**Supplemental information for**

Optogenetic defibrillation terminates ventricular arrhythmia in mouse hearts and human simulations

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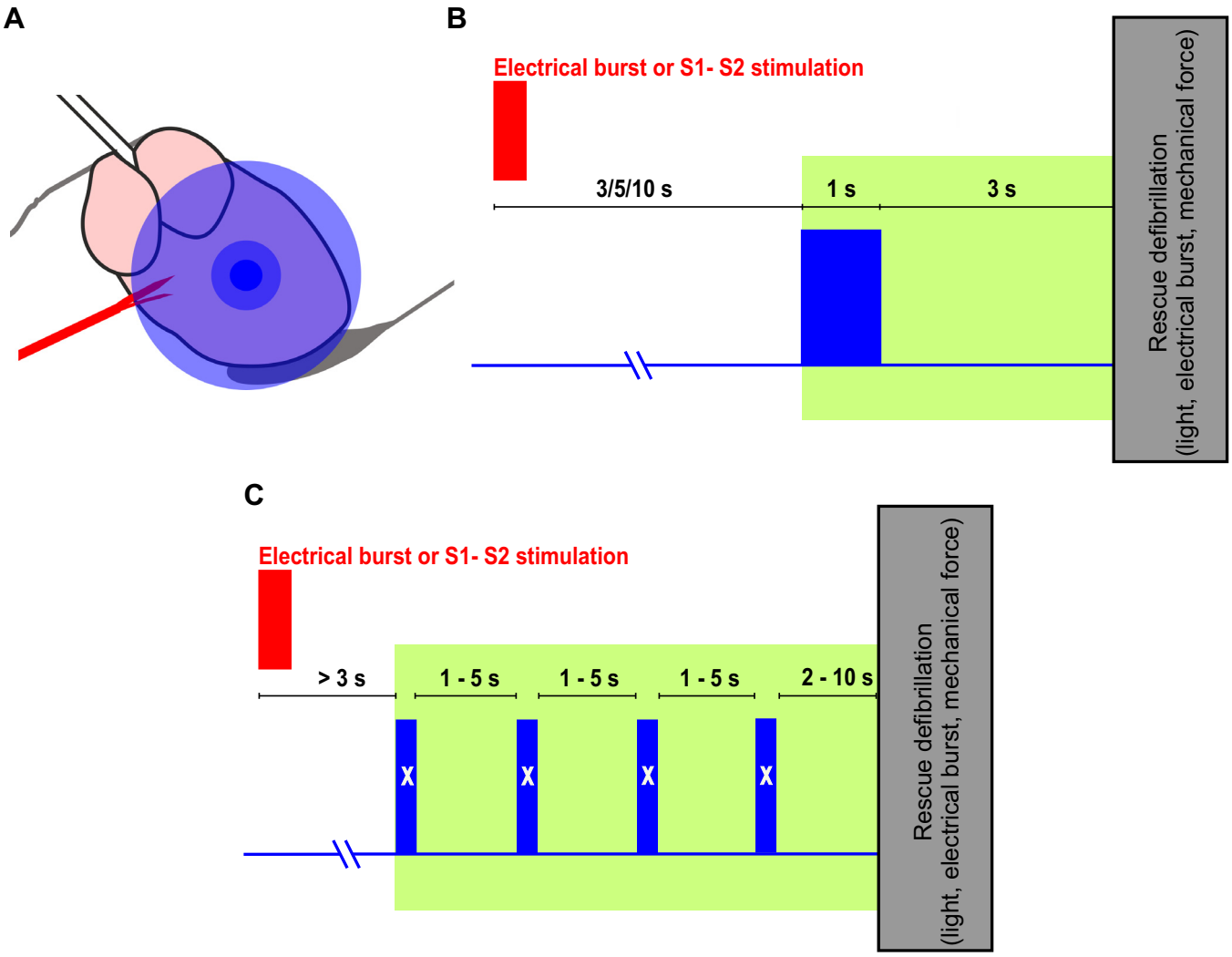
## Legends to Supplemental Movies 1-3:

**Supplemental Movie 1: Induction of VT via pacing from the apex of the human ventricular model.**
$V_m$ is rendered on the 3-dimensional surface using the same color scale as in Figure 4C. Normal (left) and cutaway (right) views are shown. Pink spheres in the left-hand panel indicate locations at which extracellular potential was recovered to reconstruct the pseudo-ECGs.

**Supplemental Movie 2: Simulation of optogenetic defibrillation in the human ventricles.**
$V_m$ propagation in the 3-dimensional human ventricular model in cutaway view (top) and corresponding pseudo-ECGs (bottom) for three configurations corresponding to Figure 4A, Supplemental Figure 6B and Figure 4B: no stimulus (left), blue light (middle), and red light (right). Same color scale as Figure 4C. Blue and red auras indicate timing of optogenetic stimuli. In pseudo-ECGs, the black boxes indicate the beginning and end of the interval shown in the movie and the dashed pink link indicates progress over time.

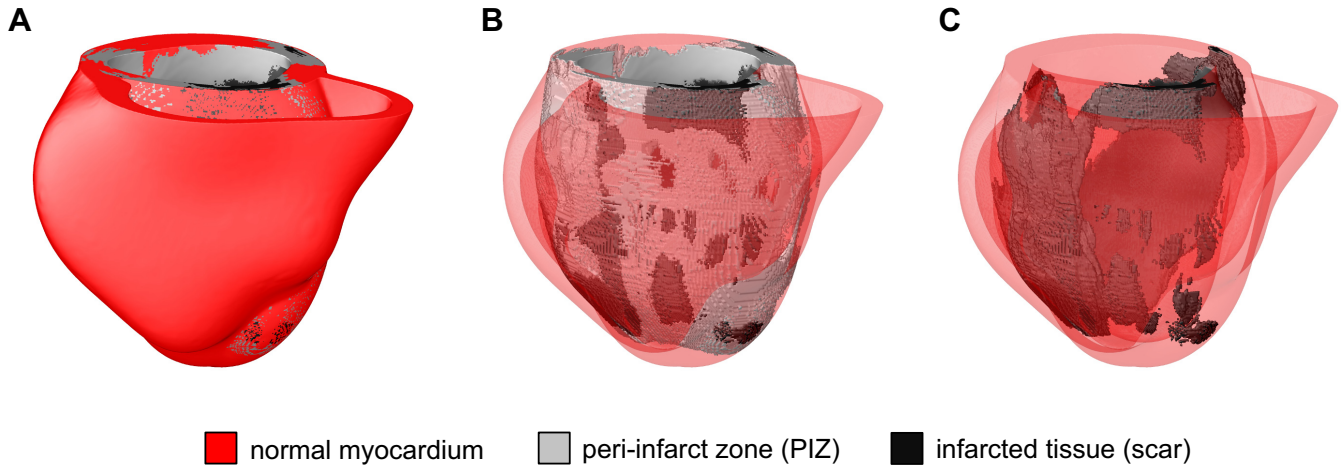
**Supplemental Movie 3: Dynamics of reentrant wavefront interaction with tissue subjected to optogenetic stimulation.**
$V_m$ propagation in the 3-dimensional human ventricular model in a zoomed-in cutaway view for blue light (left) and red light (right), corresponding to Supplemental Figure 6C and Figure 5E, respectively. Same color scale as Figure 4C. Blue and red auras indicate timing of optogenetic stimuli. Arrows appear during the movie to highlight reentrant wavefront propagation into the endocardial layer of the right ventricular free wall (blue light, left) and reentrant wavefront conduction block induced by optogenetic depolarization (red light, right).

**Supplemental Figure 1**



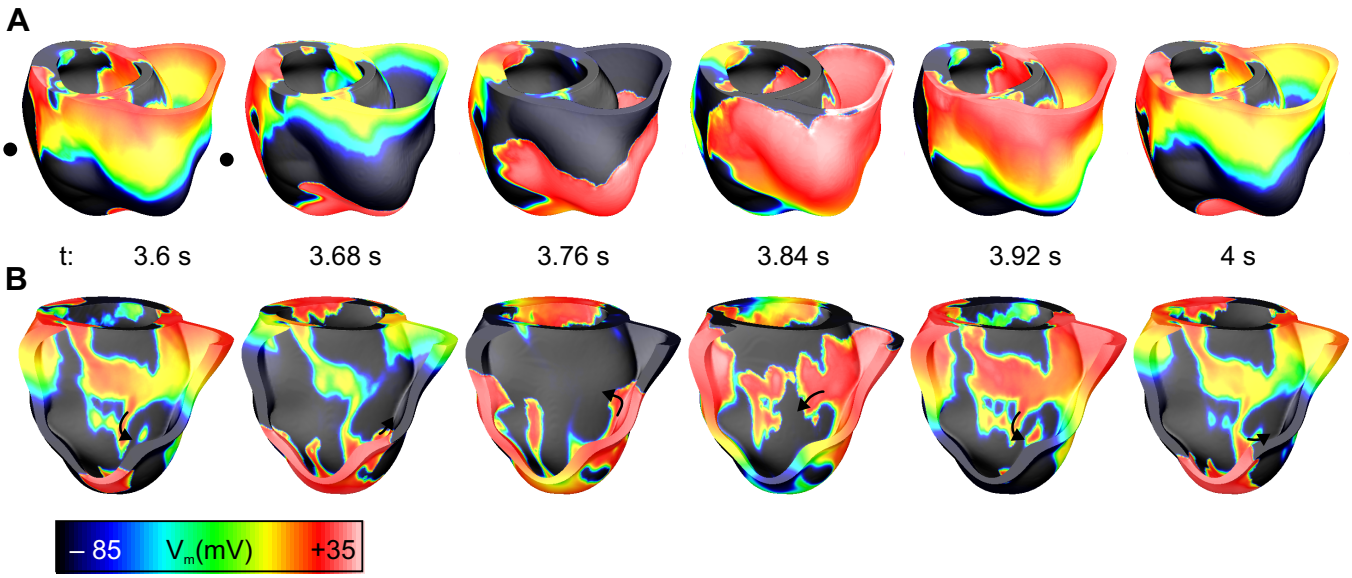

**Supplemental Figure 1: Experimental setup and protocols for optogenetic defibrillation.** (**A**) Explanted hearts were retrogradely perfused and the ECG was recorded with electrodes placed at the right atrium and the ventricular apex (gray). Ventricular arrhythmia was induced by electrical stimulation with two silver chloride electrodes (red). Optogenetic defibrillation was tested by illuminating the anteroseptal epicardium with light stimuli covering 15, 29, or 143 $mm^2$ areas (blue circles). (**B**) Schematic illustrating the one light pulse protocol: Electrical burst or S1/S2 stimulation was used to induce ventricular arrhythmia and 3, 5 or 10 s later one 1 s long light pulse (0.4 $mW/mm^2$, 143 $mm^2$) was applied. Optogenetic defibrillation was classified as successful if arrhythmia terminated within 4 s after start of the illumination (green box). If arrhythmia persisted, the attempt was classified as a failure and a rescue defibrillation procedure was performed (see Methods). (**C**) Schematic illustrating the four light pulse protocol: Arrhythmia was allowed to stabilize for 3-15 s after induction and four identical light stimuli were applied with 1 to 5 s delay in-between. Optogenetic defibrillation was classified as successful if arrhythmia terminated between the start of illumination and a predefined period of 2-10 s after the last light pulse (time period indicated by green box). If arrhythmia persisted, the attempt was classified as a failure and a rescue defibrillation procedure was performed. For control experiments in ChR2 expressing hearts without illumination and in hearts without ChR2 expression, spontaneous arrhythmia termination was assessed in a time window (green boxes in A and B) using the longest times indicated.

## Supplemental Figure 2



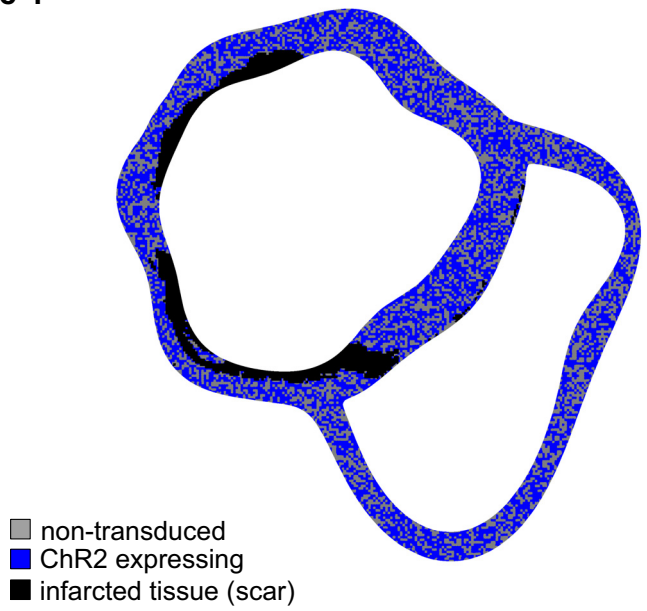

**Supplemental Figure 2: Image-based model of the diseased human ventricles.**
Different renderings of the model with (**A**) surface views of all three tissue types and translucent normal myocardium with (**B**) or without (**C**) the peri-infarct zone.

## Supplemental Figure 3



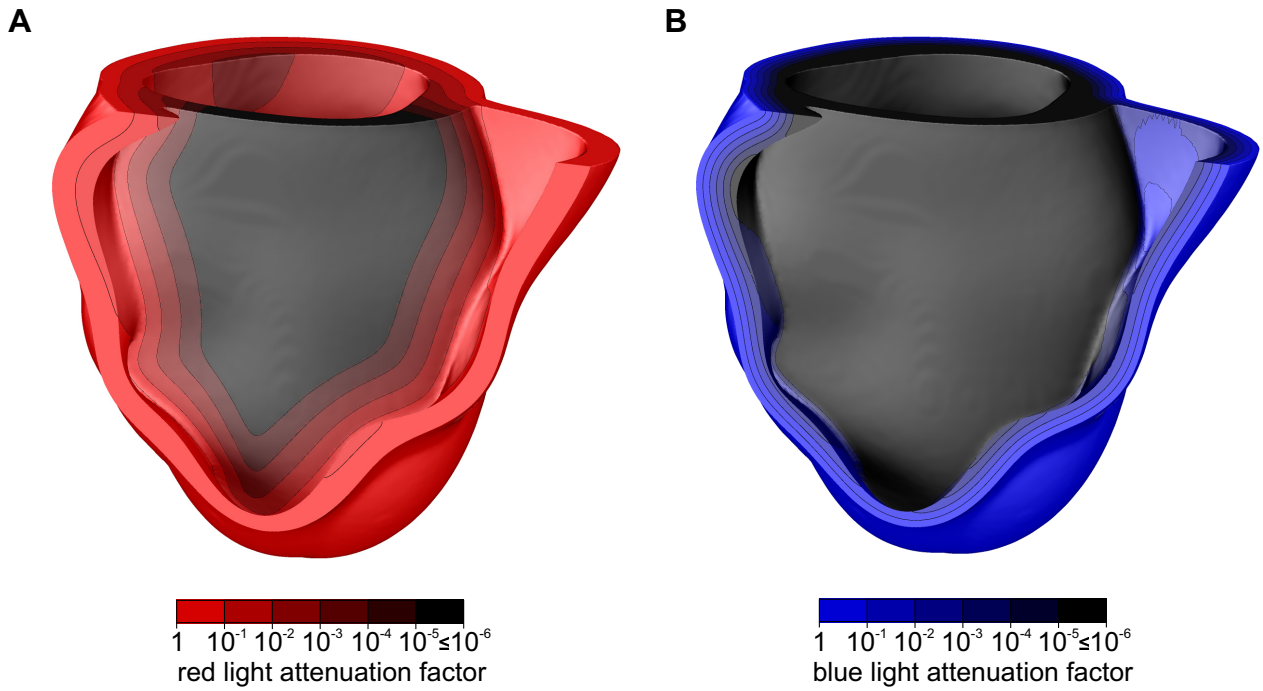

**Supplemental Figure 3: Snapshots of $V_m$ distribution during simulated VT in the diseased human heart model.**
(**A**) Whole-heart view. Black dots in left-most panel show locations near left and right ventricles where extracellular potentials were recorded to generate pseudo-ECG signals in Figures 4A,B and Supplemental Figure 6B. (**B**) Cutaway view with free wall of right ventricle removed for visualization. Black arrows indicate the direction of the propagating reentrant wavefront that perpetuated VT.

**Supplemental Figure 4**



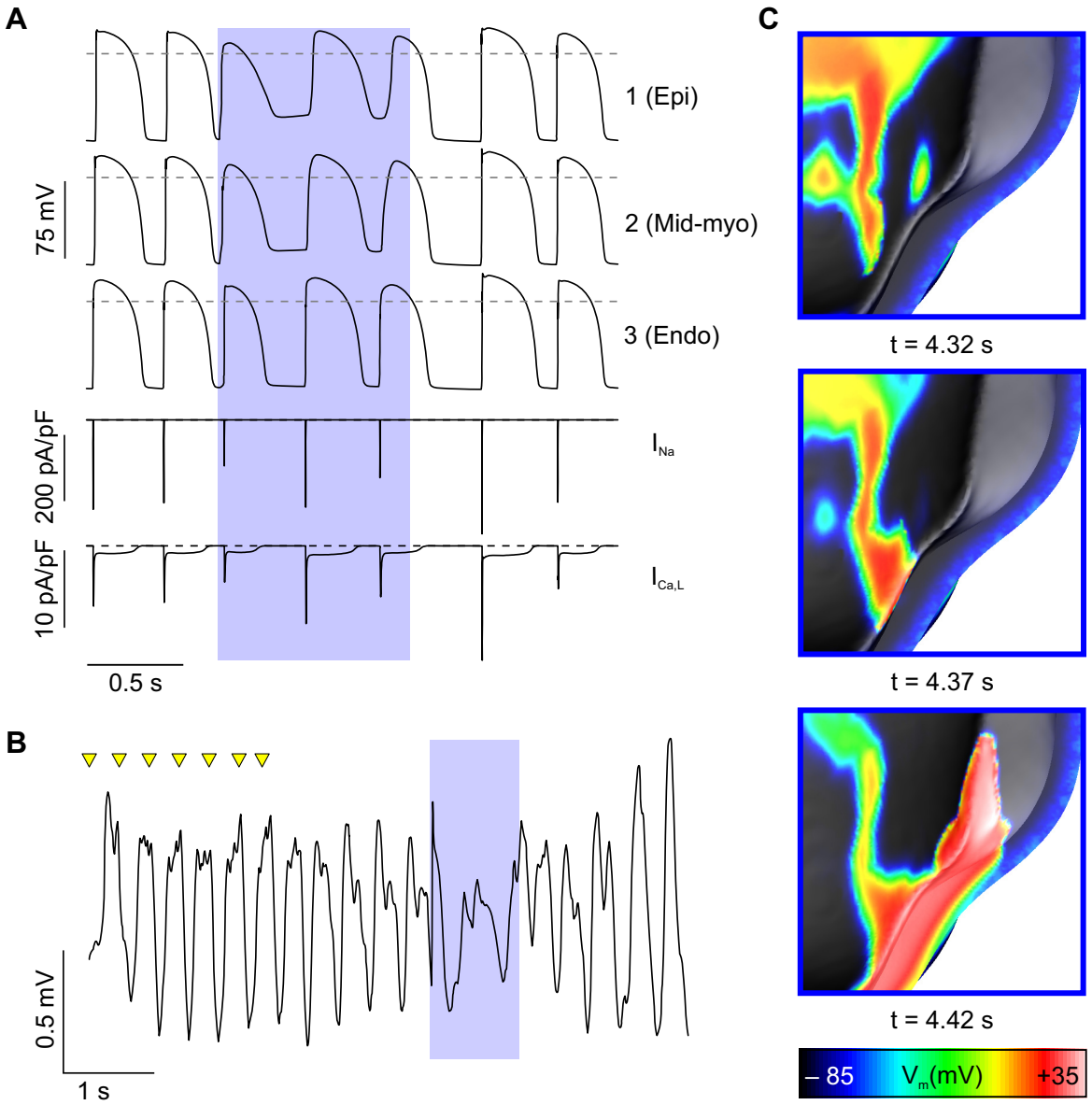

**Supplemental Figure 4: ChR2 distribution in the ventricular model.**
2D slice showing distribution of the ChR2 expressing cardiomyocytes in the normal myocardium and peri-infarct zone of the human ventricular model.

**Supplemental Figure 5**




**Supplemental Figure 5: Light attenuation characteristics in the human ventricular model.**
3D map showing light attenuation during uniform illumination of the epicardial surface with red light (669 nm, **A**) and blue light (488 nm, **B**). The right ventricular free wall is cut away to facilitate visualization. Scale bars for light attenuation factor are logarithmic.

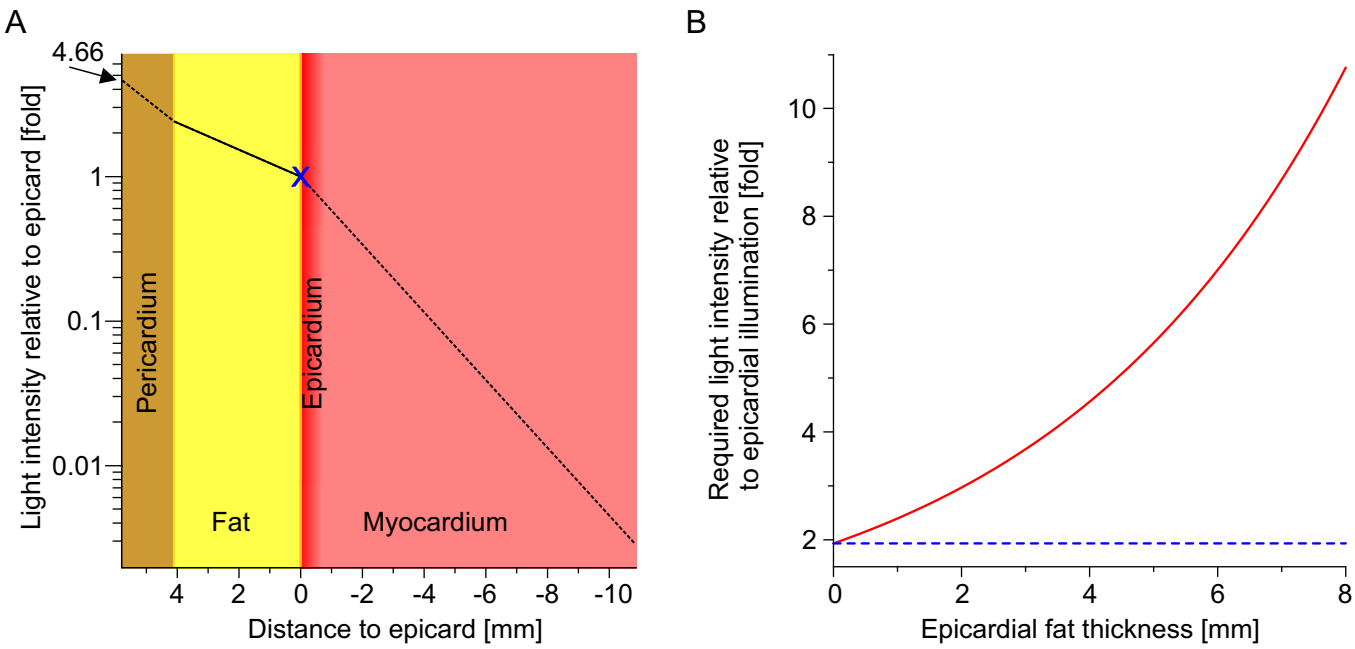
## Supplemental Figure 6




**Supplemental Figure 6: Optogenetic defibrillation failure using epicardial illumination with blue light.**

(**A**) Top: $V_m$-traces from sites 1-3 in Figure 5A during epicardial illumination with blue light. Bottom: Ionic $Na^+$ ($I_{Na}$) and L-type $Ca^{2+}$ ($I_{Ca,L}$) currents underlying $V_m$ from site 3. (**B**) Pseudo-ECG signals for the model configurations with epicardial illumination with blue light. Timing of blue illumination (488 nm, 1 s, 10 mW/mm$^2$) is indicated by blue boxes (A and B). (**C**) Zoomed-in snapshots of $V_m$ distribution during the illumination at the indicated time points (from start of simulation). Snapshots were taken from the region shown in Figure 5A top by black rectangle.

## Supplemental Figure 7




**Supplemental Figure 7: Requirements for optogenetic defibrillation for illumination from the pericardium**.

(**A**) Required increase in optical stimulus intensity due to light attenuation in epicardial fat tissue (yellow, 4.1 mm) and the pericardium (brown, 1.7 mm) relative to the light intensity reaching the epicardium (blue x) using global illumination with red light (669 nm). (**B**) Required increase in light intensity (red line) for pericardial illumination for different epicardial fat layer thickness values. Dashed blue line indicates increase in required light intensity due to light attenuation by the 1.7 mm-thick pericardium only.