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

Running title: Bishop et al.; The importance of blood vessels in defibrillation

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Abstract:

Background - The direct role of coronary vessels in defibrillation, although hypothesized to be important, remains to be elucidated. We investigate 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 25μm MR data, faithfully representing both structural and electrical 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 (5–70V) 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/LV), 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 due to initiation of new activity), compared to 8 with the simplified model (5/8 failures due to surviving activity). At stronger shocks, virtual-electrodes formed around vessels, rapidly activating intramural tissue due to break excitations, assisting the main defibrillation mechanism and eliminating all activity <15ms of shock-end in 60% of successful shocks (36% in simplified model). Subsequent analysis identified only vessels approximately >200um diameter participated via 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 towards the required resolution of cardiac imaging and model generation endeavors for mechanistic defibrillation analysis.

Key words: electrophysiology, vasculature, defibrillation, fibrillation.
Introduction

Although application of a strong defibrillation shock to the heart remains the only reliable means of terminating ventricular fibrillation (VF), 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[1] and achieve defibrillation lack comprehensive understanding.

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[5]. 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 scattering[5] have thus far prevented direct correlation of virtual-electrodes with specific intramural structures. Furthermore, restrictions in model domain size of both experiments and simulations has limited examination of the direct implications of shock-induced intramural activation upon reentry termination and defibrillation.
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[9]. Nonetheless, close agreement has been found throughout with experimental observations of global defibrillation mechanisms made from whole-ventricular surface optical mapping experiments[3,5,10], questioning the importance of incorporating such fine-scale features within models and their relevance in defibrillation. Recent advances in MR imaging[11,12], however, have facilitated the inclusion of unprecedented levels of anatomical detail, including representations of the coronary vascular system, within whole-ventricular computational models[8,12], presenting an opportunity to perform such investigation.

As blood vessels represent the largest discontinuities within the myocardial wall, they thus suggest an important substrate for virtual-electrode formation. In a recent study[8], we demonstrated how fine-scale information regarding the coronary vasculature could be incorporated into a detailed computational LV wedge model from high-resolution MR data[12], 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 this study, we aim to investigate 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 25μm MR data[12], representing both structural and...
electrical properties of blood vessels[8]. Biphasic defibrillation shocks were applied via an implanted cardioverter defibrillator (ICD) electrode set-up to a variety of different fibrillation episodes. Comparison of results to 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 (Vm) 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 1.5mm) was generated from a previously-published high-resolution rabbit MR data-set (resolution 25μm)[12] (Figure 1(a)), following prior segmentation and manual removal of free papillary muscles. The mesh (Figure 1(b)) 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 approximately 1.34 vessels/mm² with minimum vessel cavity diameter represented ~100μm.

Cardiac fiber architecture was assigned using a rule-based method[8], accounting for transmural variation in helix angle and continuous fiber negotiation around intramural structures seen in histology (Figure 1(b)). To dissect the specific role played by intramural structures, a simplified model was also produced in which all intramural cavities were filled-in during segmentation, prior to meshing. Identical stimulation protocols were applied to both vessel/simplified models throughout.
Simulating Electrical Activation

Electrical activation was simulated using the bidomain equations[13], solved with the Cardiac Arrhythmia Research Package[14]. Conductivities were based on experimentally-derived values[15], scaled to reduce conduction velocity by 25%, as occurs during heart failure. Electrical conduction through the connective tissue of the vessel lumen wall was reduced by assigning the experimentally derived conductivity[8] of 0.010S/m to extracellular bath elements that directly bordered the vessel cavity/myocardium interface. Bath conductivity, including within vessel cavities, was 1.0S/m. Membrane dynamics were represented by a recent rabbit ventricular cell model[16], slightly adjusted to produce sustained VF-like activity, and further augmented by two additional currents, activated at large potentials, to simulate membrane responses to strong shocks. See Supplemental Material for detailed descriptions of computational methods.

Simulation Protocol

Induction of Fibrillation

Fibrillation was induced as described in Supplemental Material. A selection of 6 initial states were chosen from the fibrillatory episodes, which acted as pre-shock states for defibrillation shock delivery, providing a range of possible initial conditions. As closely as possible, initial states were matched between vessel/simplified models, notwithstanding the inherent complexity of the fibrillatory-episodes (shown in Supplemental Material Figure 3).

Defibrillation Shock Application
An ICD-like electrode configuration for defibrillation shock delivery included a catheter placed in the right ventricle (RV) (diameter 6 French[17]) and active can in the bath near the posterior LV (shown in Figure 2(a)). Biphasic defibrillation shocks of shock-strength (SS) between 5–70V (leading-edge voltage) were delivered to the selected initial fibrillatory states. The RV catheter acted as the anode during the first shock phase[10] and the active can ground, with polarity reversed during the second phase with magnitude 50% of the first. Tilt and duration of each phase were 50% and 3.5ms, respectively. The distribution of extracellular potential (\(\Phi_e\)) within the simplified model is shown in Figure 2(a), showing regions of high field-gradient concentrated primarily in the posterior LV and septum. Figure 2(b) & (c) then compare the response of the vessel and simplified models to a 40V shock applied during diastole, by showing a difference map (following mapping of data between respective meshes) of induced extracellular potential gradient \(\Phi_e\) within the tissue (panel b) and induced \(V_m\) (panel c) 1ms into the shock. These difference maps highlight the significant magnitude of variation in both \(\Phi_e\) and \(V_m\) within intramural myocardial tissue, focussed around vessel cavities and within regions of high field-strength (posterior LV and septum) between vessel/simplified models.

**Data Analysis**

Induced post-shock arrhythmias were defined as sustained if reentrant activity lasted for >100ms. Tissue was classified as excitable if \(V_m<-60mV\) (inactivation threshold of sodium current[10]). Intramural tissue was defined as points lying within 0.25\(<e<0.75\), where \(e\) is the normalized transmural distance from endo- to epicardium. See Supplemental Material Section 1.4.3 regarding statistical significance of simulation data.
Results

Role of Vessels in Shock Success

Defibrillation shocks of SS 5/10/20/40/70V were applied to the 6 initial fibrillatory states of the two models. Analysis of post-shock activation patterns of the 30 episodes revealed defibrillation failed in just 5 cases in the vessel model, compared to 8 in the simplified model. Of those failed shocks, reentry was reinitiated due to new activation wavefronts induced by the shock in 4/5 of the failed vessel model shocks. In the simplified model, however, 5/8 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 15ms of shock-end in 15 (/25, 60%) cases in the vessel model, compared to just 8 (/22, 36%) in the simplified case.

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 3(a) demonstrates how successful defibrillation is achieved via this mechanism, showing evolution of activity throughout a 40V shock in the simplified model. Large excitable gaps exist in the LV and septum prior to the shock (0ms). The first shock phase strongly depolarizes the
anterior LV endocardial wall and large regions of the LV-septum endocardium (3.5ms). 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 (7ms). 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, whilst 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 (10ms).

Although this biphasic defibrillation mechanism was clearly evident for strong shocks (including 70V, not shown), its specific operation was strongly dependent upon applied SS. Figure 3(b) shows corresponding shock-end (7ms) Vm distributions following 5/10/20V shocks in the simplified model. For weak shocks (5V), the second shock phase (P2) lacks sufficient strength to reverse the negative polarization set-up by phase 1 (P1). Thus, only a single excitation from the first phase exists at shock-end, only occurring in regions of relatively high field-strength in the LV/septum. For intermediate shocks (10V), both phases have sufficient strength to elicit strong surface depolarizations and induce two 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/septum. At 20V, the break excitation pattern from the shock becomes
more similar to that seen at 40V (Figure 3(a)), although the speed at which the break excitations propagate and close-down the excitable gaps increases with SS (discussed below).

Finally, Figure 3(c) shows the corresponding post-shock 10ms image following a 40V shock in the vessel model, demonstrating a very similar mechanism to Figure 3(a). However, here less of the excitable gap remains, particularly in the septum, suggesting the presence of vessels assists in closing-down the excitable gap via this biphasic mechanism, which we now investigate further below.

Role of Vessel-Mediated Virtual-Electrode Formation in Defibrillation

During all strong shocks (20–70V), virtual-electrodes were seen to form around blood vessel structures in all defibrillation episodes in the vessel model, largely focussed around regions of high field-strength (septum/posterior LV), and being more significant around larger vessel structures. Following the shock, break excitations were elicited from these virtual-electrodes, most evident 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 4(a) shows an example of vessel-mediated virtual-electrode formation following a 40V shock applied to state II 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 40V post-shock simplified model case (Figure 4(b)) where large excitable gaps remain, most noticeable in the septum.

Figure 4(c) quantifies this effect, showing how the percentage of intramural excitable septal tissue changes pre- and post-shock 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 post-shock. 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 upon cessation of the shock, depolarizing larger amounts of tissue post-shock 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 post-shock, as break excitations from either side of the septal wall (due to 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 pre-shock excitable gaps coincide with areas of high field-strength.

*Overall Quantitative Effect of Vessels*
Above, we focussed 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 5(a) shows that the mean decrease in LV/septum intramural excitable tissue (relative to pre-shock), both at shock-end (left) and post-shock (right), is greater in the presence of vessels; a difference which increases with SS as vessel-mediated virtual-electrodes increase in size, strength and number, most evident at shock-end. For example, the simplified model shows a relatively small decrease even at high SS: 28.5% at 70V compared to 63.8% decrease in the vessel model. Post-shock, differences between the models are less, due to propagation of surface-mediated break excitations from the main mechanism into intramural regions. Overall, for all 30 pairs of defibrillation episodes (5SS, 6 initial states), the greater decrease seen in the vessel model was statistically significant for both shock-end (p<0.0003) and post-shock (p<0.0025) cases, assessed using a Wilcoxon signed-rank test (see Supplementary Methods for specific details). Note, the RV was not included as 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 5(b) shows that the percentage of defibrillation shocks to achieve entire elimination of all wavefronts <15ms 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 $p<0.03$, assessed using a McNemar test to compare proportions in the 2 models (see Supplemental Material for details). However, differences between models become most noticeable at strong SS due to the more widespread formation of virtual-electrodes surrounding vessels which also become larger and stronger.

Finally, in addition to vessels interacting via 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, described in the Supplemental Material.

Defibrillation Failure due to Intramural Wavefront Survival

In one particular strong shock episode (40V), lack of activation of intramural areas due to the absence of vessels in the simplified model resulted in defibrillation failure, shown in Figure 6; comparatively, defibrillation succeeded in all such strong shock episodes in the vessel model. Here, pre-existing refractory tissue in the anterior LV wall prevents propagation of break excitations mediated from epicardial/endocardial surfaces via the main defibrillation mechanism into intramural tissue (7ms). Furthermore, the lack of vessels means that the existing wavefront within the septum (0ms) is largely unaffected by the shock, which thus continues to propagate through the, now recovered, excitable region in the anterior LV wall (35ms). 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 (5–10V). Figure 7 shows such an example, demonstrating the occurrence of conduction block in the vessel model due to the formation of a weak, but noticeable, depolarization around a large blood vessel in the RV free-wall (highlighted), insufficient to induce break excitation itself. In contrast, the RV wall in the simplified model remains 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 close down local excitable gaps, we now identify the minimum vessel cavity size which supports this mechanism. A series of highly-simplified models representing vessel cavities of radii 50-500μm within a wedge of ventricular wall were created (see Supplemental Material) and biphasic shocks of SS 2.5-75V/cm applied. Figure 8(a) shows V_m distributions 1 & 7ms into the shock for a selection of stronger shocks applied to smaller cavity models (50-100μm).

The smaller cavities act primarily like insulators, causing virtual-electrode patterns as current redistributes between intra-/extracellular domains (due to respective differences in fiber/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 (see Supplemental Material).
Figure 8(b) plots the minimum SS at each cavity radius required to induce break excitations within the tissue. These Figures together show that even the strongest 75V/cm shock cannot induce a break-excitation within the 50μm model, and is just strong enough to induce one in the 75μm model, but that the 100μm model has an excitation threshold of just 40V/cm. Such cavity dimensions at which an appreciable effect is witnessed is of the same order-of-magnitude as the transverse length constant (~0.2mm) as expected from theoretical considerations.

To replicate potential electrotonic interactions of increased packing density of smaller vessels (50-100μm radii) the protocol was repeated to 4 vessels of each size evenly packed within a 0.81mm² square (4.9mm²). This increased packing density did not change the minimum SS predicted by Figure 8(b) for the 50-100μm radius cavities. Finally, the packing density was increased further for the 50μm vessels to 9 (11.1mm²) which still did not induce a break excitation at 75V/cm. Vₘ distributions 1ms into 75V/cm shocks are shown in Figure 8(c) for the 50μm 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 assist 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/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 re-initiation of fibrillation[2,4]. However, unlike our modelling 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 via 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 3(b)). Although a similar mechanism of biphasic defibrillation has been suggested previously in a 1D fiber model[18], here we present 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 3(a)&(c)). Such a finding provides an explanation for the lack of a significantly large difference in defibrillation success rates.
between the two models as well as the close comparison between previous simulations studies
using more simplified models[3,10] 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, our high-resolution bi-ventricular model has allowed
investigation of how fine-scale structures, such as blood vessels, impact the process of
defibrillation using a clinically-realistic ICD set-up.

This study has demonstrated that virtual-electrodes form around intramural vessel cavities,
helping 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 wide-
spread 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 post-shock
excitable gaps by faster propagating break excitations occurs. Although in our ventricular slice
model, the more rapid closing-down of post-shock 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 both through direct interaction with the wavefront itself (Supplemental Material Figure 5), and the creation of mild depolarizations in excitable gaps in its path (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 re-initiation of reentry during defibrillation[19,20]. Although here we focus primarily on extinguishing existing fibrillatory activity, we suggest that virtual-electrodes induced around vessels (representing larger heterogeneities) could also play an important role via 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 since 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 since one will promote intra- to extracellular...
current flow while the converse occurs in the other. However, the most important issue identified in this study is that virtual-electrodes, regardless of polarity and underlying mechanism, form around vessels and initiate break excitations which help defibrillate. Overall, the results from this study qualitatively strongly agree with a recent experimental study identifying the importance of vessels during low-energy defibrillation therapies[21], and reinforce their findings by providing important 3D knowledge regarding the intramural behaviour of the vasculature during such protocols. Uncovering such an important biophysical mechanism could have important applications in helping understand similar interactions of electric fields with other heterogeneities such as infarct scars or myolaminar sheets[7].

**Implications for Simplified Models**

In the simplified model, even at stronger SSs where the direct activation of the shock extends further into the mid-wall (due to virtual-electrode effects as a result of fiber curvature and bi-ventricular geometry, for example), large intramural excitable regions still exist at shock-end, which were seen to be present to a lesser extent in the vessel model. Consequently, in Figure 7 we uncovered a case in which defibrillation failed in the simplified model at a strong (40V) shock, compared to the vessel model which successfully defibrillated all episodes. Here, the absence of vessel-induced effects in the mid-wall provided an excitable avenue in the LV/septum junction through which a wholly intramural wavefront could continue to propagate, sustaining reentry. As this mechanism is similar to that of tunnel propagation (shown recently in a study using a simplified whole-ventricular model[10]), the results from our study may suggest that such tunnel propagation is suppressed in the presence of vessels. However, we believe that the high non-uniformity 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 explain differences in their location witnessed between simulations and experiment[10].

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

We have identified that only vessel cavities greater than approximately 100μm 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[21] and quantitatively predicts a similar minimum cavity radius (~150μm). This finding has significant implications for high-resolution cardiac image acquisition and computational model development[11,12] 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 >200μm across suggests that lower resolution (~100μm) MR and DTMRI may be sufficient for model construction as opposed to the potential use of histological data which presents many more challenges both for imaging and 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, widening the scope of what is tractable to simulate.
Study Limitations

Although our model incorporates an unprecedented level of structural detail, it is somewhat limited by its slice geometry. Primarily, although the bi-ventricular geometry still faithfully represents many important reentry pathways, the nature of the sustained arrhythmias pre-shock, as well as post-shock activation sequences, may differ when scaled-up to the whole ventricular level. However, throughout the study, conclusions were drawn following comparisons made between the vessel and simplified models, and care was taken to match the initial complexity of fibrillation episodes. Thus, any limitations in arrhythmia dynamics due to model size restrictions would have impacted both models equally. Finally, our model represents important heterogeneity in ICD-field gradient in x,y-directions (Figure 2(a)). Shock-induced virtual-electrode polarizations on epi-/endocardial surfaces and vessel cavities, and subsequent propagation of break excitations, also then occur primarily in this plane, thus captured well by our model.

Despite using a state-of-the-art cardiac simulation environment[14], the large, highly-detailed mesh combined with small time-steps required for strong ICD shocks resulted in significant computational demands on each simulation (10ms bidomain shock episode required ≈20hrs on 32 cores). Consequently, the number of initial fibrillatory states, maximum SS and number of SSs used were limited, preventing computation of a full DFT-90 plot[10] and assessment of whether our results of overall defibrillation success were of statistical significance.

Although our MR-derived model contains intramural vessel cavities, absent from our model is fine-scale detail regarding inter-myolaminar cleavage planes, seen in histological reconstruction models[7]. The histological pre-processing 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. Whilst simulations[7] and experiments[22] have identified the potential importance of clefts as a substrate for virtual-electrode formation, it remains an open question to what extent this is affected by accentuated cleft size.

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**Figure Legends:**

**Figure 1:** (a) Axial-slice from rabbit MR data-set[12]. (b) Finite element ventricular slice model with highlighted region showing cardiac fiber orientation assigned using rule-based method[8].

**Figure 2:** (a) ICD electrode set-up and \( \Phi_e \) distribution within simplified model 1ms into 40V defibrillation shock; Difference map of induced \( \Phi_e \) (panel (b)) and \( V_m \) (panel (c)) between vessel and simplified models.

**Figure 3:** Common mechanism of successful biphasic defibrillation. \( V_m \) distribution pre-, during and post- 40V shock (panel (a)) and at shock-end for SS5/10/20V (panel (b)) applied to simplified model state I4. (c) Post-shock \( V_m \) distribution of 40V shock applied to corresponding vessel model state I4.
**Figure 4:** Vessel-mediated virtual-electrode formation. (a) Shock-end and post-shock Vm distributions following 40V shock applied to vessel model state I1. (b) Corresponding post-shock simplified model Vm distribution. (c) Variation in percentage of excitable tissue within intramural septum throughout shock for all SS applied to states I1 of vessel (solid-lines) and simplified (dashed-lines) models.

**Figure 5:** (a) Mean percentage decrease in volume of excitable intramural tissue within LV/septum, averaged over all 6 defibrillation episodes, as a function of SS at shock-end (left) and post-shock (right) for vessel (blue solid-line, squares) and simplified (red dashed line, circles) models. (b) Percentage of successful defibrillation episodes in which all activity is entirely eliminated <15ms of shock-end as function of SS for vessel (blue solid-line, squares) and simplified (red dashed-line, circles) models.

**Figure 6:** Vm distribution during 40V episode applied to simplified model state I3 showing intramural wavefront leading to defibrillation failure.

**Figure 7:** Vm distributions during 5V shock applied to state I3 of vessel model (top) and simplified model (bottom) demonstrating conduction block due to mild virtual-electrode formation around large vessel in RV (highlighted) terminating the wavefront.

**Figure 8:** (a) Vm distributions 1/7ms into shocks applied to wedge models with different radii cavities. (b) Minimum SS required to induce break-excitation as a function of cavity radii. (c) $V_m$ distributions 1ms into shock for models with increased vessel packing densities.
Investigating the Role of the Coronary Vasculature in the Mechanisms of Defibrillation
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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 1.5 mm, 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 epi- to endocardium, 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
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
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 $> 280$ms [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
[25] 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 excitable 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 excitable 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 excitatory 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.

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 \( \mu \)m 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.

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