves after collisions with refractory tails of other waves or obstacles.4 PSs occasionally represent a center of rotation (white circles). However, more often they indicate the fragmentation of the mother waves into daughter wavelets. The daughter wavelets may be bound on each end by a PS, a PS and a boundary, or 2 boundaries.4 The phase maps in this episode demonstrate that during control VF, 6 PSs coexist on the anterior surface of the ventricles that give rise to at least 3 daughter wavelets. However, during verapamil, only 1 PS is observed, clearly demonstrating that propagation was less fragmented. During washout, once again 6 PSs are present, suggesting that the dynamics were complex and similar to those of control VF.

Figure 2D shows the quantification of PS density in all 10 experiments. For each experiment, a 500-ms episode of arrhythmia during control (5 minutes after VF induction), after 20 minutes of verapamil perfusion, and during washout was chosen at random and analyzed. There was a significant decrease in the PS density during verapamil perfusion. During VF, in control conditions and washout, the mean PS density was 1.04±0.12 and 0.96±0.15 PSs/cm², respectively (P=NS versus control), whereas during MVT the mean decreased to 0.32±0.06 PSs/cm² (P=0.0008). These data clearly suggest that the decreased breakup of activity is likely the result of the slower rate of the arrhythmia, further supporting the idea that the spatially and temporally periodic activity during MVT is the result of more homogeneous and less fragmented propagation.

Functional Reentry: Mechanism of VT

Additional support for the notion that MVT, with verapamil, resulted from functional reentry was obtained from a heart in which different ECG morphologies were observed during MVT (Figure 3). In Figure 3A and 3B, reentrant waves rotate around cores located in different regions of the anterior surface of the ventricles. In Figure 3C, the core is outside the viewing area, but the waves emanating from the apex are
likely to be from a reentrant circuit. The transition to a different QRS pattern, with minimal change in the CL, may be attributed to a change in the position of the core with respect to the fixed position of the ECG lead.

It has been shown that the rotation period of a reentrant source determines the DF of the ECG. Consequently, to further confirm that functional reentry is the underlying mechanism for VT, the rotation periods of 5 spirals identified during MVT were correlated with the inverse of the DF of the power spectrum of the corresponding episodes of MVT.

Conduction Velocity

Frequency analysis shows that conversion of VF to VT was accompanied by a decrease in the DF of the arrhythmia. Possible mechanisms for such a decrease include (1) the rotating waves traveling along a longer trajectory, ie, increase in core size, or (2) a decrease in the CV of rotating waves. Previous reports show that in addition to blocking L-type calcium current, verapamil also partially blocks sodium currents and reduces CV. To determine the effect of verapamil in our system, local CVs were measured in a group of 4 hearts. During pacing (CL = 300 ms), verapamil had a minor effect on CV. \( CV_{max} \) decreased slightly from 54.4±2.2 cm/second during control to 49.2±2.8 cm/second at 20 minutes of verapamil perfusion, but this difference was not statistically significant. Similarly, \( CV_{min} \) decreased from 35.5±2.1 to 30.8±2.0 cm/second (\( P = \text{ns} \)).

Measurement of Core Dimensions

Without a reduction in CV, the most probable mechanism for verapamil-induced decrease in the arrhythmia frequency is an increase in core size. Thus, we measured the core dimensions of several rotors during the first 5 minutes of control and after 20 minutes of verapamil perfusion. Figure 4A shows 2 representative ECG traces and their corresponding isochrone maps delineating the core of a spiral during control and verapamil perfusion. In this example, in control, the core is small (4.58 mm\(^2 \)), but during verapamil perfusion the core area increases by >2-fold (9.56 mm\(^2 \)). To illustrate the reliability of the core delineation criteria, we show optical action potentials in Figure 4B. Clearly, the amplitude of the optical action potentials within the core (Figure 4B-I) when the spiral is present (represented by the solid black line) is <50% of maximum (50% line is the dashed thin line), whereas, in the perimeter of the core (Figure 4B-II), the amplitude is slightly more than 50%, and at a distance from
the core (Figure 4B-III), it is significantly larger than 50% of maximum.

The quantification of the core area is shown in Figure 5. Significant increases in core area were seen with verapamil perfusion. During VF, in control conditions, the cores had a mean area of 4.5±0.6 mm² (n=7). After 20 minutes of verapamil perfusion, the mean core area more than doubled and measured 9.2±0.5 mm² (n=5; P=0.0002). Consistently, with the increase in core area, we observed a lengthening of the rotation period from 60.5±1.5 (control) to 79.7±5.6 ms (verapamil) (P=0.003). These data demonstrate that the slowing of the VF frequency during verapamil perfusion most likely is the result of the pivoting point of the spiral traveling a longer distance to complete a rotation due to an increased core size.

Effective Refractory Period

Verapamil decreases the ERP and APD. Therefore, the conversion of VF to VT seemed paradoxical. To confirm that verapamil has a similar effect in our experimental model, in a group of 8 hearts, we studied its effect on ERP. Figure 6 shows a plot of ERP versus CL (S1-S1 interval). At every CL tested, verapamil reduced the ERP (P=0.012) by 7% to 9% from control values. Specifically, at the CLs of 250, 200, and 180 ms, the ERP changed from 161.3±4.8, 152.5±2.5, and 142.5±4.9 ms to 150±5.6 (P=0.026), 142.5±4.8 (P=0.025), and 130±4.1 ms (P=0.008), respectively.

Computer Simulations

To further demonstrate that calcium channel blockade is responsible for the increase in core size and the subsequent increase in the rotation period, we carried out computer simulations of sustained spiral wave reentry. Figure 7 shows 3-dimensional representation of 2 stable spiral waves rotating around an elliptical core. Data are presented under control conditions (Iₛᵢ=100%). Rotation period was 133 ms, and core area at the −30 mV isopotential was 17.5 mm². B, Reduction of Iₛᵢ to 75% of control increases the core area to 23.5 mm² (at −30 mV isopotential) and the rotation period to 148 ms. C, Comparison of core sizes obtained at Iₛᵢ=100% and Iₛᵢ=25%.

Figure 5. Quantification of core areas during control and 20 minutes after verapamill perfusion.

Figure 6. Effect of verapamil on ERP. ERP was determined at CLs of 250, 200, and 180 ms. At every CL tested, verapamil reduced the ERP (P=0.012) by 7% to 9% from control values.

Figure 7. Effects of Iₛᵢ reduction on core size and rotation period during sustained rotating activity in an anisotropic 2-dimensional model of Luo-Rudy²⁶ cells. A, Three-dimensional representation of a rotating wave under control conditions (Iₛᵢ=100%). Rotation period was 133 ms, and core area at the −30 mV isopotential was 17.5 mm². B, Reduction of Iₛᵢ to 75% of control increases the core area to 23.5 mm² (at −30 mV isopotential) and the rotation period to 148 ms. C, Comparison of core sizes obtained at Iₛᵢ=100% and Iₛᵢ=25%.
of $I_{\text{Na}}$ on curvature-related failure of propagation toward the center of the core. In accordance with the theory, the reentrant wavefront forms a spiral shape and exhibits increasing curvature until a pronounced curvature is developed close to the spiral tip. Here the wavefront fails to activate tissue ahead. In this manner propagation toward the center of the spiral fails (ie, conduction block). Therefore, to determine the effect of $I_{\text{Na}}$ on propagation toward the center of the spiral, we measured curvature at the site of maximum curvature. We found that $I_{\text{Na}}$ blockade results in the earlier development of conduction block (ie, propagation toward the center of the core fails earlier), as indicated by the reduction of curvature ($\approx 9\%$ along and across fibers, respectively) at this site. Thus, the simulations show that the block of $I_{\text{Na}}$ reduces the APD and increases the rotation period of the spiral through an increase in the core size. The measured electrophysiological parameters are summarized in the Table.

### Discussion

This study demonstrates that verapamil in the isolated Langendorff-perfused rabbit heart transforms VF to MVT despite a decrease in the ERP. We have, for the first time, shown that verapamil-induced increase in the size of the core of rotating waves is a likely mechanism underlying such a transformation. The resultant lowering of the rotor frequency decreases fibrillatory propagation emanating from reentrant sources and is ultimately responsible for transforming the arrhythmia. Thus, the results demonstrate that, in addition to tissue refractoriness, the size of the core of rotating waves is likely an important factor that determines whether the arrhythmia is VF or MVT.

### Rotors During Fibrillation and Tachycardia

The study of wave propagation in the heart has explained VF in terms of self-organized 3-dimensional electrical rotors\textsuperscript{11} that may destabilize (ie, break up) and give rise to fibrillation.\textsuperscript{10,12} Recently, it has been proposed that fibrillation, at least in the atria, may depend on the uninterrupted periodic activity of discrete reentrant sites.\textsuperscript{8,9} The shorter reentrant circuits act as sources that maintain the overall activity. Chen et al\textsuperscript{9} provided further support for the notion that fibrillatory conduction may be also underlying VF in the isolated rabbit heart. They demonstrated that the rapidly succeeding wavefronts emanating from periodic sources propagate throughout the ventricles and interact with anatomic and functional obstacles, leading to fragmentation and wavelet formation. In the present study, we provide additional evidence that disordered activation sequences, characteristic of VF, may be the result of fibrillatory conduction. Furthermore, we show that frequency of the source is an important determinant of the overall manifestation of the arrhythmia.

### VF-to-VT Transitions

One possible mechanism for the VF-to-VT conversion is the anchoring of a rotor to a discontinuity or defect in the cardiac muscle (eg, blood vessel).\textsuperscript{22} However, Figures 2 and 3 demonstrate that functional reentry is underlying both VF and MVT. Furthermore, the VT-to-VF transition (Figure 2) during washout further supports our contention that reentry was functional rather than anatomic. In a functional reentrant circuit, the frequency of the source to a large extent determines whether the overall manifestation is disorganized fibrillation or organized tachycardia. VF results when the cardiac tissue is unable to keep up with the source and there is breakup of activity, ie, fibrillatory conduction. However, if the source frequency is sufficiently slow, then the emanating wave will not break up, in which case tachycardia rather than fibrillation may be observed.

### Increase in Core Size May Result in VF-to-VT Transition

We demonstrated that the dominant frequency of VF decreases from 16.2 Hz during control to 13.5 Hz after 20 minutes of verapamil perfusion (Figure 1). Simultaneously, there was a significant increase in the core area from 4.5 mm\textsuperscript{2} (control) to 9.2 mm\textsuperscript{2} (verapamil) (Figure 5). These data suggest that during verapamil perfusion, the pivoting point of the spiral wave traveled a longer distance to complete a rotation, which led to an increase in its period and a slowing in the rate of VF. To ensure that the decrease in frequency is due to a longer path length and not to slowing of propagation, we measured local CVs during control and verapamil and found that verapamil does not alter propagation velocity. Therefore, this suggests that the lower frequency is the result of the longer trajectory followed by the tip of the rotor rather than slower propagation.

### Verapamil-Induced Increase in Core Size: Mechanisms

#### Sodium Currents and Core Size

The core of a rotating wave is formed under conditions determined by the kinetics of the sodium current and curvature-related block of conduction.\textsuperscript{31,32} Experimental and numeric studies in isolated cardiac muscle\textsuperscript{11} and other excitable media\textsuperscript{32} show that when excitability is normal, the critical radius of curvature is small; thus, reentrant circuits manifest as rotors moving rapidly around small cores. However, when excitability is lowered (eg, decreased conductance), the critical radius is large, thus resulting in the increase in the core size and rotation period. Our data suggest that verapamil does not significantly alter CV. Nevertheless, we cannot discount a minor blocking action of verapamil on sodium channels at high frequencies that can result in the block of conduction at a lesser curvature (ie, larger critical radius),\textsuperscript{31} thus contributing to an increase in the size of the core.

#### Calcium Current and Core Size

Our simulation demonstrates that by blocking $I_{\text{Ca}}$, the core of the spiral wave is altered. This suggests that calcium currents...
also influence the core dynamics. Rohr et al\textsuperscript{33} showed that in the presence of reduced electrical coupling, the calcium current is necessary for sustained propagation. Similarly, a modeling study analyzing the currents involved in intercellular communication presented additional evidence for the role of the calcium current during such conditions.\textsuperscript{34} Recently, Laurita et al\textsuperscript{35} used imaging techniques that concurrently measured calcium transients and transmembrane potentials and demonstrated that calcium is a major contributor to transmembrane potential at sites of slow propagation (eg, site of steep wavefront curvature). We suggest that curvature effects at the core produce a load similar to those observed during reduced coupling. Therefore, verapamil-induced block of calcium current causes conduction to block at a lesser curvature resulting in the increase in core size.\textsuperscript{21} We have confirmed the effect of calcium channel blockade on curvature through computer simulations and have shown that in our model, 75\% block of the $I_{\text{ca}}$ resulted in reduction of curvature at the core by 10\% along and across fibers, respectively. Therefore, the mechanism for the increase in the size of the core may be the block of conduction at a lesser curvature.

**Effect of Wavelength/APD on Reentry**

Wavelength shortening is believed to increase the vulnerability to reentry and accelerate its rate, whereas an increase in wavelength has the opposite effect.\textsuperscript{13,14} Therefore, induction of high-frequency VF would be expected with verapamil. However, measurements of wavelength are not the only predictors of the behavior of the system once reentry has been established.\textsuperscript{37,38} Recent computer simulations\textsuperscript{39} show that during functional reentry both APD and wavelength change as functions of distance from the core. Similarly, experiments demonstrate that both APD and wavelength change dynamically depending on the orientation of propagation with respect to the fiber axis.\textsuperscript{40} Hence, what finally determines the arrhythmia expression (ie, VF or VT) is not simply APD or wavelength. Rather, it depends on the intricate interplay among the curvature effects, dynamics of the core, and the APD or ERP.

**Can a Decrease in APD Organize Fibrillatory Activity?**

On the basis of long-held views,\textsuperscript{13,14,36} it is expected that APD shortening leads to more rapid and disorganized reentrant activity. However, if the core of a rotating wave becomes larger and the arrhythmia frequency decreases, then the reduction of APD enables increased organization. Previous studies show that spiral wave drift is a contributor to the complexity of the ECG patterns during VF.\textsuperscript{3} In such a case, as predicted by theory,\textsuperscript{41} increasing the wavelength causes a spiral wave to drift secondary to the collision of the wavefront with the refractory tissue ahead. The opposite effect is expected if the APD shrinks; that is, the spiral drift decreases as a result of decreased wavefront interactions with fully or partially refractory tissue. Our experimental results and computer simulations demonstrate that verapamil abbreviates the ERP, thereby decreases the chance of waves interacting with refractory tails of previously propagating waves, and thus slows the speed of drift and gives rise to a more uniform ECG pattern. In addition to causing drift, inhomogeneities in electrophysiological properties may also result in the formation of wavebreaks when collisions occur. Using a new technique\textsuperscript{4} (phase analysis), we have quantified the formation of new wavebreaks (Figure 2) that result when collisions occur. Our experiments show that there are 3 times as many PSs formed during VF as compared with MVT. This does not necessarily imply that these new wavebreaks are the “sources” that maintain fibrillation.\textsuperscript{4} However, it does strongly suggest that the complex spatiotemporal patterns of excitation in the heart evident during VF are the consequence of more fragmented propagation, whereas MVT is the result of more uniform propagation.

It is also probable, as speculated by Riccio et al,\textsuperscript{30} that verapamil-induced changes in the restitution kinetics may play a role in preventing spiral wave breakup and thereby prevent induction of VF in the presence of verapamil and also convert VF to MVT. Such mechanisms, however, do not account for the frequency reduction that is accompanied by VF-to-MVT transition in our study.

**Technical Aspects and Limitations**

**Experimental.** The high spatial resolution and the large field of view of the video camera provide an invaluable tool for the study of arrhythmias in the isolated heart. However, there are limitations to this approach that should be noted.\textsuperscript{3,20,22} Mechanical artifacts are among the major limitations of video-imaging systems. However, during VF, contraction is uncoordinated and weak, and with minimal restraining these artifacts can be eliminated; this alleviates the need to use electromechanical uncouplers. Therefore, in these experiments, we placed the heart between 2 glass plates and applied moderate levels of pressure and nearly eliminated motion. Another limitation is that the video imaging system has low signal-to-noise ratio, which requires spatial filtering, resulting in a reduced effective spatial resolution of the system.\textsuperscript{20}

**Computer Simulations**

Computer simulations of 2-dimensional reentry were performed using the 1991 version I of the Luo-Rudy model.\textsuperscript{26} This model is limited in that $I_{\text{ca}}$ is not an accurate description of calcium current in ventricular myocytes. Furthermore, version I of the model does not incorporate mechanisms for the regulation of the intracellular concentrations of ions. Newer and more elaborate ionic models of cardiac excitation exist.\textsuperscript{42} However, these models require large amounts of computation time and are mostly empirical. Thus, our approach represents a good tradeoff between computational expense and description of ionic mechanisms.

**Conclusions**

Here, we demonstrated that functional reentry underlies VF and MVT in the isolated Langendorff-perfused rabbit heart. Furthermore, verapamil-induced VF-to-MVT conversion likely occurs as the result of an increase in the size of the core of rotating waves that may lead to a decrease in the rotor frequency and a reduction in fragmentation of the excitation wavefronts.
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