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Arrhythmogenesis in the heart: Multiscale modeling of the effects of defibrillation shocks and the role of electrophysiological heterogeneity

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Abstract

The mechanisms of initiation of ventricular arrhythmias as well as those behind the complex spatiotemporal wave dynamics and its filament organization during ventricular fibrillation (VF) are the topic of intense research and debate. Mechanistic inquiry into the various mechanisms that lead to arrhythmia initiation and VF maintenance is hampered by the inability of current experimental techniques to resolve, with sufficient accuracy, electrical behavior confined to the depth of the ventricles. The objective of this article is to demonstrate that realistic 3D simulations of electrical activity in the heart are capable of bringing a new level of understanding of the mechanisms that underlie arrhythmia initiation and subsequent organization. The article does this by presenting the results of two multiscale simulation studies of ventricular electrical behavior. The first study aims to uncover the mechanisms responsible for rendering the ventricles vulnerable to electric shocks during a specific interval of time, the vulnerable window. The second study focuses on elucidating the role of electrophysiological heterogeneity, and specifically, differences in action potential duration in various ventricular structures, in VF organization. Both studies share common multiscale modeling approaches and analysis, including characterization of scroll-wave filament dynamics.

Sudden cardiac death, due primarily to ventricular arrhythmias, is a major public health issue in the industrialized world. In the United States only, it results in over 350 000 deaths each year. Delivery to the heart of a strong electrical shock is currently the only effective means for prevention of sudden cardiac death, a procedure that is painful and could result in myocardial dysfunction and damage. A significant obstacle to improving treatment of ventricular arrhythmia is our limited understanding of both the mechanisms by which the arrhythmia is maintained in the heart and the mechanisms by which an electric shock interacts with the fibrillating heart. Experimental investigation of the electrical behavior in the heart has a limited scope because current experimental techniques cannot document with certainty electrical events in the depth of the cardiac wall. This article offers an alternative approach to the study of arrhythmia generation and termination in the heart: realistic three-dimensional multiscale modeling of electrical activity in the heart. It demonstrates that such modeling is a powerful

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tool in uncovering new electrophysiological insights that could be used to further the development of new anti-arrhythmia therapies.

I. INTRODUCTION

Sudden cardiac death is most commonly caused by ventricular fibrillation (VF), which is characterized by the presence of one or more reentrant circuits.¹ During reentry, action potentials circulate around a central core and are able to continually activate recovered tissue. In the heart, a reentrant wave is a scroll rotating around a filament, its three-dimensional (3D) organizing center.² The mechanisms of VF initiation as well as those behind the complex spatiotemporal wave dynamics and its filament organization during VF are the topic of intense research and the subject of much discussion and debate.

Defibrillation of the heart by timely application of a strong electric shock is now recognized as the only effective means for VF termination and prevention of sudden cardiac death. A large body of research has demonstrated that defibrillation failure and induction of VF by electric shocks are driven by the same mechanisms.^{3–5} Induction of VF by an electric shock applied during the vulnerable window (VW) is also rapidly becoming a standard clinical practice during implantation of internal cardioverter/defibrillators or postoperative defibrillation threshold testing. Nonetheless, the mechanisms by which the shock induces VF remain incompletely understood.

Experimental observations of arrhythmia induction and its subsequent organization are hampered by the inability of current experimental techniques to resolve, with sufficient accuracy, electrical behavior confined to the depth of the ventricular walls. Multiscale modeling and simulation of electrical behavior in the 3D heart that incorporate detailed biophysical representations of the nonlinear membrane kinetics are now becoming commonplace. The objective of this article is to demonstrate that realistic 3D simulations of electrical activity in the heart are not only possible, but are also capable of bringing a new level of understanding of the mechanisms that underlie arrhythmia initiation and VF maintenance. Specifically, the article does this by presenting the results of two multiscale simulation studies. The first study aims to uncover the mechanisms responsible for rendering the ventricles vulnerable to electric shocks during a specific interval of time, the VW. The second focuses on elucidating the role of action potential duration (APD) heterogeneity in the ventricles in VF organization. Both studies employ common modeling approaches and analysis, including characterization of filament dynamics as presented below.

II. MULTISCALE MODELING OF ELECTRICAL BEHAVIOR IN THE VENTRICLES

Over the last several years, our laboratory has developed a 3D finite-element bidomain model of the rabbit ventricles for use in electrophysiological studies, including defibrillation. The model has been described in detail in our recent publications.^{6–10} Here we briefly outline its major components.

A. Description of myocardial geometry and fiber architecture

Our 3D model of anatomically based rabbit ventricular geometry and fiber orientation uses the UCSD geometrical model of the rabbit ventricles¹¹ (original data available at <http://www.continuity.ucsd.edu/Continuity>). Whenever necessary, the ventricles are immersed in a conducting bath representing the perfusing chamber in which an experimental preparation is suspended. Ventricular surfaces and volumes are represented as unstructured triangular and tetrahedral meshes, respectively, with an average element edge length of 300 to 500 μm in the

tissue and 1 mm in the cavities and the perfusing bath. The fiber orientation is defined at the centroid of each tetrahedron. Local material properties are assigned to each element using the fiber orientations. Figure 1(a) illustrates the 3D geometry and fiber orientation in our rabbit ventricular model.

B. Tissue representation

Mathematical description of cardiac tissue in the rabbit ventricular model is based on the bidomain representation, which considers the tissue composed of intra- and extracellular spaces separated by a membrane. The bidomain allows representation of the extracellular/interstitial space in the myocardium and thus, an explicit representation of any volume conductor that might be in contact with the tissue. Such representation is appropriate for studies of VF organization and arrhythmia induction with electric shocks. In the rabbit ventricular model, the myocardium is characterized with unequal anisotropy ratios in the intra- and extracellular conductivities. The potentials in the ventricular cavities and the perfusing bath are governed by the Laplace's equation; conductivities in these domains are assigned the value of blood.

Numerical solutions for the bidomain equations employed the semi-implicit finite element method.^{8,10,12}

C. Representation of ionic currents and membrane electroporation

Our multiscale models of arrhythmogenesis in the heart incorporate detailed representation of membrane kinetics, typically represented by a system of ordinary differential equations. In the present study on the role of APD heterogeneities in VF organization, we used simple, eight-state variable model of the electrophysiological processes that underlie the formation of the action potential, namely a modified version of the Luo-Rudy 1 (LR1) model.¹³ The reasons for the modification of the ionic model from its original version are the following. A single-cell electrophysiological study by Samie *et al.*¹⁴ have shown that LV myocardial cells have larger background potassium current as compared to RV cells. The study by Samie *et al.* incorporated spline functions in the LR1 model (available at the journal website) to represent the experimental current-voltage relationship the authors obtained for isolated LV and RV cells. Fig. 1(b) presents the single cell action potential resulting from the two modified models, referred to in the rest of the text as LR1(LV) and LR1(RV), and implemented here to represent cells in regions of short and long APD. The larger potassium current in the LR1(LV)IK1 channel causes the APD shortening. Fig. 1(c) shows the division of our rabbit ventricular model into LV and RV regions (regions of short and long APD); it is based on data from Jalife's lab on perfusion of the heart via the left coronary artery that shows dye saturation only of the RV and septum,¹⁵ thus providing a natural demarcation between the two regions. Transmural differences in cell electrophysiology was not taken into account here since they are not believed to contribute to the differences in VF organization between LV and RV, as observed experimentally.¹⁶ To gain a better understanding of the effects of APD heterogeneity on VF organization, we also analyze the characteristics of VF in homogeneous ventricular models consisting of only LV (short APD) and only RV (long APD) cells.

For studies examining the effects of shocks on the ventricles, membrane models are typically modified to ensure stability during the shock,¹⁷ when a dramatic change in transmembrane potential takes place. It is important to understand, however, that shocks induce complex changes in transmembrane potential, some of which have been consistently observed in experiments, but never reproduced by membrane models, mostly because membrane models were developed for the study of action potential conduction and arrhythmogenesis and not defibrillation. Based on a version of the Luo-Rudy dynamic (LRd) model,¹⁸ we recently developed the aLRd membrane model that can accurately reproduce the membrane responses to shocks.¹⁹ The aLRd model also incorporates an ordinary differential equation representing

the creation of membrane pores under high-strength electric fields (electroporation) and the subsequent resealing of these membrane pores.¹⁹ The aLRd model is employed here in the study of arrhythmia initiation with electric shocks.

D. Shock electrodes and waveforms

In the study of arrhythmia induction with electric shocks, shock electrodes are represented as 3D isocurrent density or isovoltage surfaces within the 3D computational grid (ventricles plus perfusing bath and blood in cavities); these are chosen to mimic geometry and location of electrodes in optical mapping experiments. The example in this article uses external plate electrodes (4.30 cm × 3.74 cm separated by 3.92 cm at the boundaries of the perfusing chamber) [Fig. 1(d)] represented as isovoltage surfaces. The waveforms used in our vulnerability study are (truncated exponential) monophasic shocks of 8 ms duration and 65% tilt.^{10,20,21} Shock polarity is referred to as RV⁻ when the RV was the cathode, and the one near the LV was a grounding electrode. The opposite polarity is referred to as LV⁻. Shock strength refers to the leading-edge value of the electric field between electrodes.

E. Analysis of spatiotemporal dynamics of reentrant circuits

To better analyze arrhythmogenesis and arrhythmia organization in the rabbit ventricles, we developed postprocessing^{19,22} that allows us to investigate the dynamics of scroll-wave filaments, the organizing centers of reentrant activity in the heart. The filaments are the 3D analog of a phase singularity around which a spiral wave rotates in two dimensions (2D). The type of each filament, I, U, or O, is typically documented. Type I is assigned to a filament the ends of which are in contact with the endo- and epicardial surfaces of the LV or RV free walls, or the endocardial surfaces of the LV and RV in the case of a septal location. Type U is a filament both ends of which are in contact with an endo- or epicardial surface. A filament of type O is a closed loop (vortex ring).

Furthermore, to quantify the complexity of VF, fast Fourier transform is performed for the transmembrane potential time trace at each myocardial node in our ventricle model. The power spectrum is calculated to determine the frequency with the highest peak which is then taken to be the dominant frequency (DF). 3D DF maps are constructed to determine the spatial distribution of DFs and the presence of DF domains.

F. Study protocols

In the study of arrhythmia induction with electric shocks, we focus on determining the VW; i.e., the widest range of coupling intervals at which arrhythmia is induced, for all shock strengths tested. The rabbit ventricular model is paced at the apex at a basic cycle length (BCL) of 250 ms. The shock timing (coupling interval, CI) is defined as the time interval between the last pacing stimulus and the onset of the shock. Shocks of increasing strengths are administered at various coupling intervals (CI) in order to determine, for each shock strength, the lowest and highest CI (CI_{min} and CI_{max}) at which sustained arrhythmia is induced. An arrhythmia is considered sustained if more than two cycles of activations were induced following the shock. The VW is taken to be the largest difference between CI_{min} and CI_{max}; the shock strength at which it occurred is also noted.

In the study of the role of APD heterogeneity in VF organization, we focus on the differences in VF dynamics in the heterogeneous and in two homogeneous rabbit ventricular models, one with short APD, and one with long APD. We pace each ventricular model from an electrode located at the apex [E1 in Fig. 1(c)] at a BCL of 250 ms for seven beats (transmembrane stimuli). VF is initiated by the delivery of high frequency pulses via an electrode on the LV epicardium [E2 in Fig. 1(c)] at a BCL of 50 ms for ten beats. Following the end of the pulse train, 3 s of VF is simulated.

III. ARRHYTHMIA INDUCTION WITH ELECTRIC SHOCKS: EFFECTS OF SHOCK TIMING AND ELECTRODE POLARITY

A. Overview

Optical mapping experiments and computer simulation studies have demonstrated that the activity following the delivery of a shock to the heart depends on the shock-induced virtual electrode polarization (VEP).^{10,23,24} Shock-induced areas of negative polarization represent excitable areas through which postshock activations, generated at the borders between oppositely polarized areas, could propagate. Tissue strongly depolarized by the shock remains refractory for a significant period of time after the shock ends, blocking propagation of postshock activations.

The distribution of shock-end VEP in the ventricles results from the interaction between the tissue state at time of shock delivery and the electric field applied; only shocks applied during a particular interval of time, the VW, result in arrhythmia induction. Here we determine the mechanisms underlying the existence of the VW in the framework of the VEP theory. Reversal of electrode polarity changes the orientation of the uniform applied field with respect to the ventricles, resulting in a different VEP; this allows us to evaluate how differences between LV and RV geometry result in differences in the dependence of shock outcome on the timing of shock application (i.e., the CI).

Following the study protocol as described in Sec. II, we determined that the VW for RV shocks extends from $CI_{\min} = 110$ to $CI_{\max} = 170$ ms, while for LV shocks it is from $CI_{\min} = 130$ to $CI_{\max} = 160$ ms. In both cases, the VW occurs for shock strengths of 17 V/cm. The VW limits, as determined in our simulations, are in close agreement with experimental results using a similar protocol and electrode configuration, where the VW extends from 116 ± 8.9 to 184 ± 16.7 ms for RV and from 116 ± 16.7 to 188 ± 17.9 ms for LV shocks.¹⁰ In order to understand the mechanisms by which shock timing (i.e., CI) affects arrhythmia induction by electric shocks for both polarities, we analyzed VEP and postshock electrical activity for shocks applied at CIs shorter than $CI_{\min}$ (CI = 100 ms), CIs within the VW (CIs of 130 and 160 ms), and at CIs longer than $CI_{\max}$ (CI = 190 ms).

B. Shock-end distributions of transmembrane potential and of scroll-wave filaments

Figure 2 presents transmembrane potential distributions at the time of shock delivery (panels A and B, anterior epicardial view) and at shock end (panels C and D, anterior epicardial and transmural views) at the end of 17 V/cm shocks applied at CIs of 100, 130, 160, and 190 ms for RV and LV shock polarities, respectively. Figures 2(e) and 2(f) show the distribution of scroll-wave filaments in the 3D volume of the ventricles at the end of the same shocks as in Figs. 2(c) and 2(d). The epicardial surface has been rendered semitransparent and anterior epicardial and apical views are shown.

Images in Figs. 2(a) and 2(b) show that increasing the CI leads to an increase in the amount of tissue repolarized at the time of shock delivery. As shown in Figs. 2(c) and 2(d), for all shock timings the epicardial VEP is similar, consisting of two main areas of opposite-in-sign polarization of nearly the same spatial extent, as shown by previous simulation and experimental studies.^{10,24} The epicardium is depolarized in the vicinity of the cathode (RV tissue for RV^- , and LV free wall tissue for LV^- shocks), whereas it is negatively polarized in the vicinity of the grounding electrode (LV free wall for RV^- and RV wall for LV^- shocks). Thus, for both shock polarities, varying shock timing has a negligible effect on epicardial transmembrane potential distribution at shock end.

In contrast to the surface VEP, transmural views in Figs. 2(c) and 2(d) present a very complex shock-end distributions of transmembrane potential within the bulk of the ventricles. For both shock polarities, the extent and location of the areas of positive and negative polarization vary significantly with the CI at which the shock is applied. This is quantified in Fig. 3, which presents the amount of myocardial tissue experiencing potentials $> +20$ mV and < -90 mV (calculated as percentage of all nodes in the ventricular volume) at shock end, plotted as a function of CI. As illustrated in the transmural views of Figs. 2(c) and 2(d), and in Fig. 3, with increasing CI, the amount of positively polarized areas decreases for $CI < 150$ ms but increases significantly for $CI > 150$ ms, for both polarities. Thus, the extent of the areas of positive polarization is smaller for shocks applied within the VW than for shocks applied outside the VW. For all CIs within the VW, positively polarized tissue represents less than 35% and 31% of the myocardial mass for RV^- and LV^- shocks, respectively. This is tissue that remains refractory for a significant period of time following the shock, blocking postshock activations. In contrast, Fig. 3 demonstrates that for both shock polarities the amount of negatively polarized tissue increases with increasing CI until $CI = 170$ ms and then decreases for longer CIs. Varying CI within the limits of the VW results in changes in the amount of negatively polarized tissue from 17% to 26% of the myocardial mass for RV^- and from 18% to 23% for LV^- shocks.

While the overall extent of positively and negatively polarized areas and its dependence on shock timing is similar for RV^- and LV^- shocks, the spatial distribution of these areas is significantly altered with reversing electrode polarity [compare transmural views in Figs. 2(c) and 2(d)]. For RV^- shocks, most of the midmyocardial tissue in the RV wall is positively polarized at shock end for all CIs, while the LV free wall hosts the main shock-end excitable area, which extends towards the base of the ventricles as CI increases. In contrast, for LV^- shocks, most of the midmyocardial tissue in the LV free wall experiences strong positive polarization at shock end, and the excitable gap is located within the thin RV free wall and the septum. Interestingly, the transmural views in Figs. 2(c) and 2(d) also demonstrate that the septum exhibits a strong and nonlinear dependence on shock timing for both electrode polarities. In fact, our results show that for shocks of both polarities, varying CI between 100 and 190 ms results in changes in the extent of the positively polarized regions of up to 163% in the septum, while only of up to 97% and 44% in the LV and RV free walls, respectively. As shown in Fig. 2, both RV^- and LV^- shocks applied outside the VW (i.e., at CIs of 100 and 190 ms), result in the majority of septal tissue being positively polarized at shock end, while for shocks applied inside the VW, most of the septum is either negatively polarized (blue areas in the $CI = 160$ ms panel) or experiences intermediate transmembrane potentials (yellow-green areas in the $CI = 130$ ms panel). Thus, for shocks applied within the VW, a large amount of septal tissue is excitable at shock end or shortly thereafter, allowing propagation of postshock activations.

Figures 2(e) and 2(f) demonstrate that for both shock polarities, the complex VEP induced by the shock in the depth of the ventricular wall is associated with a large density of shock-end filaments in the ventricles. At the end of an RV^- shock, the filaments are located everywhere, in the septum and in the RV and LV free walls, while for LV^- polarity, shock-end filaments concentrate predominantly in the RV free wall and septum, where the main shock-end excitable areas are located [see transmural views in Figs. 2(c) and 2(d)]. As time progresses after the end of the shocks, these filaments evolve in a restricted tissue volume, frequently being annihilated at the tissue boundaries or by contact with each other. If any of these filaments survive after this transition period, the shock results in an arrhythmia induction. The events and mechanisms that underlie this transitional post-shock period are examined below.

C. Postshock behavior

Our simulation results demonstrate that, for both polarities, varying shock timing leads to changes in the shock-end distributions of transmembrane potentials and the associated filaments; these ultimately determine the outcome of shocks applied at different CIs, and are thus responsible for the existence of a VW. Figures 4 and 5 illustrate the evolution of postshock electrical activity for the same shocks as in Fig. 2 (shock strength is 17 V/cm, and CI=100, 130, 160, and 190 ms) for RV⁻ and LV⁻ shocks, respectively. In the figures, the epicardium is rendered semitransparent to allow visualization of the filaments (in pink), and anterior and apical views are shown.

As shown in Figs. 4 and 5, the number of filaments in the ventricles decreases very rapidly following the end of the shock for both polarities and for all CIs. For both polarities, the number of filaments remaining in the ventricles 15 ms postshock is significantly lower for shocks applied outside than inside the VW. This is due to the fact that for CIs outside the VW, positively polarized tissue represents more than 35% and 31% of all myocardial mass for RV⁻ and LV⁻ shocks, respectively (as shown in Fig. 3). The large amount of tissue strongly depolarized at the end of shocks applied outside the VW leads to blockade of propagation and consequently to the annihilation of most of the filaments shortly after shock end. Thus, no sustained arrhythmia is induced for CIs outside the VW.

For shocks of both polarities applied at CIs < CI_{min} (e.g., CI=100 ms), only a few O-type filaments remain in the ventricles at 15 ms postshock. These filaments are located in the LV free wall for RV⁻ shocks and in the septum for LV⁻ shocks, which corresponds to the location of the main excitable areas at shock end [Figs. 2(c) and 2(d), transmural views]. However, all O-type filaments eventually collapse on themselves and sustained arrhythmia is not induced. For shocks applied at CIs > CI_{max} (CI=190 ms), the postshock activations traverse quickly the postshock excitable areas so that at 15 ms postshock, the entire ventricles are depolarized and all filaments have disappeared. The same behavior is observed for shocks of both polarities.

As shown in Fig. 3, for both polarities, shocks applied within the VW result in an amount of shock-end depolarized tissue that is smaller than 35% of total tissue volume. The large amount of tissue either excitable or mildly depolarized at shock end for shocks applied within the VW underlies the observation that large excitable areas and a significant number of filaments are still present in the ventricles 15 ms post-shock for RV⁻ and LV⁻ shocks applied within the VW. Following RV⁻ shocks, the filaments are predominantly located within the LV free wall and the septum (see Fig. 4), while following LV⁻ shocks they are located within the RV free wall and the septum (see Fig. 5). The number of filaments decreases progressively following shock end, resulting in an increase in the spatial organization of ventricular electrical activity and in a stable pattern of reentry, which is shown in Fig. 6.

For RV⁻ shocks applied inside the VW, the sustained arrhythmia induced by the shock is a figure-of-eight reentry with two rotors, one counterclockwise and one clockwise, on the anterior and the posterior of the ventricles, respectively, as shown in Figs. 6(a) and 6(b); similar patterns of reentry were obtained in previous studies of ours.^{10,25} Each of the rotors corresponds to a phase singularity on the epicardium (marked with a solid black circle in Fig. 6), which is the epicardial surface contact of an I-type filament through the LV free wall (Fig. 4, CI=130 ms, 195 ms panel, and CI=160 ms, 205 ms panel). However, for the RV⁻ shock applied at CI=160 ms, an additional U-type filament remains attached at the LV endocardium 205 ms postshock. Activity associated with this U-type filament appears focal on the anterior epicardium [Fig. 6(b), black arrow].

For LV⁻ shocks, the type of arrhythmia induced is different for short versus long CIs within the VW. When applied at a CI of 130 ms, the LV⁻ shock induces a figure-of-eight reentry with

two rotors on the posterior of the ventricles, which correspond to two I-type filaments attached to the RV endocardium and the posterior epicardium [black circles in Fig. 6(c)]. In contrast, for LV^- shocks applied at long CIs within the VW (e.g., $CI=160$ ms), the type of arrhythmia induced is a quatrefoil reentry with a figure-of-eight on the anterior and another on the posterior of the ventricles. The greater complexity of this pattern of reentry corresponds to a larger number of filaments as compared to the previous cases. For the LV^- shock applied at $CI=160$ ms, five I-type filaments are present in the ventricles 205 ms postshock: three filaments attached to the LV endocardium and the epicardium (two on the anterior and one on the posterior), one between the posterior epicardium and the RV endocardium, and one within the septum. This corresponds to four phase singularities present on the epicardium of the ventricles as shown in Fig. 6(d).

D. What do these finding mean?

Similar to previous studies,^{10,20} our results demonstrate that the midmyocardium exhibits a complex shock-induced VEP, which is not predictable from the epicardial VEP. Furthermore, the effect of varying shock timing on VEP differs significantly in the bulk of the midmyocardium and on the epicardial surface. On the epicardium, the shock induces two large areas of opposite-in-sign polarization of nearly the same extent for all CIs [Figs. 2(c) and 2(d), epicardial views in 0 ms panel]. In contrast, in the depth of the ventricular wall, different shock timings results in differences in the extent and location of VEP [Figs. 2(c) and 2(d), transmural views in 0 ms panel]. These changes ultimately determine the outcome of shocks applied at different CIs, and thus explain the existence of the VW.

Our bidomain simulations reveal that varying the CI in the range 100 to 190 ms results in large changes in the extent of positively polarized areas, of up to 69% and 82% for RV^- and LV^- polarities, respectively, while the extent of negatively polarized areas changes only by up to 45% and 32% for RV^- and LV^- shocks, respectively. For both shock polarities, these large changes in the extent of the shock-end positively polarized areas result mostly from the strong dependence of the shock-end transmembrane potential distribution in the septum on CI. Our results show that for CIs outside the VW, for both polarities, septal tissue is strongly depolarized at shock end and the total extent of the positively polarized regions represents more than 35% of the total myocardial volume. Thus, a large amount of tissue remains refractory for tens of milliseconds after shock end, blocking propagation of the postshock activations (Figs. 4 and 5). In contrast, for CIs within the VW, septal tissue is either negatively polarized by the shock, or it is weakly depolarized and thus it recovers shortly after shock end. Thus, for CIs inside the VW, postshock propagation proceeds through the excitable regions while tissue that is refractory at shock-end recovers. This allows for the establishment of reentrant activity of varying complexity depending on shock timing and polarity, as shown in Figs. 4–6. Therefore, our simulation results clearly demonstrate that for shocks of both polarities, the effect of shock timing on shock-end transmembrane potential distribution in the septum is a major factor in the mechanisms underlying the existence of the VW.

The results of this study clearly demonstrate the contribution of ventricular anatomy to shock-induced polarization and postshock propagation and thus, to shock outcome. Understanding this contribution fully could provide the background for rational rather than trial-and-error design of new shock delivery systems that can target specific critical ventricular structures, thus achieving the most favorable post-shock behavior and resulting in a significant decrease in defibrillation threshold.

IV. VF ORGANIZATION: ROLE OF INTRINSIC HETEROGENEITIES IN ACTION POTENTIAL DURATION

A. Overview

Experimental studies have demonstrated the presence of electrophysiological heterogeneities in the ventricles. Examples include the endocardial-epicardial^{26,27} and base-apex²⁸ APD gradients, and differences in APD between LV and RV.²⁹ These intrinsic APD heterogeneities are believed to play a role in the complex spatiotemporal patterns of wave propagation during VF.³⁰ The shorter APD in the LV vs. the RV has been suggested as underlying the presence of higher frequency rotors in the LV during VF in the guinea pig.¹⁴ Indeed, 2D simulations confirm that tissue with short APD supports spiral waves of high rotation rate, while in regions of longer APD wave front-tail interactions take place, resulting in spiral-wave instability^{31, 32} and fibrillatory propagation.¹⁴

Do regional differences in APD in the left versus right ventricle in the rabbit manifest themselves in VF organization in a fashion similar to the behavior observed in 2D simulations and guinea pig experiments? Modeling studies have shown that wall thickness as well as rotational anisotropy across the ventricular wall could result in destabilization of scroll-wave filaments and wave breakup via filament twist.^{33–35} In addition, as demonstrated in the first part of this article, the complex ventricular geometry could play an important role in 3D wave propagation.

Using the ventricular rabbit model with intrinsic LV versus RV APD heterogeneities, as described in Sec. II, this study aims to characterize VF organization in 3D in this species and to determine whether APD differences indeed result in maintenance of stable rotors in the LV (region of shorter APD) and fibrillatory conduction in the RV (longer APD). VF dynamics in the heterogeneous APD ventricles is compared to two cases with homogeneous distribution: one where all cells have (long) RV APD and another where all cells have (short) LV APD. Scroll-wave dynamics is quantified by determining the location and number of filaments over the time course of VF. Regions of different activation rates are determined by constructing DF maps.

B. Spatiotemporal characteristics of scroll-wave filaments

Figure 7 shows anterior epicardial views of transmembrane potential distributions in VF at intervals of 1 s for the ventricular model with APD heterogeneity and the two electrophysiologically homogeneous ventricular models. At the bottom of each panel, the corresponding apical view is presented, with the epicardium rendered semitransparent to visualize scroll-wave filaments (in pink). The dashed line in the heterogeneous APD case denotes the demarcation line between the LV (short APD) and RV (long APD) regions. As described in Sec. II, in all three cases, VF is initiated with a 20 Hz train of ten pulses delivered through a wire electrode located on the LV epicardium; the pulse terminates at $t=0$ ms.

The three representative episodes portrayed in Fig. 7 provide a glimpse of the trends in spiral wave dynamics during the three seconds of VF. The epicardial images show that a larger number of filaments are in contact with the epicardium (the epicardial phase singularities, PS, shown as black dots) in the heterogeneous APD case as compared to the homogeneous cases. At $t=1000$ ms, there are seven PS present on the anterior epicardium. In contrast, there is only one anterior epicardial PS in each homogeneous case. As VF progresses through the 3 s of observation, the ventricles with heterogeneous APD consistently have a higher number of epicardial PS present on the anterior epicardium as compared to the homogeneous cases (see $t=2000$ ms and $t=3000$ ms panels).

The semitransparent views reveal the presence of numerous filaments of complex geometry within the 3D ventricular volume. Figure 8 assesses the level of complexity of each VF episode by quantifying the corresponding filament dynamics. The number of filaments and their location within the ventricles (LV, RV, and septum) was determined in intervals of 50 ms throughout the 3 s of VF, as described in Sec. II. The average number of filaments for each location during 3 s of VF is presented in Fig. 8. Student's t-tests ($p=0.05$) were used to compare the average number of filaments for each VF episode. The average number of filaments in the ventricles with heterogeneous APD, 17.21 ± 4.65 , is significantly higher than that in either electrophysiologically homogeneous ventricle. The LV APD case is characterized with 11.3 ± 3.98 average number of filaments, which is significantly higher than that in the RV APD case; i.e., 9.49 ± 1.98 . This is consistent with the apical views presented in Fig. 7, which show increased number of filaments from RV APD to LV APD to heterogeneous APD cases.

The average filament number in the different ventricular regions, as graphed in Fig. 8, provide an additional insight into effects of chamber geometry on VF organization. In the homogeneous cases, the average number of septal filaments for the LV APD is 4.23 ± 1.95 , which is significantly higher than the number for the RV APD, 2.07 ± 1.01 . In the LV free wall, the average filament numbers in the LV APD case (4.66 ± 1.32) and in the RV APD case (4.95 ± 1.69) are statistically equal. Likewise, there is also no difference in the average filament numbers in the RV wall (LV APD 2.41 ± 1.83 versus RV APD 2.48 ± 1.06). This indicates that the higher overall average filament number in the LV APD case is due exclusively to filament formation in the septum. Both homogeneous models exhibit no significant difference in filament formation in the LV and the RV free walls.

The ventricles with heterogeneous APD exhibit a more complex filament dynamics in VF. Recall that, as shown in Fig 1(c), the LR1(LV) ionic model represents the electro-physiology of the cells in the LV free wall, while the longer APD model, LR1(RV), is used in the RV and septal regions. If these two regions of different electrophysiology had no electrotonic interaction, then the average filament number in the LV free wall in the heterogeneous APD ventricles would be the same as in the LV APD ventricles. Indeed, simulations with the heterogeneous APD ventricles show that the average number of filaments in the LV free wall, 5.02 ± 1.49 , is not significantly different from the average filament number in the LV APD ventricles (4.66 ± 1.32). This result demonstrates that the average filament number in the LV free wall is not affected by the fact that neighboring regions have a longer APD.

The situation is however, different, when examining the number of filaments in the regions characterized with long APD. Despite having the same electrophysiology (LR1 RV), the average number of filaments in the septum of the heterogeneous ventricles is significantly higher (5.84 ± 2.01) compared to the number of septal filaments in the RV APD case (2.07 ± 1.01). Similarly, in the RV wall, a larger average filament number is found in the heterogeneous APD case (6.36 ± 2.36) compared to the RV APD case (2.48 ± 1.06). These results show that the introduction of APD heterogeneity increases the average filament number for the ventricular regions characterized by a longer APD.

Analysis of our simulations demonstrate that in the ventricles with heterogeneous APD, the increase in the average number of filaments in the regions of long APD is a consequence of dispersion of refractoriness at the LV/RV border. Fig. 9 shows transmembrane potential distributions in the heterogeneous APD ventricles that highlight the role of the border in promoting wave break (formation of new rotors and thus new filaments). Presented are two posterior epicardial views; in one of them the epicardium is rendered semi-transparent. The broken white line represents the demarcation between short and long APD regions.

The source of activity in Fig. 9 is a rotor anchored in the LV (black arrow at $t=1001$ ms). The longer APD in the RV region results in a slower tissue recovery there, while tissue in the LV has already recovered. As the wave front (white arrows) propagates towards the RV, it encounters refractory tissue. The semitransparent view shows that the encounter results in a filament forming within the wall (colored in black and pointed to by the black arrow). At $t=1004$ ms, as the epicardial view shows, the wave front breaks and two epicardial PS appear (black dots). The semitransparent view reveals that the two epicardial PS are actually the ends of a U-type filament that had developed. At $t=1028$ ms, the epicardial PSs now have a distinct figure-of-eight reentry around them with a U-type filament now fully located within the long APD region. This reentrant circuit persists for four full cycles before being annihilated by wave fronts emanating from the original rotor. This mechanism of filament formation persists over the entire course of VF in the heterogeneous APD model.

C. Dominant frequency distribution

It is well understood that one of the effects of APD shortening is the acceleration of functional reentry.³⁶ We calculate the dominant frequency (DF) for each myocardial node in our rabbit ventricles to quantify the average activation rate at that node. Figure 10(a) portrays, for each ventricular model, cross sections through the ventricles with DF distributions mapped on them. It is evident from the images that both the magnitude and the distribution of DFs differ significantly among the three different scenarios. To quantify the DF distribution in the ventricles, the histogram in Fig. 10(b) presents DF ranges, in 1 Hz intervals, and the percentage of the ventricular volume that exhibits a particular DF. For the RV APD case, the DF values in Fig. 10(b) are clustered in a range from 21 to 24 Hz, with an average DF of 22.54 ± 0.47 Hz. The relatively low DF values and their small variation are evident in Fig. 10(a), where the entire ventricles are in bluish colors. In fact, the average DF in the RV APD case is the lowest among all three cases studied. VF in the LV APD case exhibits an average DF of 25.04 ± 1.17 Hz, higher than in the RV APD ventricles; DF values are distributed in the range 22 to 28 Hz [Fig. 10(b)], with colors ranging from green to yellow-red in Fig. 10(a). Clearly, shorter APD results in VF characterized by faster activation rates. The DF distribution in the ventricles with heterogeneous APD has the widest range of frequencies (19–28 Hz) of all cases [Figs. 10(a) and 10(b)], with an average DF of 23.49 ± 2.19 Hz.

Figure 10(c) quantifies the differences in DF distribution between regions of short and long APD in the heterogeneous ventricles. The histogram presents DFs binned in 1 Hz intervals and the percentage of ventricular volume, either of long APD (RV/septal region) or of short APD (LV region), that exhibits the particular DF. Clearly, the existence of APD heterogeneity in the ventricles extends the DF range both in the short and in the long APD region. For instance, compare the DF domains in two regions of the same (long) APD [Fig. 10(a)]: the RV region in the heterogeneous ventricles is in yellow and blue colors (20 to 28 Hz, with 26% of the tissue having a low DF of 21–22 Hz), while the RV APD ventricles are all in bluish color. Similar considerations are valid for the regions of short APD in the electrophysiologically heterogeneous and homogeneous ventricles. The increase in DF range within the RV region is consistent with the findings from the filament dynamics analysis (see above), where we demonstrated that APD heterogeneity leads to an increase in rotor (and thus filament) formation in the region of long APD.

Although the two regions of different APD in the heterogeneous ventricles both contain high and low DF values, the region of short APD (i.e., LV) has a large amount of tissue, i.e., 62%, encompassing high DF values (at least 24 Hz) compared to only 30% of tissue in the region of long APD (i.e., RV/septal region). Our results clearly demonstrate that the majority of the tissue within the LV has a higher DF than the rest of the ventricles. The high activation rate in the LV contributes to the wave front fractionation observed at the LV/RV border (Fig. 9). Higher

activation rate in the LV results in an increase in production of wave fronts that propagate towards the RV, encounter refractory tissue in the RV and thus, result in wave break and filament formation (Fig. 9).

D. What do these findings mean?

Previous experimental studies of VF have reported the presence of high frequency rotor activity on the cardiac surface that drives wave fractionation at a distance away from the main rotor.^{14,37} The mechanisms that underlie this type of VF organization are not fully understood. 2D simulations have shown that APD heterogeneity could underlie the production of fast, stable rotors within the short APD region and wave fractionation, due to dispersion of refractoriness, at the border of the region with increased APD.¹⁴ The goal of this study was to determine whether similar mechanisms underlie VF organization in a realistic 3D rabbit ventricular model with intrinsic RV versus LV APD heterogeneity, and whether the geometric complexity of the 3D organ could override or alter APD heterogeneity-induced VF organization. To achieve the goal of the study, we employ a realistic 3D rabbit ventricular model that incorporates regions of long and short APD that are represented by the same ionic models, LR1(LV) and LR1(RV), and thus, have the same action potential morphology as the aforementioned 2D simulation study.¹⁴ VF organization in this 3D model is compared to two electrophysiologically homogenous ventricular models, one with short APD [LR1(LV) ionic model], and one with long APD [LR1(RV) model]. VF organization is quantified by examining 3D filament dynamics and DF distributions in the three ventricular models.

Analysis of our modeling results demonstrates that VF organization in the heterogeneous APD ventricles differs from simulation results regarding VF in the 2D sheet,¹⁴ although the ionic models representing the regions with long and short APD are exactly the same. In 2D, a single stable rotor is formed within the short APD region; the same behavior is observed in experiments with (small in size) guinea pig hearts where a stable spiral wave was documented on the epicardium of the LV, shown to exhibit a shorter APD than that of the RV.^{14,38} The position of the stable rotor correlates with the presence of a high DF domain on the epicardium. Our simulations with the heterogeneous APD rabbit ventricular model document the formation of multiple rotors within the region of short APD, the LV free wall. This complexity in VF organization is mirrored by the complex distribution of DF throughout the LV wall. As opposed to a single high DF domain within the short APD region, VF organization in our electrophysiologically heterogeneous ventricular model exhibits multiple high and low DF domains interspersed throughout the LV. This finding is consistent with experimental studies that did not find the presence of a single dominant high DF region that was temporally or spatially stable in guinea pig hearts³⁹ and swine ventricular wedges.⁴⁰

The lack of a single stable rotor (single filament) in the LV of our heterogeneous rabbit ventricular model is likely due to the much larger volume of the region of short APD as compared to the size of the same region in the guinea pig ventricle or in the 2D sheet model, as well as to the fact that filament destabilization and breakup takes place in the thicker wall possessing rotational fiber anisotropy. Indeed, theoretical studies have implicated tissue thickness and fiber orientation as destabilizing factors in filament behavior.^{34,35} Thus, the thickness of the LV wall and its convoluted fiber orientation result in a complex spatiotemporal VF organization there, with multiple filaments and complex reentry patterns, although the region is characterized with a short APD.

Our modeling results demonstrate that the introduction of APD heterogeneity leads to increased complexity of VF organization via a twofold increase in the number of filaments within the long APD region. This increase in filament formation is due to wave fractionation caused by dispersion of refractoriness across the border between short and long APD regions. Heterogeneity-induced breakup occurs for wavefronts traveling from the short APD region to

the long APD region; thus the reported increase of filaments in the long APD region and no change within the short APD region. Wave fronts propagating from short to long APD are more likely to encounter functional block at the heterogeneity border due to tissue remaining refractory from a previous excitation. Xie *et al.* report similar behavior in 2D simulations of reentry with APD dispersion;⁴¹ the phenomenon is also observed in experimental studies of VF.^{14,42}

The accurate characterization of intrinsic heterogeneities within the ventricles is important for the development of a targeted treatment of VF. Our simulations demonstrate that decreasing APD difference in the ventricles results in a decrease of the pro-fibrillatory effect of APD heterogeneity at the border between short and long APD, and thus in a reduced filament formation and diminished VF complexity. A recent experimental study⁴³ has shown that application of a potassium channel selective blocker, an APD lengthening agent, in fibrillating feline ventricles results in a decrease in complexity of activation within the RV and consequently, in an overall decline in VF rate. Hence, targeted pharmacologic intervention to reduce APD differences within the ventricles could ultimately lead to an improved anti-arrhythmia therapy.

V. CONCLUDING REMARKS

This article presents two multiscale simulation studies that underscore the power of realistic modeling in revealing electrical behavior throughout the 3D volume of the ventricles. The first study examined induction of ventricular arrhythmia with electric shocks, providing information regarding the mechanisms that underlie the existence of a vulnerable window. The second study investigated the role of electrophysiological heterogeneity in VF maintenance, characterizing VF dynamics in terms of filament formation and DF domains formed in the ventricular volume. Both studies reveal events that take place within the ventricular walls and provide new insights into arrhythmogenesis that are unachievable with current experimental methodology due to its inability to provide, with sufficient resolution, information about the 3D electrical activity in the heart. It is the hope of the authors of this article that with the advancements in computational power, realistic multiscale modeling, combined with experimental observations, will become a commonplace tool for studying the electrical behavior of the heart in health and disease.

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FIG. 1.

(Color) (A) Rabbit ventricular model: geometry and fiber orientation (denoted by short white lines). (B) Action potential from the LR1(RV) and LR1(LV) ionic models. (C) The division of the ventricle into an LV region (region with short action potential duration, colored in blue) and RV/septal region (long action potential region, colored in green) for the study of VF maintenance mechanisms. E1 denotes the pacing site from which the ventricles were paced at a 250 ms basic cycle length. E2 is the electrode site used in VF induction, from which 20 Hz frequency pulses were given. (D) Experimental preparation for shock-induced arrhythmia study. The transmembrane potential distribution in the ventricles corresponds to the seventh pacing stimulus (given from the apex).

FIG. 2.

(Color) Transmembrane potential distributions at time of shock delivery (panels A and B, anterior epicardial view) and at shock end (panels C and D, anterior epicardial and transmural views) for a 17 V/cm shock applied at coupling intervals (CIs) of 100, 130, 160, and 190 ms for RV⁻ and LV⁻ polarities, respectively. In panels (E) and (F), the epicardial surface has been rendered semitransparent to allow visualization, in pink, of the filaments at the end of the same shock as in panels (C) and (D). Anterior epicardial and apical views are shown in panels (E) and (F). Color scale is saturated, i.e., transmembrane potentials above +20 mV and below -90 mV appear red and blue, respectively.

FIG. 3. Percentage of myocardial nodes that are of transmembrane potential above +20 mV (black bars) and below -90 mV (gray bars) at the end of a 17 V/cm shock applied at CIs in the range 100 to 190 ms.

FIG. 4.
 (Color) Evolution of postshock electrical activity following an RV^- shock of 17 V/cm strength applied at CIs of 100, 130, 160, and 190 ms. Color scale as in Fig. 2.

FIG. 5. (Color) Evolution of postshock electrical activity following an LV^- shock of 17 V/cm strength applied at CIs of 100, 130, 160, and 190 ms. Color scale as in Fig. 2.

FIG. 6. (Color) Transmembrane potential distributions on the anterior and the posterior of the ventricles 195 ms after the end of 17 V/cm shocks applied at CI=130 ms (A and C) and CI=160 ms (B and D) for RV^- and LV^- polarity. Phase singularities on the epicardium are marked with solid black circles. White arrows indicate direction of propagation. Color scale as in Fig. 2.

FIG. 7.

(Color) Transmembrane potential distribution for 3 s of VF (in intervals of 1 s) for heterogeneous APD, LV APD, and RV APD ventricular models. The time $t=0$ corresponds to the end of the VF-inducing high-frequency pacing. For each case, the top image is anterior epicardial view and the bottom image is apical view with the epicardium rendered semi-transparent to show the scroll-wave filaments (colored pink). The dashed black line at $t=1000$ ms over the heterogeneous APD model transmembrane potential map denotes the border between regions characterized with a different APD. Epicardial phase singularities are marked with solid black circles.

FIG. 8.

Average number of filaments (over the 3 s of VF) for heterogeneous APD, LV APD, and RV APD ventricular models. The total average number of filaments is broken down into filaments in the LV, septal, and RV regions. The boundaries of the three different ventricular regions, as used for filament sorting, are outlined below the graph.

FIG. 9.

(Color) Top panels: Posterior epicardial views of transmembrane potential distribution in the heterogeneous APD ventricles. Epicardial phase singularities are marked with solid black circles. Direction of wave front propagation is indicated with white arrows. In the top left image, the black arrow points towards the rotor that is the source of the wave fronts propagating towards the RV. Bottom panels: the same view but with the epicardium rendered semitransparent to display scroll-wave filaments (colored pink). In the bottom left image, the black arrow points towards a new filament formation. The same filament (colored in black) is shown in the other two bottom panels; its ends are colored in white to underscore the fact that it is a U-type filament (both ends of the filament are attached to the epicardial surface). The white dashed line at the $t=1001$ ms and $t=1028$ ms panels is the border between regions characterized with a different APD.

FIG. 10. (Color) (A) Cross sections through the ventricle with mapped dominant frequency (DF) distribution for each ventricular model. (B) DF ranges, in 1 Hz intervals, and the percentage of the ventricular volume that exhibits a particular DF for each ventricular model. (C) DF ranges, in 1 Hz intervals, and the percentage of ventricular volume in the heterogeneous APD ventricular model, either of long APD (RV/septal region) or of short APD (LV region), that exhibits the particular DF.