Investigating the Role of the Coronary Vasculature in the Mechanisms of Defibrillation

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Background—The direct role of coronary vessels in defibrillation, although hypothesized to be important, remains to be elucidated. We investigated how vessel-induced virtual electrode polarizations assist reentry termination.

Methods and Results—A highly anatomically detailed rabbit ventricular slice bidomain computer model was constructed from 25-μm magnetic resonance data, faithfully representing both structural and electric properties of blood vessels. For comparison, an equivalent simplified model with intramural cavities filled in was also built. Following fibrillation induction, 6 initial states were selected, and biphasic shocks (5–70 V) were applied using a realistic implanted cardioverter-defibrillator electrode configuration. A fundamental mechanism of biphasic defibrillation was uncovered in both models, involving successive break excitations (after each shock phase) emanating from opposing myocardial surfaces (in septum and left ventricle), which rapidly closed down excitable gaps. The presence of vessels accelerated this process, achieving more-rapid and successful defibrillation. Defibrillation failed in 5 cases (all because of initiation of new activity) compared with 8 with the simplified model (5/8 failures because of surviving activity). At stronger shocks, virtual electrodes formed around vessels, rapidly activating intramural tissue because of break excitations, assisting the main defibrillation mechanism, and eliminating all activity <15 ms of shock end in 60% of successful shocks (36% in simplified model). Subsequent analysis identified that only vessels >200 μm in diameter participated through this mechanism. Consequently, wavefronts could survive intramurally in the simplified model, leading to reentry and shock failure.

Conclusions—We provide new insight into defibrillation mechanisms by showing how intramural blood vessels facilitate more-effective elimination of existing wavefronts, rapid closing down of excitable gaps, and successful defibrillation and give guidance toward the required resolution of cardiac imaging and model generation endeavors for mechanistic defibrillation analysis. (Circ Arrhythm Electrophysiol. 2012;5:210-219.)

Key Words: electrophysiology • vasculature • defibrillation • fibrillation

Although application of a strong defibrillation shock to the heart remains the only reliable means of terminating ventricular fibrillation, many aspects underlying its success still remain a mystery. Specifically, the exact mechanisms by which externally applied electric fields interact with cardiac tissue structure to successfully activate a sufficient mass of myocardium and achieve defibrillation lack comprehensive understanding.

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Experimentally, much of our current understanding of defibrillation mechanisms has been derived from whole-ventricle optical mapping investigations,2–4 which only probe polarization patterns from tissue layers close to the epicardial surface. However, fine-scale discontinuities in tissue structure, known to be present throughout the myocardial wall, have been postulated to play a crucial role in defibrillation through the creation of virtual electrodes as current induced by the applied field is redistributed, assisting in the bulk activation of myocardium. More recent transmural optical mapping recordings from excised left ventricular (LV) wedge preparations,6 alongside similar high-resolution computer bidomain simulations,7,8 have confirmed the existence of intramural virtual electrodes following shocks applied during diastole. However, experimental limitations in optical resolution and distortion due to photon scattering5 have thus far prevented direct correlation of virtual electrodes with specific intramural structures. Furthermore, restrictions in model domain size of both experiments and simulations have limited examination of the direct implications of shock-induced intramural activation on reentry termination and defibrillation.

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Despite the theorized importance of intramural structures in virtual electrode formation and defibrillation, existing knowledge of the effects of shocks at the whole-ventricle level has been obtained largely from more-simplified computer models, lacking any form of intramural structures. Nonetheless, close agreement has been found throughout with experimental observations of global defibrillation mechanisms made from whole-ventricular surface optical mapping experiments, questioning the importance of incorporating such fine-scale features within models and their relevance in defibrillation. Recent advances in MRI, however, have facilitated the inclusion of unprecedented levels of anatomic detail, including representations of the coronary vascular system, within whole-ventricular computational models, presenting an opportunity to perform such an investigation.

Because blood vessels represent the largest discontinuities within the myocardial wall, they suggest an important substrate for virtual electrode formation. In a recent study, we demonstrated how fine-scale information regarding the coronary vasculature could be incorporated into a detailed computational LV wedge model from high-resolution magnetic resonance (MR) data, showing how virtual electrodes form around blood vessels following shocks applied during action potential plateau, assisting intramural myocardium activation. However, the study did not directly relate its findings to clinical defibrillation mechanisms.

In the present study, we investigated the causal link between vessel-mediated virtual electrode formation during clinically realistic defibrillation shock application and successful reentry termination. To facilitate our investigation, a highly anatomically detailed rabbit ventricular slice bidomain model was constructed from 25-μm MR data, representing both structural and electric properties of blood vessels. Biphasic defibrillation shocks were applied through an implanted cardioverter-defibrillator (ICD) electrode setup to a variety of different fibrillation episodes. Comparison of results with a simplified model (lacking any form of intramural structures) allowed dissection of the specific role played by the coronary vasculature made possible through direct examination of transmembrane potential (V_m) dynamics throughout the full 3D volume of the myocardial walls, thus overcoming an inherent limitation of experimental investigations.

Methods

Computational Model

A tetrahedral finite-element ventricular slice model (thickness, 1.5 mm) was generated from a previously published high-resolution rabbit MR data set (resolution, 25 μm) following prior segmentation and manual removal of free papillary muscles. The mesh (Figure 1B) consisted of both myocardial tissue and surrounding extracellular bath, filling ventricular and intramural cavities. Blood vessels within the slice model were identified and tagged. Mean vessel density was ~1.34 vessels/mm², with minimum vessel cavity diameter represented ~100 μm.

Cardiac fiber architecture was assigned using a rule-based method, accounting for transmural variation in helix angle and continuous fiber negotiation around intramural structures seen in histology (Figure 1B). To dissect the specific role played by intramural structures, a simplified model was produced in which all intramural cavities were filled in during segmentation, before meshing. Identical stimulation protocols were applied to both vessel and simplified models throughout.

Simulating Electric Activation

Electric activation was simulated using the bidomain equations solved with the Cardiac Arrhythmia Research Package. Conductivities were based on experimentally derived values scaled to reduce conduction velocity by 25%, as occurs during heart failure. Electric conduction through the connective tissue of the vessel lumen was reduced by assigning the experimentally derived conductivity of 0.010 S/m to extracellular bath elements that directly bordered the vessel cavity/myocardium interface. Bath conductivity, including within-vessel cavities, was 1.0 S/m. Membrane dynamics were represented by a recent rabbit ventricular cell model slightly adjusted to produce sustained ventricular fibrillation-like activity and augmented by 2 additional currents activated at large potentials to simulate membrane responses to strong shocks. The online-only Data Supplement contains detailed descriptions of the computational methods.

Simulation Protocol

Induction of Fibrillation

Fibrillation was induced as described in the online-only Data Supplement. A selection of 6 initial states were chosen from the fibrillatory episodes, which acted as preshock states for defibrillation shock delivery, providing a range of possible initial conditions. As closely as possible, initial states were matched between vessel and
simplified models, notwithstanding the inherent complexity of the fibrillatory episodes (online-only Data Supplement Figure III).

**Defibrillation Shock Application**

An ICD-like electrode configuration for defibrillation shock delivery included a 6-F catheter placed in the right ventricle (RV)\(^1\) and an active can in the bath near the posterior LV (Figure 2A). Biphasic defibrillation shocks of shock strength (SS) between 5 and 70 V (leading-edge voltage) were delivered to the selected initial fibrillatory states. The RV catheter acted as the anode during the first shock phase\(^1\) and the active can as ground, with polarity reversed during the second phase with a magnitude of 50% of the first. Tilt and duration of each phase were 50% and 3.5 ms, respectively. The distribution of extracellular potential within the simplified model is shown in Figure 2A, showing regions of high field gradient concentrated primarily in the posterior LV and septum. Figure 2B and 2C compare the response of the vessel and simplified models to a 40-V shock applied during diastole, showing a difference map (following mapping of data between respective meshes) of induced extracellular potential gradient (Figure 2B) and induced V\(_m\) (Figure 2C) 1 ms into the shock. These difference maps highlight the significant magnitude of variation in both extracellular potential gradient and V\(_m\) within intramural myocardial tissue, focused around vessel cavities and within regions of high field strength (posterior LV and septum) between the vessel and simplified models.

**Data Analysis**

Induced postshock arrhythmias were defined as sustained if reentrant activity lasted for >100 ms. Tissue was classified as excitable if V\(_m\) was \(<-60\) mV (inactivation threshold of sodium current\(^1\)). Intramural tissue was defined as points lying within 0.25\(\leq e \leq 0.75\), where \(e\) is the normalized transmural distance from endocardium to epicardium. See online-only Data Supplement section 1.4.3 regarding statistical significance of simulation data.

**Results**

**Role of Vessels in Shock Success**

Defibrillation shocks of SS 5, 10, 20, 40, and 70 V were applied to the 6 initial fibrillatory states of the 2 models. Analysis of postshock activation patterns of the 30 episodes revealed that defibrillation failed in just 5 cases in the vessel model compared with 8 in the simplified model. Of those failed shocks, reentry was reinitiated because of new activation wavefronts induced by the shock in 4 of 5 of the failed vessel model shocks. In the simplified model, however, 5 of 8 failures were due to existing activity, which failed to be extinguished by the shock.

The presence of vessels also affected the time course over which successful defibrillation occurred. Of those successful shocks, all wavefronts throughout the model were entirely extinguished within 15 ms of shock end in 15 of 25 (60%) cases in the vessel model compared with just 8 of 22 (36%) in the simplified model.

**Uncovering a Common Biphasic Defibrillation Mechanism**

Analysis of activation patterns during successful defibrillation episodes revealed a common mechanism of biphasic defibrillation, witnessed throughout all initial states and SS. Importantly, the fundamental basis of this mechanism was found to be common to both models, independent of the presence of vessels.

Figure 3A demonstrates how successful defibrillation is achieved through this mechanism, showing the evolution of

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Figure 2. A, Implanted cardioverter-defibrillator electrode setup and \(\phi_e\) distribution within simplified model 1 ms into a 40-V defibrillation shock. The difference map of induced \(\Delta \nabla \phi_e\) (B) and \(\nabla V_m\) (C) between vessel and simplified models is shown. \(\phi_e\) indicates extracellular potential; \(\nabla \phi_e\), extracellular potential gradient; \(V_m\), indicates transmembrane potential.

Figure 3. Common mechanism of successful biphasic defibrillation. Transmembrane potential distribution before, during, and after 40-V shock (A) and at shock end for shock strength 5, 10, and 20 V (B) applied to simplified model state I4. C, Postshock transmembrane potential distribution of 40-V shock applied to corresponding vessel model state I4. P1 indicates phase 1; P2, phase 2.
activity throughout a 40-V shock in the simplified model. Large excitable gaps exist in the LV and septum before the shock (0 ms). The first shock phase strongly depolarizes the anterior LV endocardial wall and large regions of the LV–septum endocardium (3.5 ms). At the end of this first phase, break excitations are elicited from these strongly polarized walls, which are free to propagate into the large intramural excitable gaps in the LV and septum. However, the second phase of the shock now strongly depolarizes the RV–septum endocardium as well as the anterior LV epicardium (7 ms). As witnessed previously,4 the energy delivered in the second phase of the shock is sufficient only to reverse the negative polarization previously established by the shock, while partially preserving positive polarization. At shock end, a second set of break excitations is thus elicited, which propagate into the intramural excitable gaps of the LV and septum, in the opposite direction to the first set following phase 1. Consequently, these successive break excitations from opposing myocardial surfaces, elicited at the end of each shock phase, very rapidly close down intramural excitable regions in the LV and septum, like drawing a curtain (10 ms).

Although this biphasic defibrillation mechanism was clearly evident for strong shocks (including 70 V, not shown), its specific operation strongly depended on applied SS. Figure 3B shows corresponding shock-end (7 ms) \( V_m \) distributions following 5-, 10-, 20-V shocks in the simplified model. For weak shocks (5 V), the second shock phase lacks sufficient strength to reverse the negative polarization set up by phase 1. Thus, only a single excitation from the first phase exists at shock end, occurring in regions of relatively high field strength in the LV and septum. For intermediate shocks (10 V), both phases have sufficient strength to elicit strong surface depolarizations and induce 2 separate break excitations; however, their extent is not as widespread as for stronger shocks, leading to an asymmetrical (and slower) closing down of excitable gaps in the LV and septum. At 20 V, the break excitation pattern from the shock becomes more similar to that seen at 40 V (Figure 3A), although the speed at which the break excitations propagate and close down the excitable gaps increases with SS (discussed later).

Finally, Figure 3C shows the corresponding postshock 10-ms image following a 40-V shock in the vessel model, demonstrating a very similar mechanism to that shown in Figure 3A. Here, however, less of the excitable gap remains, particularly in the septum, suggesting that the presence of vessels assists in closing down the excitable gap through this biphasic mechanism, which we further investigate next.

### Role of Vessel-Mediated Virtual Electrode Formation in Defibrillation

During all strong shocks (20–70 V), virtual electrodes were seen to form around blood vessel structures in all defibrillation episodes in the vessel model, largely focused around regions of high field strength (septum and posterior LV) and more significant around larger vessel structures. Following the shock, break excitations were elicited from these virtual electrodes, most evidently in intramural regions containing excitable areas, which themselves were relatively unaffected by the direct action of the shock.

### Interaction With Main Biphasic Defibrillation Mechanism

Figure 4A shows an example of vessel-mediated virtual electrode formation following a 40-V shock applied to state I1 of the vessel model. Here, vessel-induced break excitations produce new wavefronts, which propagate through excitable intramural tissue between the larger break excitation wavefronts (originating from myocardial surfaces) brought about by the main defibrillation mechanism. Consequently, the intramural excitable gap, located predominantly within the septum, is more rapidly closed down than in the corresponding 40-V postshock simplified model case (Figure 4B) where large excitable gaps remain most noticeably in the septum.

Figure 4C quantifies this effect, showing how the percentage of intramural septal tissue changes preshock and postshock for all SS applied to states I1. In the vessel model, as SS increases, less excitable tissue exists within the intramural septum both at shock end and at postshock. For higher SS, the virtual electrodes formed around vessel cavities become stronger and larger, increasing the amount of intramural tissue depolarized at shock end. These larger virtual electrodes are then more able to elicit break excitations on cessation of the shock, depolarizing larger amounts of tissue postshock as they propagate away from cavities.

In contrast, the amount of intramural septal excitable tissue within the simplified model remains relatively constant throughout the shock for all SS in the absence of intramural cavities around which virtual electrodes may form and because the direct effect of the shock decays exponentially from the tissue surface, not affecting intramural tissue. Although there is a decrease in excitable tissue postshock, as break excitations from either side of the septal wall (because of the main defibrillation mechanism) invade the intramural area, the extent of the excitable area is still significantly greater than the corresponding area in the vessel model. Note, however, that such an effect is most significant where regions of large preshock excitable gaps coincide with areas of high field strength.

### Overall Quantitative Effect of Vessels

Up to now, we have focused on one particular defibrillation episode, demonstrating how vessel-mediated virtual electrodes assist defibrillation by closing down intramural excitable gaps. Here, we quantify this trend across all episodes, investigating how applied SS affects the witnessed mechanism.

Figure 5A shows that the mean decrease in LV and septum intramural excitable tissue (relative to preshock), both at shock end (left) and at postshock (right), is greater in the presence of vessels, a difference that increases with SS as vessel-mediated virtual electrodes increase in size, strength, and number, which is most evident at shock end. For example, the simplified model shows a relatively small decrease even at high SS: 28.5% at 70 V compared to a 63.8% decrease in the vessel model. Postshock, differences between the models are less because of propagation of surface-mediated break excitations from the main mechanism into intramural regions. Overall, for all 30 pairs of defibrillation episodes (5 SS, 6 initial states), the greater decrease seen in the vessel model was statistically significant for both shock-end
and postshock (P<0.0003) cases, assessed using a Wilcoxon signed rank test (see online-only Data Supplement for details). Note that the RV was not included because the direct action of the shock strongly affected all intramural regions.

Such a vessel-assisted reduction in intramural excitable regions following the shock also affected the overall time course over which successful defibrillation occurred. Figure 5B shows that the percentage of defibrillation shocks to achieve entire elimination of all wavefronts <15 ms following the shock is greater in the vessel model over all SS. This difference is, again, statistically significant, considering this binary outcome over all 30 matched pairs of defibrillation episodes with P<0.03 as assessed by McNemar test to compare proportions in the 2 models (see online-only Data Supplement for details). However, differences between models become most noticeable at strong SS because of the more widespread formation of virtual electrodes surrounding vessels that also become larger and stronger. Finally, in addition to vessels interacting via break excitation wavefronts formed through the main defibrillation mechanism, they were frequently seen to play an important role through their interaction with existing activation wavefronts (online-only Data Supplement).

Defibrillation Failure Because of Intramural Wavefront Survival

In one particular strong shock episode (40 V), lack of activation of intramural areas because of the absence of vessels in the simplified model resulted in defibrillation failure.
failure (Figure 6); comparatively, defibrillation succeeded in all such strong shock episodes in the vessel model. Here, preexisting refractory tissue in the anterior LV wall prevents propagation of break excitations mediated from epicardial and endocardial surfaces through the main defibrillation mechanism into intramural tissue (7 ms). Furthermore, the lack of vessels means that the existing wavefront within the septum (0 ms) is largely unaffected by the shock, which thus continues to propagate through the now recovered excitable region in the anterior LV wall (35 ms). Consequently, this sole existing intramural wavefront continues its progression, eventually breaks up, and causes defibrillation failure.

**Effect of Vessels During Weak Defibrillation Shocks**

Although most evident during strong shocks, vessels were also seen to have an important impact during weaker shocks (5–10 V). Figure 7 shows such an example, demonstrating the occurrence of conduction block in the vessel model because of the formation of a weak, but noticeable depolarization around a large blood vessel in the RV free wall (highlighted) that was insufficient to induce break excitation itself. In contrast, the RV wall in the simplified model remained unaffected by the shock; thus, the wavefront (present in a similar location to that in the vessel model) can propagate freely through the wall, assisting the sustenance of the arrhythmia.

**Identification of Minimum Vessel Cavity Size of Importance**

Having identified that vessels play their most important role in defibrillation by providing the nucleus for break excitations, which help to close down local excitable gaps, we now identify the minimum vessel cavity size that supports this mechanism. A series of highly simplified models representing vessel cavities of radii 50 to 500 μm within a wedge of ventricular wall was created (online-only Data Supplement), and biphasic shocks of SS 2.5 to 75 V/cm were applied. Figure 8A shows $V_m$ distributions 1 and 7 ms into the shock for a selection of stronger shocks applied to smaller cavity models (50–100 μm).

The smaller cavities act primarily as insulators, causing virtual electrode patterns as current redistributes between intracellular and extracellular domains (because of respective differences in fiber and cross-fiber conductivities) as it is diverted around the cavity. However, intriguing to note is that larger cavity sizes act primarily like conductors, causing different virtual electrode patterns as current passes through the extracellular space of the cavity (online-only Data Supplement).

Figure 8B plots the minimum SS at each cavity radius required to induce break excitations within the tissue. Together, Figure 8A and 8B show that even the strongest 75-V/cm shock cannot induce a break excitation within the 50-μm model and is just strong enough to induce one in the...
75-μm model, but the 100-μm model has an excitation threshold of just 40 V/cm. Such cavity dimensions at which an appreciable effect is witnessed is of the same order of magnitude as the transverse length constant (≈0.2 mm) as expected from theoretical considerations.

To replicate potential electrotonic interactions of increased packing density of smaller vessels (50- to 100-μm radii) the protocol was repeated in 4 vessels of each size evenly packed within a 0.81 mm² square (4.9 mm²). This increased packing density did not change the minimum SS predicted by Figure 8B for the 50- to 100-μm radius cavities. Finally, the packing density was increased further for the 50-μm vessels to 9 (11.1 mm²), which still did not induce a break excitation at 75 V/cm. V_m distributions 1 ms into 75-V/cm shocks are shown in Figure 8C for the 50-μm cavity for 4 and 9 vessels.

**Discussion**

In this study, we highlight the importance of the coronary vasculature during clinically realistic defibrillation using an MR-derived high-resolution rabbit ventricular bidomain model, which facilitated unprecedented access to intramural polarization distributions during and following biphasic shocks. Specifically, we elucidate the mechanisms by which vessel-mediated virtual electrode formation assists termination of existing reentrant activity, acting synergistically with the main biphasic defibrillation mechanism also uncovered (driven by excitation of external myocardial walls), and identify a minimum cavity size necessary for this mechanism.

**Common Mechanism for Biphasic Defibrillation**

At the tissue and organ level, the main experimentally driven theories for the increased efficacy of biphasic (as opposed to monophasic) defibrillation shocks have centered on how biphasic waveforms fail to produce a substrate for reinitiation of fibrillation. However, unlike our modeling approach, such surface measurement techniques cannot elucidate how biphasic shocks effectively eliminate existing intramural activity.

Our explicit analysis of intramural polarization levels during and after both shock phases allowed us to uncover a fundamental mechanism by which successful biphasic defibrillation was achieved over a range of SS and initial states (Figure 3). The mechanism involved the rapid closing down of excitable gaps through successive break excitations from exterior myocardial walls (set up after each shock phase). Strong shocks induced stronger and more-complete break excitations, extending more fully along myocardial walls than weaker shocks, eliminating excitable tissue more efficiently (Figure 3B). Although a similar mechanism of biphasic defibrillation has been suggested previously in a 1D fiber model, the present study presents novel elucidation of the mechanistic analysis of its operation during clinically relevant defibrillation at the ventricular level.

Although assisted by the presence of vessels, the fundamental basis of the mechanism was seen to be common to both vessel and simplified models (Figure 3A and 3C). Such a finding provides an explanation for the lack of a significantly large difference in defibrillation success rates between the 2 models as well as the close comparison between previous simulation studies using more simplified models with experimental findings.

**Interaction Between Vessel-Mediated Virtual Electrodes and Defibrillation**

Fine-scale intramural discontinuities in tissue structure have been postulated to play a crucial role in defibrillation through
creation of virtual electrodes, assisting bulk activation of a critical myocardial mass. For the first time to our knowledge, the present high-resolution biventricular model has allowed investigation of how fine-scale structures, such as blood vessels, affect the process of defibrillation using a clinically realistic ICD setup.

This study has demonstrated that virtual electrodes form around intramural vessel cavities, helping to eliminate pre-shock intramural excitable gaps and extinguish existing reentrant activity. Such shock-induced vessel-mediated effects were seen to increase, and thus depart further from the simplified model, with SS; as virtual electrodes become larger, stronger, and more widespread with increasing SS (as field strength is sufficiently high in more areas), a larger volume of intramural tissue is directly activated by the shock, and quicker eradication of postshock excitable gaps by faster propagating break excitations occurs. Although in our ventricular slice model the more rapid closing down of postshock excitable gaps due to vessels did slightly increase defibrillation success, this mechanism may be of more importance at the whole-ventricle level.

Even at weak shocks, mild shock-induced depolarizations around large vessels were seen to result in conduction block, assisting reentry termination. In addition, such mild effects can interact more subtly, slightly slowing intramural wavefronts through both direct interaction with the wavefront itself (online-only Data Supplement Figure V) and the creation of mild depolarizations in excitable gaps in its path (data not shown). Consequently, both these effects demonstrate how vessels can assist in the disruption of existing (intramural) fibrillatory activity, even at weak shocks, suggesting an explanation for the overall defibrillation success of the vessel model.

Finally, previous conceptual studies in 2D sheet models have suggested the importance of small-scale virtual electrodes formed by microscopic fluctuations in tissue conductivity in preventing reinitiation of reentry during defibrillation. Although in the present study we focused primarily on extinguishing existing fibrillatory activity, we suggest that virtual electrodes induced around vessels (representing larger heterogeneities) could also play an important role through this mechanism.

**Virtual Electrode Patterns Produced by Vessels**

The wedge model in Figure 8 allowed careful analysis of how the shock-induced break excitation mechanism scaled with vessel size. It also uncovered an intriguing fundamental biophysical interaction between shock-induced current flow and the vessel cavity. Specifically, the insulating effects of the low-conductivity lumen wall combined with the highly conducting bath within the cavity leads to size-dependent polarization. Small-diameter vessels act as insulators because the resistance of crossing the lumen is large relative to the added intracellular resistance encountered negotiating the vessel. With larger diameters, intracellular path length increases while increased surface area reduces lumen resistance, making the vessel act more like a conductor. Conductor and insulator effects differ in their induced polarity because one will promote intracellular to extracellular current flow, whereas the converse occurs in the other. However, the most important issue identified in this study is that regardless of polarity and underlying mechanism, virtual electrodes form around vessels and initiate break excitations that help to defibrillate. Overall, the results from the present study qualitatively strongly agree with a recent experimental study identifying the importance of vessels during low-energy defibrillation therapies and reinforce its findings by providing important 3D knowledge regarding the intramural behavior of the vasculature during such protocols. Uncovering such an important biophysical mechanism could have important applications in helping to understand similar interactions of electric fields with other heterogeneities, such as infarct scars or myolaminar sheets.

**Implications for Simplified Models**

In the simplified model, even at stronger SS where the direct activation of the shock extends further into the midwall (eg, because of virtual electrode effects as a result of fiber curvature and biventricular geometry), large intramural excitable regions still exist at shock end, which were seen to be present to a lesser extent in the vessel model. Consequently, as shown in Figure 7, we uncovered a case in which defibrillation failed in the simplified model at a strong (40-V) shock compared with the vessel model that successfully defibrillated all episodes. Here, the absence of vessel-induced effects in the midwall provided an excitable avenue in the LV-septum junction through which a wholly intramural wavefront could continue to propagate, sustaining reentry. Because this mechanism is similar to that of tunnel propagation (shown recently in a study using a simplified whole-ventricular model), the results from the present study suggest that such tunnel propagation is suppressed in the presence of vessels. However, we believe that the high nonuniformity of the ICD field (particularly within a full ventricular model) will in fact leave many regions of the thick LV wall with an insufficient field strength to produce virtual electrodes around vessels, thus leaving intramural excitable gaps through which tunnel propagation may occur. Nevertheless, we could expect the presence of vessels within the model to attenuate the degree of potential tunnel propagation avenues and possibly help to explain differences in their location witnessed between simulations and experiments.

**Implications for High-Resolution Cardiac Imaging and Model Generation**

We have identified that only vessel cavities greater than ~100 μm radius play an important role in defibrillation by providing the nucleus for shock-induced break excitations, which rapidly close down excitable gaps in the vicinity of the cavity (Figure 8). The specific relationship between cavity size and required SS agrees qualitatively with that predicted in a recent analytic study using a simplified linearized bidomain approximation and quantitatively predicts a similar minimum cavity radius (~150 μm). This finding has significant implications for high-resolution cardiac image acquisition and computational model development for...
mechanistic defibrillation investigation, providing an important lower limit on the required resolution of a particular imaging modality used to generate the model. Identifying features >200 μm across suggests that lower resolution (~100 μm) MR and diffusion tensor MRI may be sufficient for model construction as opposed to the potential use of histological data, which present many more challenges both for imaging and for model generation.7,11 Finally, coarser computational models may facilitate the future use of finite element meshes with fewer degrees of freedom, lowering the burden of such highly computationally intensive simulations and widening the scope of what is tractable to simulate.

Study Limitations

Although our model incorporates, to our knowledge, an unprecedented level of structural detail, it is somewhat limited by its slice geometry. Primarily, although the biventricular geometry still faithfully represents many important reentry pathways, the nature of the sustained arrhythmias preshock, as well as postshock activation sequences, may differ when scaled up to the whole-ventricular level. However, throughout the study, conclusions were drawn for comparisons made between the vessel and simplified models, and care was taken to match the initial complexity regarding the intermyolaminar cleavage planes seen in histological success were of statistical significance.7,14 the large, highly detailed mesh combined with small time steps required for strong ICD shocks resulted in significant computational demands on each simulation (a 10-ms bidomain shock episode required ~20 hours on 32 cores). Consequently, the number of initial fibrillatory states, maximum SS, and number of SS used were limited, preventing computation of a full defibrillation threshold-90 plot16 and assessment of whether the present results of overall defibrillation success were of statistical significance.

Although our MR-derived model contains intramura lar vessel cavities, absent from our model is fine-scale detail regarding the intermyolaminar cleavage planes seen in histological reconstruction models. The histological preprocessing stage used to acquire such data involves dehydrating the tissue, reducing myocyte volume, and exacerbating apparent cleft sizes. However, such structures are not visible in lower-resolution (fully hydrated) MR data. Although simulations7 and experiments22 have identified the potential importance of clefts as a substrate for virtual electrode formation, it remains an open question as to what extent this is affected by accentuated cleft size.

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Disclosures

Drs Vigmond and Plank are affiliated with Cardiosolv LLL (Baltimore, MD).

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CLINICAL PERSPECTIVE

The effects of electrical shocks for defibrillation are incompletely understood. Specifically, exactly how externally applied electric fields successfully activate a sufficient mass of myocardium to defibrillate and the effect of fine-scale heterogeneous cardiac anatomical features, such as blood vessels, remain unknown, in part because of limitations of mapping resolution. We studied computer simulations of shocks applied to an anatomically detailed ventricular myocardium model. We found that intramural blood vessels play a vital role in defibrillation by providing additional virtual electrode-induced postshock excitations, which facilitate a more-rapid closing down of preshock excitable gaps and consequent elimination of fibrillation wavefronts. A novel explanation for the greater efficacy of biphasic as opposed to monophasic defibrillation shocks is also suggested. These findings provide guidance about the degree of resolution of fine-scale anatomy required for computational models that can help to further unravel defibrillation processes. Such studies are hoped to facilitate development of novel low-voltage and patient-specific defibrillation methods.
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Investigating the Role of the Coronary Vasculature in the
Mechanisms of Defibrillation:
SUPPLEMENTAL MATERIAL

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1 Methods
1.1 Computational Model
1.1.1 Geometrical Model Generation

A ventricular slice model, of thickness 1.5mm, was generated directly from a previously published high resolution rabbit MR data set (voxel resolution \(\approx 25\mu m\) isotropic) [1]. The full resolution grey-scale MR data was segmented using a series of level-set filters (Insight Toolkit Library) combined into a sequential processing pipeline, as described previously [1]. Manual morphological cleaning operations were performed to remove small segmentation artifacts, and free papillary muscles removed.

Blood vessel cavities within the slice were identified and tagged using a connected component algorithm applied to the segmented image stack, through manual selection of seed points at the top of main vessel trees, along with constant referral back to the original MR data. Of all of the intramural cavities and spaces visible in the MR data, over \(\sim 95\%\) were believed to be blood vessels, with the rest being composed of large extracellular cleft spaces.

The meshing software Tarantula (www.meshing.at), based-upon a recently published mesh generation algorithm [2], was used to generate a tetrahedral finite element mesh directly from the segmented (and tagged) voxel image stack, shown in Fig. 1 (left). The total mesh produced (consisting of myocardial tissue, plus surrounding bath volume within the intramural and ventricular cavities) consisted of 3256138 nodes defining 18858822 tetrahedral elements with a mean myocardial element edge length of 62.3\(\mu m\). Due to the high-resolution mesh required in order to faithfully represent intramural structures, performing a whole ventricular study was unfeasible.

To faithfully represent the in-tact ventricular preparation, no bath was represented above or below the cutting-plane of the slice.

1.1.2 Cardiac fiber Architecture Assignment

Cardiac fiber architecture was assigned to the model using the rule-based method described previously [3], developed to successfully represent two key aspects of cardiac fiber orientation:

1. Cardiac fibers run primarily in a circumferential direction through the myocardial wall with an additional inclination angle in the apex-base direction [4, 5], which varies transmurally by approximately 120 degrees from epicardial to endocardial, being approximately zero in the mid-wall [4, 5];

2. fibers negotiate around intramural structures in a continuous manner [6].

Briefly, the method involves computing the solution of an electric potential, \(\Phi\), within the tissue between two electrodes using Laplace’s equation \((\nabla^2 \Phi = 0)\) where isotropic conductivity
Figure 1: Finite element ventricular slice model with highlighted region showing orientation of cardiac fibers assigned using the rule-based method described in Section 1.1.2.

is assumed. A voltage is assigned between the electrodes and no flux boundary conditions are imposed on all other surfaces. Field lines will therefore terminate only on the electrodes and be tangential to all other surfaces. The resulting potential gradient will be smooth and globally point from one electrode to the other, but importantly, navigate around local discontinuities, i.e. holes in the tissue. By solving for two electrode configurations which are orthogonal to each another, a basis set was constructed which describes the transmural, apicobasal and circumferential fiber components.

Fig. 1 shows the fiber architecture within a transmural slice along the $xy$-plane, with the color bar representing the out-of-plane component of the fiber vectors. As can be seen, the rule-based fiber-assigment approach successfully accounts for the well-documented transmural variation in helix angle [4, 5], as well as the continuous negotiation of fibers around intramural structures seen in histology [6, 3].

1.1.3 Absence of Surface Polarization Effects

Due to our particular fiber orientation distribution described above, combined with the specific electric field configuration, we do not see any shock-induced surface polarization effects (on the upper/lower sides of our slice model) which can be induced by a shock when fibers approach a sealed boundary at an angle, as shown previously in Roth (1999) [7]. Our electrode set-up (shown in Fig. 2) induces a field which is almost always transmural, as is mostly the case during external electric field stimulation. In addition, fibers run approximately tangential to the surface (with an additional small helix angle inclination) and are, therefore, always approximately perpendicular to the applied field. Transmural rotation of fibers still maintains a tangential fiber direction. Therefore, in the ventricular slice set-up, we have no (or very little) variation in conductivity in the direction of the transmural field, which is a requirement for inducing surface polarization via this mechanism.

1.1.4 Blood Vessel Representation

Blood vessel cavities were identified as tagged regions transferred to the finite element mesh from the segmented voxel image stack. As in our previous study, to represent the reduced electrical conduction through the connective tissue of the vessel lumen wall, elements within the extracellular bath that directly bordered the blood vessel/myocardium interface were tagged and subsequently assigned a distinct electrical conductivity measured experimentally [3].
The competing constraints of attempting to attain a specified mean element edge-length whilst still faithfully resolving the intricate details of small vessel cavities means that the specific thickness of the lumen wall represented in our finite element models approximates well the physiologically-witnessed increase in lumen wall thickness to cavity diameter ratio [8]. Overall, we believe this provides a very good approximate representation of realistic lumen wall thicknesses for the range of vessel sizes included within the model. Furthermore, our model does not at this stage represent different lumen wall thicknesses for arteries and veins. However, in a previous study we demonstrated the weak sensitivity of shock-induced effects with respect to the specific wall conductivity over plus/minus an order of magnitude [3]. Thus, we believe any differences between artery/vein thicknesses (expected to be less than a factor of 2) would not represent a significant change in the results of this present study.

1.1.5 Comparison with Simplified Model

To facilitate direct dissection of the role played by intramural structures, a simplified model was also produced in which all intramural cavities (blood vessels, extracellular cleft spaces) were filled-in at the segmentation stage, prior to meshing. The simplified model (shown in Fig. 2) contained only myocardial tissue throughout, and had fiber architecture assigned using the same rule-based approach described above. Identical stimulation protocols were applied to both complex and simplified models throughout via similarly placed electrodes.

![Figure 2: Simple ventricular slice model, demonstrating electrode set-up used for biphasic defibrillation shocks described in Section 1.3.2.](image)

1.1.6 Applicability and Scalability of Bi-Ventricular Slice Model

Although slightly limited in the size in the apex-base direction, we nonetheless believe that our ventricular slice model provides a faithful representation of reality and that the results obtained in this model apply and scale fully to the whole ventricles. Specifically, the bi-ventricular nature of the model still faithfully represents the important reentry pathways and captures the strongest variations in fiber architecture (circumferential and transmural). These features, combined with the fact that it does in fact represent an appreciable size in the $z$-direction (1.5 mm) means that it still captures the important features and complexity of fibrillatory activity, with the overall patterns and number of filaments scaling with what would be expected in the whole ventricles. Furthermore, our model successfully represents important heterogeneity in electric field such that the field direction is approximately always transmural, and thus captured well within our slice model. Consequently, the most important feature of the transmural field is the strong polarization it causes of epicardial/endocardial walls which our model correctly represents, matching well those results seen from previous whole-ventricular studies. In addition, the majority of larger blood vessels tend to run primarily in an apex-base direction ($z$), having their axes perpendicular to the applied electric field. Therefore, the virtual-electrode patterns
formed around the vessel cavities will show the largest variation in the \( xy \)-plane and be relatively uniform in \( z \) (due to the transmural field direction). Consequently, as shown in the study (and in Fig. 5, for example), the break excitation wavefronts from the vessel cavities will always propagate primarily in a transmural direction, having little variation in \( z \).

1.2 Simulating Electrical Activation

1.2.1 Governing Equations

Electrical activation throughout the ventricular model was simulated using the bidomain equations [9]

\[
\begin{align*}
\nabla \cdot \hat{\sigma}_i \nabla \phi_i &= \beta I_m \\
\nabla \cdot \hat{\sigma}_e \nabla \phi_e &= -\beta I_m - I_e \\
I_m &= C_m \frac{\partial V_m}{\partial t} + I_{ion}(V_m, \eta) - I_s,
\end{align*}
\]

where \( \phi_i \) and \( \phi_e \) are the intracellular and extracellular potentials, respectively, \( V_m = \phi_i - \phi_e \) is the transmembrane voltage, \( \hat{\sigma}_i \) and \( \hat{\sigma}_e \) are the intracellular and extracellular conductivity tensors, respectively, \( \beta \) is the membrane surface to volume ratio, \( I_m \) is the transmembrane current density, \( I_e \) is an extracellular stimuli, \( I_s \) is a transmembrane stimulus, \( C_m \) is the membrane capacitance per unit area, and \( I_{ion} \) is the membrane ionic current density which depends on \( V_m \) and a set of state variables \( \eta \). At tissue boundaries, no flux boundary conditions are imposed on \( \phi_i \), with \( \phi_e \) and the extracellular current being continuous. The tissue is surrounded by a conductive bath with no flux boundary conditions for \( \phi_e \).

1.2.2 Tissue Parameter Assignment

Conductivities along the fiber and cross-fiber directions were based on previous experimentally-derived values [10] within the intracellular (0.174S/m, 0.0193S/m) and extracellular (0.625S/m, 0.236S/m) domains, respectively, which were then uniformly scaled to reduce conduction velocity by 25%, in-line with similar reductions shown during heart failure [11]. Such a reduction is made to account for the experimentally-observed lateralization and hypophosphorylation of Cx43 during heart failure which controls the flow of current between cells [12, 13]. The vessel lumen wall was assigned the experimentally-derived conductivity from our previous study [3] of 0.010S/m (isotropic) in the extracellular domain. Conductivity of the surrounding extracellular bath (including bath within vessel cavities) was set to 1.0S/m (isotropic), representing a perfused tissue arrangement.

Cell membrane dynamics within the myocardial tissue were represented by a recent rabbit ventricular cell model [14]. To represent a fibrillatory-like state, APD restitution was increased in the ventricular cell model through a slight modification of the parameter controlling the recovery from inactivation of the L-type calcium channel, which has been shown to control restitution and spiral-wave stability without significantly impacting APD morphology. The parameter, termed \( R(V) \) in the Mahajan et al. (2008), was multiplied by a factor of 3. Furthermore, to reproduce the asymmetry of the membrane response to strong shocks delivered during the plateau phase of the action potential, the cell model was further augmented [15] with two additional currents, an electroporation current and a hypothetical potassium current that activates at larger positive polarizations beyond +160mV.
1.2.3 Computational Considerations

The bidomain equations were solved with the Cardiac Arrhythmia Research Package (CARP) [16, 17]. The specifics of the numerical regimes used in CARP have been described extensively elsewhere [18, 16]. Briefly, the bidomain equations are recast to retain $V_m$ and $\Phi_e$ as the independent variables. CARP then solves the bidomain equations by using an operator-splitting technique which separates-out the ODE system from the PDEs, producing 3 components: an elliptic PDE, a parabolic PDE and a non-linear system of ODEs. Solutions are then found by leap-frogging between the decoupled components where either $V_m$ or $\Phi_e$ are considered constant. Discretization of the decoupled equations leads to a 3-step scheme, which involves finding a solution to the parabolic PDE, the elliptic PDE and the nonlinear ODEs at each time-step. In the case of a fine mesh, it is advantageous to employ the computationally more expensive semi-implicit Crank-Nicolson scheme, as this method supports larger time-integration steps. The Rush-Larsen method is used to solve the system of ODEs. An ODE time-step of 20$\mu$s was used during pre- and post-shock activity with 0.25$\mu$s used during shock application to ensure computational accuracy.

Simulations were performed on the Oxford Supercomputing Centre clusters. Visualisation of results was performed with the custom written Meshalyzer software.

1.3 Simulation Protocol

1.3.1 Induction of Fibrillation

Fibrillation was induced in both models through rapid pacing at a progressively decreasing cycle length followed by the application of a strong external monophasic shock of shock strength (SS) 10 – 20V via a plate electrode set-up similar to that described previously [1] along the $yz$ outer planes of the surrounding bath. The pacing was conducted along the lower face ($z = 0$) of the slice model to approximate propagation following an apical stimulus.

The induced episodes of sustained VF had mean filament numbers of between 2.5 – 4.1. Using scaling arguments through consideration of the reduced myocardial tissue volume represented by our slice model, this is in line with previously reported numbers of filaments within whole ventricle computational simulations of VF in the rabbit [19] and numbers of epicardial phase singularities observed in experiments [20]. A selection of initial states, separated by at least 50ms intervals, were chosen from the fibrillatory episodes, which then acted as preshock states for the defibrillation shock delivery. A total of 6 initial states were selected, chosen to provide a wide range of possible initial conditions, in terms of number of individual reentrant wavefronts present, total volume of tissue activated/excitable in LV/RV/septum and distribution and location of the respective wavefronts and excitable regions.

As closely as possible, initial states were matched between complex and simple models, notwithstanding the inherent complexity of the fibrillatory-episodes. The initial states chosen are shown in Fig. 3.

1.3.2 Defibrillation Shock Application

ICD electrode set-up for defibrillation shock delivery was based upon that used in Constantino et al. [21], modified for use in our ventricular slice model. The set-up, shown in Fig. 2, included a catheter placed in the right ventricle (RV) of diameter 6 French [22] and an active can in the bath near the posterior left ventricle (LV).

Biphasic defibrillation shocks of SS between 5–70V (referring to the leading-edge voltage) were delivered via the ICD set-up to the tissue in the selected initial fibrillatory states, described above. In-line with previous studies [21], the RV catheter acted as the anode during the first
Figure 3: Transmembrane potential distributions within the 6 chosen initial fibrillatory states (I1–I6) in vessel (top) and simplified (bottom) models.

phase of the shock with the active can acting as ground. During the second phase of the shock, polarity was reversed with its magnitude 50% of the first. Tilt and duration of each phase were 50% and 3.5ms, respectively [22, 21].

Note that here we specify SS in terms of absolute voltage. However, as the thickness of the LV/septal walls is approximately 0.3–0.6 mm, the shortest path taken between electrodes will drop all of the applied voltage over a tissue thickness of approximately 1 cm. Thus, the maximum SS applied in terms of V/cm can be approximated by dividing the specified SS by 1.0 cm i.e. a SS of 40 V corresponds to maximum field strength of 40 V/cm.

1.4 Data Analysis

1.4.1 Filament Detection

The organizing center of a reentrant waveform is represented by a scroll-wave filament, the 3D analogue to the phase singularity. The algorithm used for filament detection was based-on the approach of Fenton & Karma (1998) [23], which was adapted for use within an unstructured finite element regime. The method defines the location of a filament as the intersection of the isosurfaces of $V_m = V_{iso}$ and $\frac{dV_m}{dt} = 0$. If an intersection is found to occur within a finite element, that element is tagged as containing a filament. The coordinates of the point of entry and exit of the filament section through the element are also computed. Extensive testing was performed with the implemented algorithm and optimised values of $dt = 8$ms (the time-delay over which the condition $\frac{dV_m}{dt} = 0$ is computed) and $V_{iso} = -40$mV were found specifically for the Mahajan et al. (2008) [14] rabbit ventricular cell model used. Filaments were analysed through episodes of VF, and used to assist the comparison and matching of initial fibrillatory states between vessel and simplified models in terms of number of filaments and their locations.

1.4.2 Quantification of Shock-Induced Effects

Previous studies have defined induced post-shock arrhythmias as sustained if reentrant activity lasts for > 280ms [21]. Due to the reduced myocardial volume of our slice model, we approximately scaled this limit accordingly to 100ms, thus approximately accounting for the time take for reentrant waves which leave the domain of the slice to disperse the rest of the ventricular volume.

Tissue was classified as excitable if $V_m < -60$mV, the threshold for inactivation of the sodium current. Intramural tissue was defined as points lying within $0.25 < e < 0.75$, where $e$ is the normalised transmural distance in the direction endocardium to epicardium.
1.4.3 Statistic Significance

Due to the huge computational burden involved in performing strong defibrillation shocks using a small numerical time-step (0.25 $\mu$s) over a fine computational grid ($> 3$ m degrees of freedom), the number of initial fibrillatory states examined was therefore limited to 6 (per SS), as described above. We feel that this was sufficient to assess whether the presence of vessels within the model increased or decreased the success and rate of defibrillation, providing enough scenarios to allow us to analyse in detail the mechanisms responsible for this change. However, in certain cases it did not allow us to fairly test whether any change was statistically significant as, due to the very low number of trials (6 per SS), computation of the null hypothesis probability was not sufficiently robust in these binary outcome events. Ideally, a much larger number of shock episodes would have been performed to more accurately assess the assumed probability of successful defibrillation at each SS with the simple model (perhaps $> 100$), providing the required null hypothesis probability against which the results from adding the presence of vessels could be tested.

The highly complex nature of the initial reentrant activity prior to shock delivery did lead to a large variability in initial pre-shock states considered, particularly in terms of location, extent and magnitude of excitable gaps. This, combined with the low number of initial states used to perform quantitative analysis of certain metrics throughout the study, did, at times, lead to relatively large statistical variances in calculated means meaning that attaching a high-level of statistical significance to these results is challenging. None-the-less, such quantitative analysis is included within the manuscript to demonstrate the quantitative differences in mean data which do exist between the vessel and the simplified models, and importantly to reinforce the qualitative mechanisms which are the fundamental focus of our simulation study. In certain cases, due to the fact that initial states were closely matched between vessel and simplified models, tests were performed based on matched pairs, as described below.

1.4.4 Statistical Methods

In Figure 5(a) of the main manuscript, the mean decrease in excitable gap within the LV/septum both at shock-end and post-shock was calculated at each SS for vessel and simplified models. However, in order to assess whether the larger decrease seen in the vessel model (relative to the simplified model) in each episode was statistically significant, a Wilcoxon signed-rank test [24] was performed upon all 30 matched pairs of defibrillation episodes i.e. 5 SS for each of the 6 initial states in both models. Such a method is suited to this situation as it is a non-parametric test which does not require the population data to be normally distributed. The method ranks the absolute differences between data pairs $|X_a - X_b|$ (excluding cases in which $|X_a - X_b| = 0$) in numerical order and then assigns a sign to each rank being positive if $X_a - X_b > 0$ and negative if $X_a - X_b < 0$. The $W$ statistic is then calculated as the sum of the signed ranks from which a $p$-value is derived. For sample sizes of approximately more than 20 matched pairs, the distribution of all possible ranks tends towards a normal distribution. Here, we have 30 matched pairs of defibrillation episodes and so use a normal distribution to obtain one-tailed probabilities. We use a one-tailed test as we are assessing whether the vessel model induces a larger decrease in intramural excitable tissue than the simplified model, and thus direction is important. $p$-values quoted in the manuscript associated with Figure 5(a) are calculated in this manner.

In Figure 5(b) of the main manuscript, the percentage of shocks which have activity entirely eliminated within $< 15$ ms of shock-end for each of the two models is shown. This metric thus represents a binary outcome in which the McNemar test can be used to compare the proportions in the two models over all 30 matched defibrillation episode pairs. The McNemar
test is a non-parametric test which assesses the marginal homogeneity of matched pairs. In our particular case, it is used to assess whether there is a significant difference between the total number of times in which a matched pair successfully eliminated activity < 15 ms in the vessel model but not in the simplified model (B), relative to the total number of times in which a pair successfully eliminated activity < 15 ms in the simplified model but not in the vessel model (C). Due to our relatively small number of matched pairs (B + C < 25), the probability of obtaining our results (p-value) was obtained directly using a binomial distribution, as quoted in the text.

1.5 Generation of Toy Wedge Models for Cavity Size Analysis

In addition to the anatomically-realistic ventricular slice model, a series of highly simplified toy models were also generated representing small wedges through the LV or septal wall. The toy models were regular in shape, measuring 4 × 2 × 1 mm, where the x-direction represents the approximate width of the LV/septal wall, y is the circumferential direction and z the apex-base direction. Cylindrical vessel cavities, of varying radii between 50–500 µm, were then defined within the center of the wedge with the axis of the cylinder in the apex-base direction, thus representing the most common orientation of vessels within the wall. As in the anatomically-realistic slice model, a perfusing bath was defined to surround the wedge outside the epicardial/endocardial walls (i.e. in the x-direction) as well as within the vessel cavity. However, no bath was placed either above/below the wedge nor outside in the y-direction to approximately represent the continuous myocardium which would be present in the intact ventricles (and in the slice model of Fig. 1). Exterior to the epicardial/endocardial surfaces of the toy wedge model were placed plate electrodes (parallel to, and 1 mm distance from, the surfaces). Fig. 4(a) shows an example of the toy model set-up for a 300 µm radius vessel cavity including electrode placements.

Both fiber orientation and the reduced conductivity of the vessel cavity lumen wall were assigned to the toy wedge models using an identical approach to that used in the ventricular slice model (described in Section 1.1.2 & 1.1.4 and [3]), shown in Fig. 4(b). To replicate the electrophysiological state of the tissue during VF, and the appearance of an excitatory gap, the toy wedge models were paced rapidly (over the entire z = 0 lower face) for 10 beats. Biphasic shocks were then applied to the tissue 200 ms following the last pacing beat such that the tissue had almost completely recovered, replicating the formation of an excitatory gap. Shocks, of SS between 5–75 V/cm, were applied via the electrode set-up shown in Fig. 4(a) with the same temporal features and numerical details as used in the slice model (described in Section 1.3.2). Post-shock activity was then simulated to assess whether the vessel cavity induced a break excitation or not.

2 Results

2.1 Interaction of Shock-Induced Vessel Effects with Existing Wavefronts

In addition to the shock-induced effects of vessels interacting with the break excitation wavefronts formed through the main defibrillation mechanism, they were also frequently seen to play an important role through their interaction with existing activation wavefronts.

Fig. 5 shows an example of such a scenario. Pre-shock, the large reentrant wavefront in the posterior LV of the vessel model is slightly less advanced than the corresponding wavefront in the simplified model (dashed arrow). Upon shock application, activation of intramural tissue surrounding vessel cavities within the vessel model directly interacts with the wavefront, attenuating its progress (1.5ms), compared to the wavefront in the simplified model which is
largely unaffected by the shock. Furthermore, vessel cavities lying in advance of the main wavefront prior to shock application form break excitations which close-down the excitable region in its path, coalescing with the remaining parts of the fragmented wavefront in the vessel model (3.5ms). Consequently, a similar extent of excitable tissue remains in this region at shock-end (7ms), between the two models, despite the wavefront in the vessel model being less advanced pre-shock.

![Figure 4](image)

**Figure 4:** Toy model representation of ventricular wedge with different sized vessel cavities in center. (a) Toy model with 300 µm radius vessel including electrode placements. (b) Fiber architecture within short-axis slice though center of toy model where color of vectors indicates out-of-plane components of fiber helix angle.

![Figure 5](image)

**Figure 5:** $V_m$ distributions at different stages during application of a 20 V shock to states I2 of the vessel (top) and simplified (bottom) models.

### 2.2 Role of Vessel Cavity Size in Virtual-Electrode Pattern

Fig. 6 shows $V_m$ distributions 1 ms into a 50 V/cm shock applied to toy wedge models with cavity sizes 50, 100, 200, 300, 400 and 500 µm radius, as described in Section 1.5. Note that here the color-bar scale is adjusted from previous figures such that diastolic tissue approximately represents 0 mV, allowing the both the depolarizing and hyperpolarizing virtual-electrode effects to be witnessed more clearly.
2.2.1 Vessels Acting Like Insulators

Fig. 6 shows that for smaller vessel cavity sizes, the low conductivity of the lumen wall means that it is preferential for current to pass around the cavity, as opposed to passing through. The vessel is thus seen to act like an insulator, forcing the current induced by the shock to negotiate around the obstacle and inducing a characteristic virtual-electrode pattern with the cathodal side of the cavity depolarized and the anodal side hyperpolarized. Such a pattern occurs as the global fiber orientation is perpendicular to the applied field. Thus, away from the cavity, the current is travelling primarily in the cross-fiber (x-) direction. As the current approaches the vessel (from the anodal side), in order to negotiate the cavity, it must travel partly along the fiber direction. However, because the ratio of intracellular to extracellular conductivity is greater in the fiber direction than in the cross-fiber direction, current re-distributes between the domains such that more current flows in the intracellular space. This movement of current from the extracellular to the intracellular domain causes the localized tissue to become hyperpolarized [26]. Conversely, on the cathodal side of the vessel, the opposite effect occurs: current changes from flowing in the fiber to the cross-fiber directions so there is a movement from intracellular to extracellular domains, causing local depolarization. Note that, had the global fiber orientation been along the direction of the applied field, the virtual-electrode pattern would have been reversed, with the anodal side depolarized and the cathodal side hyperpolarized [27].

2.2.2 Vessels Acting Like Conductors

Fig. 6 then shows that for the larger vessel cavity sizes (400–500 µm), the virtual-electrode patterns are significantly different to the cases above for smaller vessels. Here, the vessel is seen to act as a more substantial barrier to current flow, and a larger proportional of current is forced to flow through the cavity itself, passing through both the lumen wall and highly conducting lumen cavity. The vessel is thus seen to act like a conductor, and a virtual-electrode pattern of opposite polarity to the case above for smaller vessels is formed: the anodal side is depolarized, with the cathodal side hyperpolarized. In this case, the preferential current path is through the cavity wall. However, the lumen wall and the cavity itself represent only extracellular space.
Thus, as intracellular current approaches the vessel on the anodal side, it must pass into the extracellular domain in order to traverse the cavity, causing depolarization. On the cathodal side, the current is free to pass back into the intracellular domain, causing hypolarization.

2.2.3 Overall Effect of Vessels

In reality, for a vessel of any given size both competing insulating and conducting effects are present and a proportion of current will both negotiate around the cavity and pass through it, explaining the complexity of the virtual-electrode patterns witnessed in Fig. 6, particularly at the larger cavity sizes. Furthermore, when tissue is surrounded by a layer of perfusing (highly-conducting) bath on the cut transmural surface, for example as is the case during optical mapping recordings from transmural LV wedge preparations [3, 28], additional low-resistance pathways for current to flow are introduced which are expected to further affect the complexity of the virtual-electrode patterns induced. Finally, we note here that large vessels tend to be sub-epicardial, and thus the tissue immediately local to them is expected to be strongly affected by the direct action of the shock itself.

The results presented in this study underscore those of a recent experimental investigation by Luther et al. (2011) who demonstrated the importance of conductive heterogeneities, such as vessels, during low-energy defibrillation therapy [29]. Overall, there is close qualitative agreement between our findings and these experiments, particular regarding the overall importance of vessels acting as structural substrates to induce intramural break excitations, with stronger shocks recruiting more excitations and causing faster activation time of the tissue. Quantitatively, the comparison is also close with the theoretical aspects of the Luther et al. (2011) study. For example, their linearized bidomain approximation yields a similar minimum cavity size (~150 µm radius) at which break excitations can be induced to that which we uncovered using our modelling approach in Figure 8 of the manuscript.

References


