Defibrillation Simulations in an Inhomogeneous Bidomain Model

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Summary

This article discusses a new bidomain model for investigating defibrillation mechanisms and presents the preliminary results of simulations in the myocardium. The mathematical model is based on the cell model created by Drouhard and Roberge (DR model), whose gate variables were modified in order to achieve a better voltage stability of the differential equations of the model at high transmembrane potentials. The developed cell model was integrated into a biodomain model, which is made up of a resistor network. Other characteristics of this tissue model are the voltage dependency of the gap junctions and the inhomogeneous structure of the myocardium. A comparison of the morphology of the simulated action potentials with the DR model shows that the action potentials are almost identical. This means that both models behave almost in the same manner in the physiologic area of the transmembrane potential. If a defibrillation pulse (–100 or –300 V) is delivered to the tissue, then there are differences between the homogenous and inhomogeneous substrates. In the homogenous case, a concentric excitation wave is formed around the pacing electrode. In the inhomogeneous case, however, the myocardium depolarizes globally. The preliminary results show that the differential equations of this model remain stable at high transmembrane potentials and inhomogeneities play an important role during defibrillation.

Key Words

Bidomain model, defibrillation, inhomogineities

Introduction

Defibrillation therapy of the human heart has been gaining more and more importance in recent years. This is due to the increased incidence of sudden cardiac death, which is usually triggered by persistent ventricular fibrillation. To restore the normal heart rhythm (sinus rhythm) in cases of ventricular fibrillation and to eliminate the electrical chaos in the heart, a defibrillation shock has to be delivered to the heart within the shortest possible time. This can either be done manually from the outside (external defibrillator) or by a device implanted in the patient (implantable defibrillator). From the beginning, defibrillation therapy was characterized by a "trial and error" approach since mainly empirically obtained data were used to further develop this form of therapy. Even though the first mathematical models were already worked out a short time after the discovery of ventricular fibrillation [1-3], it took almost until the middle of the 20th century before the first defibrillation models were developed [4,5].
After these first attempts, various experimental and theoretical mechanisms were detected and models created that describe partial aspects of defibrillation. To gain further knowledge about the nature of defibrillation, a new bidomain model was developed that is made up of a resistor network and makes it possible to include inhomogeneities in the myocardium. This article introduces this model and presents the preliminary results of the defibrillation simulations.

The Cell Model

The used cell model is based on the Beeler-Reuter cell model (BR model) [6] modified by Drouhard and Roberge [7]. This model, in turn, was supplemented by Skouibine et al. to perform defibrillation simulations (BRDefi model) [8]. Various simulations with the BRDefi model showed that the differential equations of this model become unstable at transmembrane potentials > 1000 mV. For this reason, the gate variables were revised once more to allow simulations to

be conducted, in the course of which transmembrane potentials > 1000 mV are tolerated. The number of ion currents that describe the action potential of a myocyte was not changed. Thus, just like the BRDefi model, the model contains four ion currents: the fast inward sodium current (I_{Na}); the slow inward current I_S, which is mostly upheld by calcium ions; a time-dependent outward current I_{X1}; and the time-independent outward potassium current I_{K1}. The modified BRDefi model will be referred to as BRDefi-A in the following.

The sodium current I_{Na}: The implemented modifications have the following effect on the behavior of the sodium gate: No changes result for the physiologic potential range when compared to the BR and BRDefi models. If high positive transmembrane potentials occur (V > 1000 mV), activation gate *m* is activated in the BRDefi-A model. In contrast, *m* remains in the resting state if high negative transmembrane potentials (V < –1000 mV) occur. The inactivation gate *h* of the sodium channel remains opened in the case of high negative transmembrane potentials, and it closes with high positive potentials.

The potassium compensation current I_{K1}: In the potential range of –100 to 100 mV, the equation for I_{K1} of the BRDefi-A model is identical to the equation of the BRDefi model. Because the function shows a point of discontinuity at V = 23 mV, I_{K1} was progressed continuously at this point. In case of transmembrane potentials higher than –1000 mV or 1000 mV, the solutions for the ion current I_{K1} are set to a constant value. This value is 15 or -15 μA, respectively.

The potassium current I_{X1}: The sectional definition of the gate variables shows no influence on the kinetics of the ion channel in the physiologic range of the transmembrane potential. The sub-functions that describe the high potential ranges cause a constant opening of the potassium channel for positive values, and a closure for negative values.

The calcium current I_S: The sectional definition of the calcium current shows the same behavior as the calcium current of the BRDefi model in the physiologic range of the transmembrane potential. At higher positive transmembrane potentials, the intracellular calcium concentration [Ca_i] is prevented from assuming negative values.

The Tissue Structure

To simulate the coupling of the individual cells, this project chose the bidomain model, which reduces the three-dimensional structure of the myocardium to two dimensions [9]. The coupling in the extracellular and in the intracellular space can take place diffusively or electrically in a bidomain model. Both possible solutions clearly differ in their reaction to an external electrical pulse. The diffusion network only provides a local solution to the problem since only the immediate neighbors of the cells are taken into account each time the transmembrane potentials are calculated. In contrast, a simulated myocardium made up of an electrical network reacts globally. The ions move according to the electrical resistance, over the gap junctions, to the next cell, or over the cell membrane along the concentration and potential gradient. When a stimulus is delivered, the potentials caused by the individual resistors in the network are instantaneously present at all cells.

Despite the considerably higher mathematical effort, the electrical network is used to simulate the defibrillation of the heart in this paper because of the above-listed reasons. Applying the diffusive network is not possible because a stimulus delivered to the myocardium cannot reach all cells instantaneously.

Voltage-Dependent Gap Junctions

Gap junctions are an accumulation of ion channels that stretch from one cell to a neighboring cell across the extracellular space. Corresponding to other ion channels, the gap junctions are capable of changing their conductance depending on the transcell voltage. The gap junctions are mostly concentrated at the ends of the myocytes, where they are combined in so-called "intercalated disks" [10].

Three different connexin isotypes are present in the heart (Cx43, Cx45, Cx40), and they can occur with varying frequency in different heart regions [11]. Mostly the connexin Cx43 is found in the gap junctions of the ventricular working myocardium [12].

The conductance (g_j) of the gap junctions is experimentally determined by patch-clamp measurements at two neighboring myocytes [13]. The measurement results can be described by the Boltzmann equation

$$g_j = \frac{(g_{\max} \cdot g_{\min})}{1 + e^{A(V \cdot V_0)}} + g_{\min} \qquad (1)$$

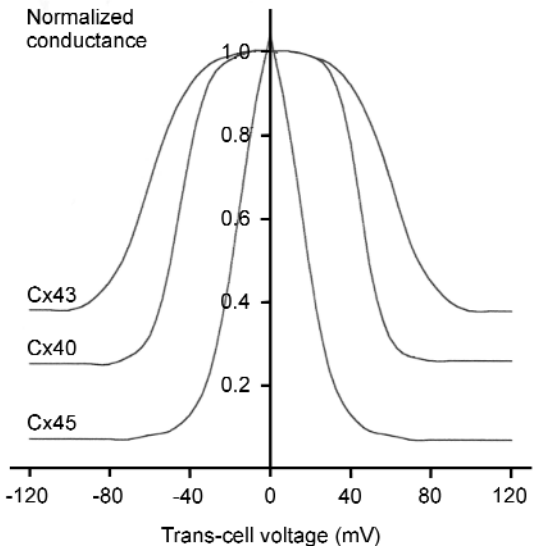


Figure 1. Dependency of the conductance of the iso-connexins from the transcell voltage V_j. The shown conductances G_j are standardized to the maximum conductance at 0 mV transcell voltage [13].

The parameters g_{max} and g_{min} describe the highest and lowest conductance of the gap junctions, depending on the transcell voltage. V_0 is the voltage value at which the voltage-dependent parts of g_j, described by $g_{max} - g_{min}$, are reduced to 50%. The parameter *A* is a slope factor by means of which the number of changing gap junctions can be determined [14]. Further analysis of the data shows that the conductance of the connexins, and especially of the Cx43 connexin, lies symmetrically around the zero point (Figure 1) [15]. The used parameters for g_{max} and g_{min} were taken from the above-mentioned references.

Inhomogeneities

The heart is built up on a collagen skeleton in the shape of a ring made up of tendon fibers that is situated at the atrioventricular connection. The heart muscle is constructed of individual muscle fibers and blood vessels. The myocytes that form the muscle fibers are surrounded by tissue fluids and possible plaque deposits. The conduction system, which is electrically insulated from the rest of the heart, runs within the heart muscle. This description indicates that the heart is not a homogeneous medium.

The inhomogeneous structure of the heart also affects the electrical properties and thus the spread of an excitation wave triggered by an external stimulus [16-18]. Defibrillation shocks delivered to the heart are unable to depolarize a sufficient amount of tissue if the myocardium behaves like a continuum. Inhomogeneities within the tissue allow a local depolarization by the application of the external shock, even at a greater distance to the electrode. These local depolarizations are termed secondary sources. The inhomogeneities cause a higher voltage drop over the cells and thus shift the transmembrane potential. If the transmembrane potential is raised above the threshold of the sodium channel, the cells depolarize, and an excitation wave spreads, starting from the secondary source. Figure 2 depicts the difference in the voltage course between a homogeneous chain of myocytes and a chain with a built-in inhomogeneity when a stimulus is delivered through external electrodes.

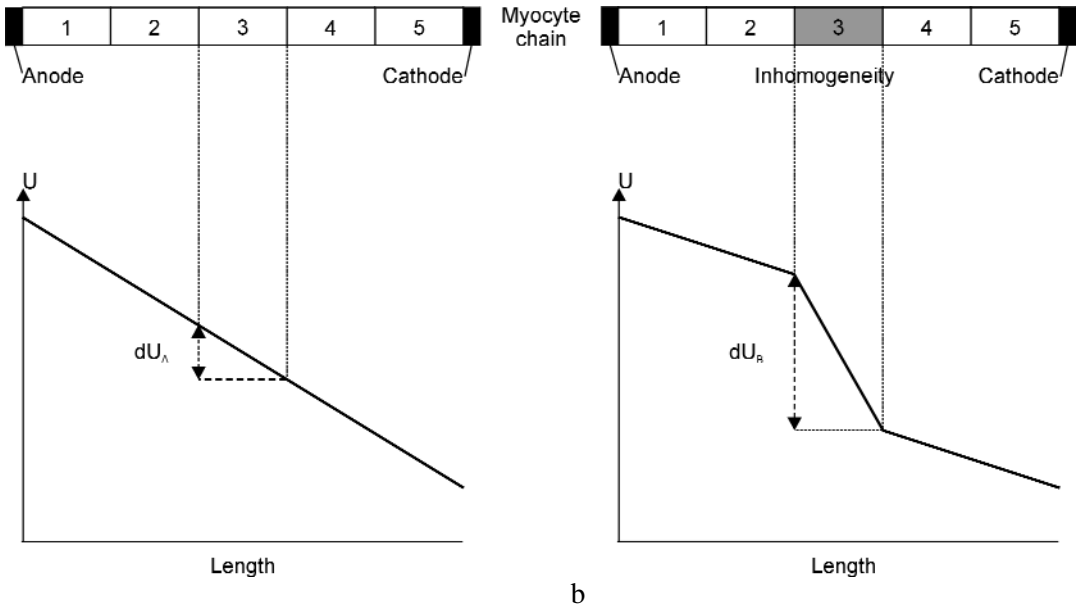
The secondary excitation waves cause a global depolarization of the myocardium over the course of time and thus prevent the further spread of fibrillation waves. This enables successful defibrillation of the heart. At the start of the simulation, the conductances in the bidomain model are decreased according to the inhomogeneities.

Results

Validation of the Model

Since a cell and myocardium model in the presented form has never been used before, an intensive validation is necessary to verify the parameter settings of the model for physiologic and pathophysiologic excitation spreads. To allow a comparison between the DR and the BRDefi-A model, a simulation program of an isolated cardiac cell was generated in addition to the BRDefi-A cell model, applying the differential equations by Drouhard and Roberge [7]. In the course of the simulation experiment, the transmembrane potential and the occurring ion currents are measured continuously. This makes it possible to compare the simulation results of the two cell models.

Figure 3 shows the transmembrane potentials V of the two cell models in relation to the time t, after an effective stimulus. The two action potentials principally have the same morphology. The repolarization phase of the BRDefi-A cell model lies minimally below the transmembrane potential of the DR cell model, resulting in a somewhat higher repolarization speed. To compare the two cell models in more detail, various parameters were numerically analyzed. These parame-



a b

Figure 2. Influence of inhomogeneities on the voltage course within a one-dimensional chain of myocytes during application of an external electrical field. If the chain has a homogeneous structure, a continuous drop of the voltage U from the anode to the cathode (panel a) results. The addition of inhomogeneities (myocyte 3) causes an increased voltage drop over cell 3 ($dU_A < dU_B$), thus affecting a depolarization of the respective cell (panel b).

ters and a description of their significance are listed in Table 1. Table 2 shows the corresponding values that result from the analysis of the two action potentials. In summary, it can be noted that the BRDefi-A model differs only slightly from the DR model. The differences are of a scale that is negligible.

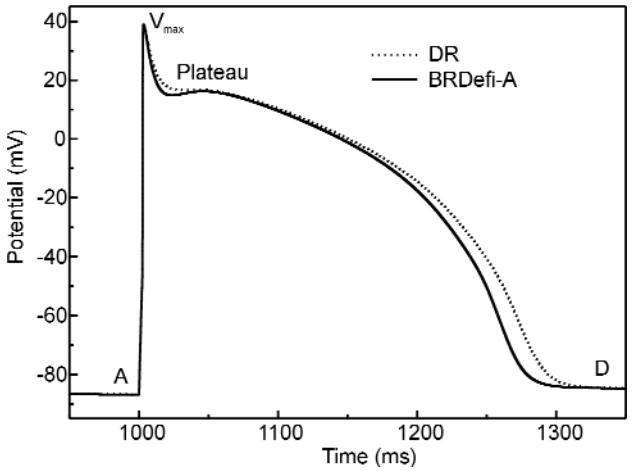


Figure 3. Morphology of an action potential, simulated with both the BRDefi-A cell model and the Drouhard-Roberge cell model. The section between A and V_{max} is called the depolarization phase. The maximum V_{max} marks the overshoot of the sodium ions. This is followed by the plateau phase typical for myocytes. Between plateau and D, the cell repolarizes and can then be excited again.

Defibrillation in the BRDefi-A Model

Defibrillation of ventricular fibrillation is done in humans or animals by delivering a high-energy shock to the fibrillating heart. The subsequent sections of this paper simulate the defibrillation process on a section of the myocardium with the help of the BRDefi-A model developed for this purpose. To simulate such a process, a square piece of tissue of 85 mm side length was created. The tissue piece is completely surrounded by the indifferent electrode, which serves as reference or zero potential. An extracellular pacing electrode through, which a defibrillation shock is emitted, is situated in the center of the tissue. Electrodes that measure the transmembrane potential and the ion currents of the cells are built into the myocardium. The intracellular and extracellular conductance, as well as the conductance of the gap junctions is chosen in such a manner so as to result in an excitation spread velocity of 24 cm/s.

During the delivery of a shock, the potential of the indifferent electrode is set to 0 V, and the different electrode is decreased to the desired negative potential. Figure 4 shows the structure of the extracellular domain

Parameter	Description
V_{max} (mV)	Maximum of the transmembrane potential caused by the overshoot of the sodium current
dV/dt_{max} (V/s)	Maximum slope of the transmembrane potential in the depolarization phase
t_0 (ms)	The time at which dV/dt_{max} occurs
Peak I_{Na} ($\mu A/cm^2$)	Maximally occurring sodium current
Plateau (mV)	Amplitude of the plateau phase

Table 1. Description of the analyzed parameters of the BRDefi-A model and the DR model.

Parameter	DR model	BRDefi-A modell
V_{max} (mV)	38.89	38.89
dV/dt_{max} (V/s)	360.31	402.19
t_0 (ms)	3.57	3.61
Peak I_{Na} ($\mu A/cm^2$)	471.84	422.57
Plateau (mV)	17.35	16.72

Table 2. Comparison of the BRDefi-A model with the DR model in regard to the parameters V_{max}, dV/dt_{max}, t_0, peak I_{Na}, and plateau. The absolute values determined with the simulation experiments for both models are indicated for all parameters.

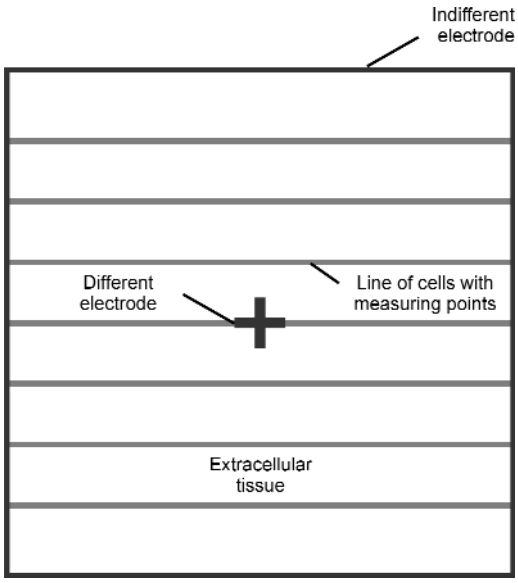


Figure 4. Structure of the extracellular domain for the study of defibrillation. The tissue piece is completely surrounded by the indifferent electrode. An extracellular stimulation electrode through which the shock is delivered is located in the center of the tissue. Measuring points that measure the transmembrane potential and the ion currents of the cells are built into the myocardium.

of the BRDefi-A tissue model that was used for this series of experiments. The gap junctions are dependent on the transcell voltage, in accordance with their natural properties. If a defibrillation shock is delivered to a non-excited myocardium, it is to be expected that an excitation wave will spread. The form of the spread depends, in turn, on the properties of the substrate to be studied. In particular, this poses the question of how and to what degree inhomogeneities in the myocardium affect the probability of a successful defibrillation.

Homogeneous Myocardium

Defibrillation pulses were delivered to a homogeneous substrate as described above. The entire tissue was in an excitable state. Two different defibrillation pulses were tested, with the potential of the different electrode against the indifferent electrode being –100 V and –300 V, respectively. The duration of both shocks was T = 10 ms. Figure 5 shows various snapshots of the substrate that were stored at the same moments in the simulations. After delivery of the defibrillation shocks at t = 0 ms, a concentric excitation wave forms around the different electrode in both simulations (Figure 5, 60 ms). A sequence of images results, much like what can also be observed during stimulation (in contrast to the defibrillation performed in this case). Both excitation waves spread outward from the center of the tissue with a speed of 24 cm/s. The spread velocity is to be expected due to the pre-settings of the conductances in the BRDefi-A model. The shape of the excitation wave, which is similar to a rectangle, is caused by the geometry of the tissue piece. Just like the depolarization, the repolarization of the substrate proceeds concentrically from the center point to the outside (Figure 5, 310 ms), and it is concluded at t = 460 ms (Figure 5, 460 ms).

Inhomogeneous Myocardium

The inhomogeneities were integrated into the above-described system such that a statistical distribution of the conductances resulted. The same defibrillation shocks were delivered as in the previous section. The sequence of images in Figure 6 represents the delivery of the two defibrillation shocks to the inhomogeneous tissue. The two upper rows of images depict the simulation results for a 100-V shock, and the two lower rows of images the effects of a 300-V shock. While still being subjected to the voltages, a multitude of depolarization centers form in the substrate (Figure 6,

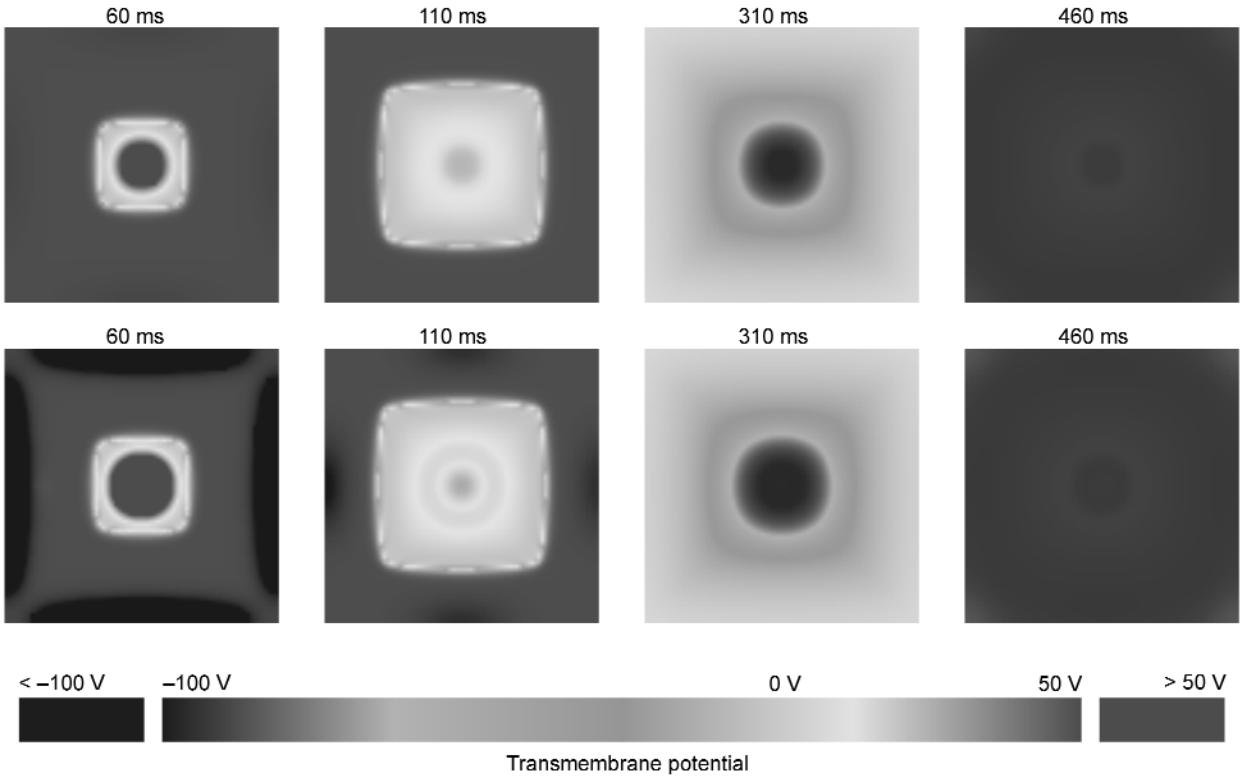


Figure 5. Distribution of the transmembrane potential of the individual cells after delivery of a defibrillation shock to non-excited homogeneous tissue. The excitation spreads for a 100-V (upper row of images) and for a 300-V shock (lower row of images) are shown. The times stated in the images are in relation to the time t = 0 ms at which the shock is triggered. In both cases, a concentric excitation spread around the different electrode results. For better information, see the color version of this figure on the last page of this issue.

5 ms), recognizable by their red coloration. In these areas, the shock causes an opening of the sodium channels and thus the initialization of an action potential. After the defibrillation shock has been turned off, the excitation waves spread, starting from the excited cells, and a global depolarization of the substrate results (Figure 6, 15 ms – 100 ms). The excitation does not spread around the different electrode to the edges as in a stimulation or the defibrillation of the homogeneous tissue (Figure 5), but it depolarizes the entire substrate by the formation of secondary sources. Since the repolarization does not spread from the inside to the outside, the inhomogeneous tissue is already completely repolarized after 350 ms, in contrast to the homogeneous tissue (Figure 6, 350 ms).

Discussion

The BRDefi-A cell model differs only minimally from the DR model. The differences in the individual parameters studied (V_{max}, dV/dt_{max}, t_0, peak I_{Na}, and plateau) are of a negligible degree. Therefore, despite higher voltage resistance, the BRDefi-A cell model describes the transmembrane potential of a myocyte during the action potential without any losses in quality. In combination with the introduced bidomain model, a simulation system has been created that is suitable for testing the delivery of defibrillation pulses.

In case of homogeneity, the high-energy pulses cause a depolarization of the tissue, as expected for a normal stimulation. Despite the high-energy stimuli, the myocardium is only excited in a radius of 5 to 7 mm around the indifferent electrode until the voltage is turned off. The slope of the transmembrane potential during the shock is not sufficient to have a significant effect on the ion channels at a greater distance from the shock electrode.

In contrast, an inhomogeneous distribution of the intracellular and extracellular conductances causes a globalization of the excitation in regard to the tissue

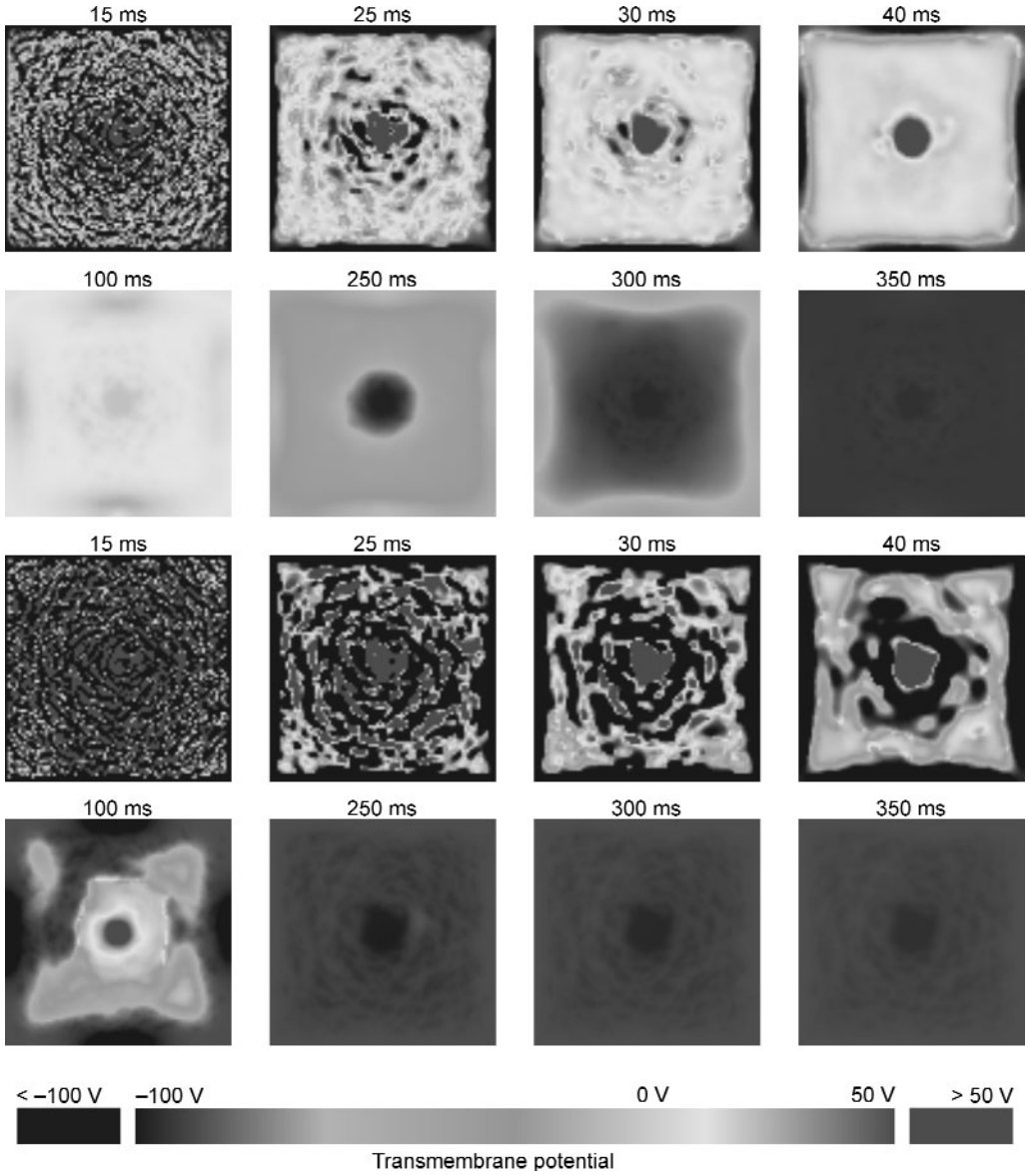


Figure 6. Distribution of the transmembrane potential of the individual cells after delivery of a defibrillation shock to non-excited inhomogeneous tissue. The excitation spreads for a 100-V (upper 2 rows of images) and for a 300-V shock (lower two rows of images) are shown. The shock is triggered at t = 0 ms. A global depolarization of the myocardium results in both cases. For better information, see the color version of this figure on the last page of this issue.

response to high-energy pulses. The increase in the transmembrane potential of individual cells by a local reduction of the conductance in the myocardium allows the induction of secondary depolarization sources at a greater distance to the different electrode. The excitation spreads from the local depolarization sources with the preset velocity of 24 cm/s. The distribution of the sources in the myocardium significantly shortens the paths for the spread of the excitation waves, and the entire tissue is depolarized within only 40 ms. This way, any excitation spread to the myocardium is blocked. This also means that any existing ventricular fibrillation would be terminated because depolarized or refractory tissue cannot be depolarized again by an excitation wave. Consequently, inhomogeneities are a decisive sub-aspect in simulated tissue that has to be taken into consideration when developing defibrillation models.

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