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A simulation study of the reaction of human heart to biphasic electrical shocks

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Abstract

Background: This article presents a study, which examines the effects of biphasic electrical shocks on human ventricular tissue. The effects of this type of shock are not yet fully understood. Animal experiments showed the superiority of biphasic shocks over monophasic ones in defibrillation. A mathematical computer simulation can increase the knowledge of human heart behavior.

Methods: The research presented in this article was done with different models representing a three-dimensional wedge of ventricular myocardium. The electrophysiology was described with Priebe-Beuckelmann model. The realistic fiber twist, which is specific to human myocardium was included. Planar electrodes were placed at the ends of the longest side of the virtual cardiac wedge, in a bath medium. They were sources of electrical shocks, which varied in magnitude from 0.1 to 5 V. In a second arrangement ring electrodes were placed directly on myocardium for getting a better view on secondary electrical sources. The electrical reaction of the tissue was generated with a bidomain model.

Results: The reaction of the tissue to the electrical shock was specific to the initial imposed characteristics. Depolarization appeared in the first 5 ms in different locations. A further study of the cardiac tissue behavior revealed, which features influence the response of the considered muscle. It was shown that the time needed by the tissue to be totally depolarized is much shorter when a biphasic shock is applied. Each simulation ended only after complete repolarization was achieved. This created the possibility of gathering information from all states corresponding to one cycle of the cardiac rhythm.

Conclusions: The differences between the reaction of the homogeneous tissue and a tissue, which contains cleavage planes, reveals important aspects of superiority of biphasic pulses. ...

Background

Ventricular fibrillation is a major health problem. One of its characteristics is that death can occur in few minutes if no therapeutical intervention is applied. Up to now, electrical shocks are the only effective known therapy against ventricular fibrillation. It is important to understand the related phenomena in order to identify the optimal parameters of the applied defibrillation shocks.

Recently, studies were done to evaluate cardiac rhythms following the first defibrillation shock, comparing biphasic truncated exponential, monophasic damped sinusoidal and monophasic truncated exponential waveforms in patients experiencing out-of-hospital ventricular fibrillation cardiac arrest [1]. The results of this research illustrated the defibrillation chances through a statistical method. The impacts of a specific waveform of electrical shocks can also be studied with computer models, which could actually bring a more detailed look over the phenomena. The theoretically obtained data should be in the end compared to the experimental ones.

The exogenous electric current- applied for defibrillating the heart- is redistributed in the cardiac tissue according to the conductivity variation. This is given by the anisotropic electric properties: the conductivity along the cellular axis being greater than the average conductivity across it. Experimental measurements revealed that the orientation of ventricular myocytes depends on the intramural position [2]. This dependence can be approximated by a helix. In the human left ventricular epicardium the angle of the myocytes fiber orientation is equal to -75°, it is 0° in the midwall and 70° in the endocardial area.

Another factor, which modifies the path of the electric current, is the discontinuous character of the cardiac muscle. Cleavage planes are the most important source of discontinuity. They are parting the myocardium in distinct layers. The muscle sheets have a predominantly radial orientation in apicobasal transmural sections. Nevertheless, these layers are not perfectly parallel. They intersect each other forming an interconnected system [3].

Studies of electrical response of the heart to external stimuli include inhomogenity and discontinuity of the cardiac tissue. It is acknowledged that defibrillation shocks would not be successful if the myocardium would be homogeneous and continuous [4].

An interesting feature that can be observed after an electrical shock is applied, is the volume ratio of the tissue, which is immediately affected. The areas from which the depolarization could spread forming depolarization fronts are therefore identified. Muscle discontinuities like blood vessels, collagenous septa and cleavage planes induce the appearance of secondary electrical sources. This means that in the neighboring regions depolarization fronts are produced [5].

This article reports on the influence of biphasic electric shocks and the corresponding waveforms on human ventricular myocardium. For this investigation a three-dimensional computer model of human cardiac tissue was used. It included realistic fiber orientation and cleavage planes.

Methods

Many aspects of physiologic and pathophysiologic behavior of the myocardium could be explained with basic electrophysiologic principles [6]. This motivated the experimenters to gather data of intra-, extra- and intercellular electrophysiologic quantities from specific functional regions and from the whole heart. Flow and concentrations of ions, as well as voltages across membranes were of special interest to them. The components which are considered to be relevant for the cell membrane, were: its conductance, ionic channels, pumps, exchangers and some intracellular structures, e.g. the sarcoplasmic reticulum with the storage and release of Ca^{2+}. The measurement results were used for constructing mathematical models of different levels of abstraction.

For the simulations presented in this article the Priebe-Beuckelmann model of human ventricular tissue had been used [7]. It was basically constructed from a Luo-Rudy ventricular model [8]. The modifications adopted were five currents based on experimental data obtained from human myocytes: I_{Kr}, I_{Ks}, I_{Ca}, I_{to} and I_{K1}. The remaining currents were scaled to fit human cell data. Through these a more refined description of acquired arrhythmogenic substrates was brought.

As all the other electrophysiological models, the used one provided the possibility of calculating the values of its specific ionic currents of different type passing through the membrane and the transmembrane voltage. The transport of ions was correlated to the resistance of the ion channels, which is nonlinear depending on time and voltage. This type of relationship was given by the existence of both passive and active transport mechanisms of the cell membrane channels.

The transmembrane voltage V_m, which is defined as intracellular minus extracellular potential, is varying in time (fig. 1) according to the following equation:

$$\frac{\partial V_m}{\partial t} = -\frac{1}{C_m}\left(I_{mem} - I_{inter} \right) \quad (1)$$

where C_m is the membrane capacity, I_{mem} represents the total transmembrane current and I_{inter} is the intercellular source current. The transmembrane current consists in this model of:

$$I_{mem} = I_{Na} + I_{Ca} + I_{to} + I_{Kr} + I_{Ks} + I_{K1} + I_{NaCa} + I_{NaK} + I_{bNa} + I_{bCa} \quad (2)$$

A schematic illustration of Priebe-Beuckelmann model is shown in fig. 2.

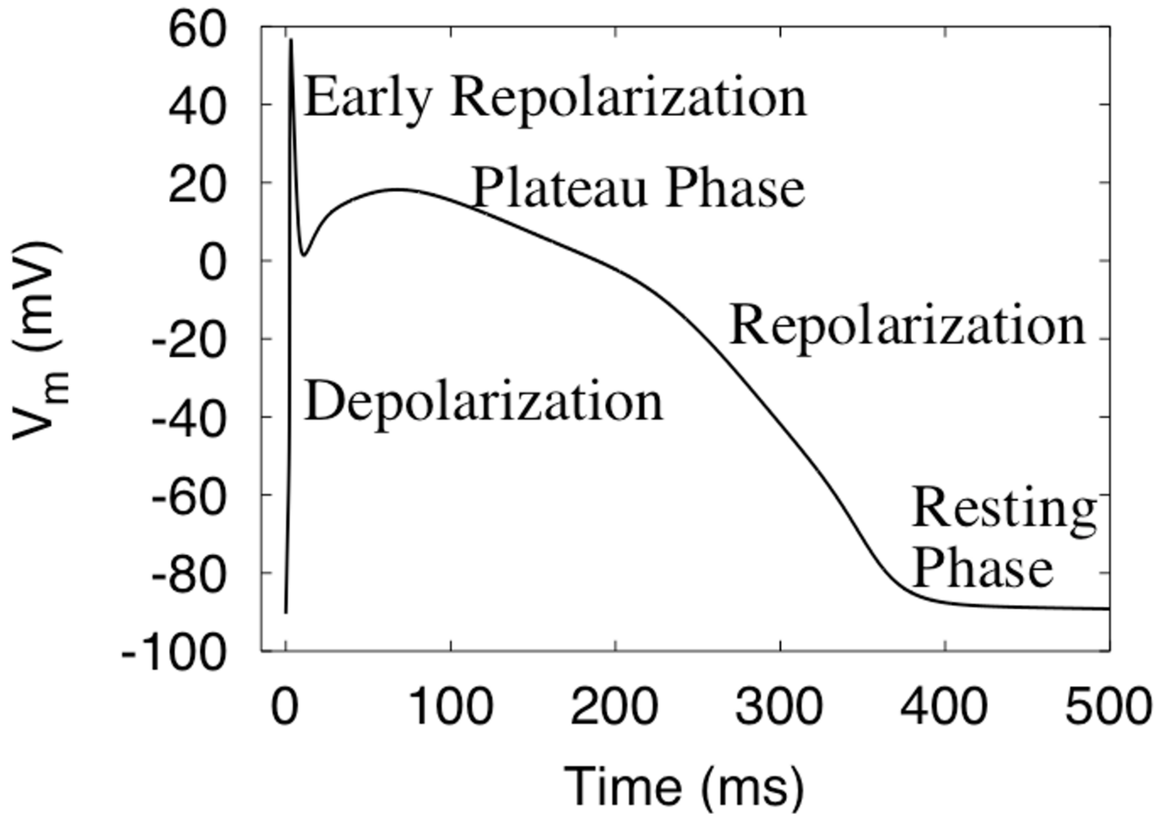

Figure 1
Transmembrane voltage, V_m as function of time in Priebe-Beuckelmann model.

The excitation propagation in the cardiac tissue is described by a bidomain reaction diffusion model [9]. In this representation the myocardium was reproduced as a net of cells embedded in an interstitial medium. The myocytes are electrically coupled by an anisotropic current flow through the intra- and extracellular domain and through the gap junctions. In the two domains, the current flow is calculated using Poisson's equations for stationary electrical fields. This model presents a realistic description of the electrical coupling of human ventricular myocytes. The anisotropic electrical properties are incorporated using realistic fiber orientation of the cardiac muscle. The bidomain equations, which were giving us the variation of I_{inter} and Φ_e(extracellular potential) as function of the given V_m, were implemented with finite difference method and solved with the Gauss-Seidel technique.

$$\nabla\left((\sigma_i + \sigma_e)\nabla\Phi_e\right) + \nabla\left(\sigma_i\nabla V_m\right) = 0 \quad (3)$$

$$\nabla\left(\sigma_i\nabla V_m\right) + \nabla\left(\sigma_i\nabla\Phi_e\right) = -I_{inter} \quad (4)$$

where σ_i and σ_e are conductivity tensors of the intra- and extracellular domain, respectively. The blood is a conductive medium (σ_b) and does not contain excitable cells. According to theses characteristics its mathematical description is given by the following equation:

$$\nabla\left((\sigma_b)\nabla\Phi_e\right) = 0 \quad (5)$$

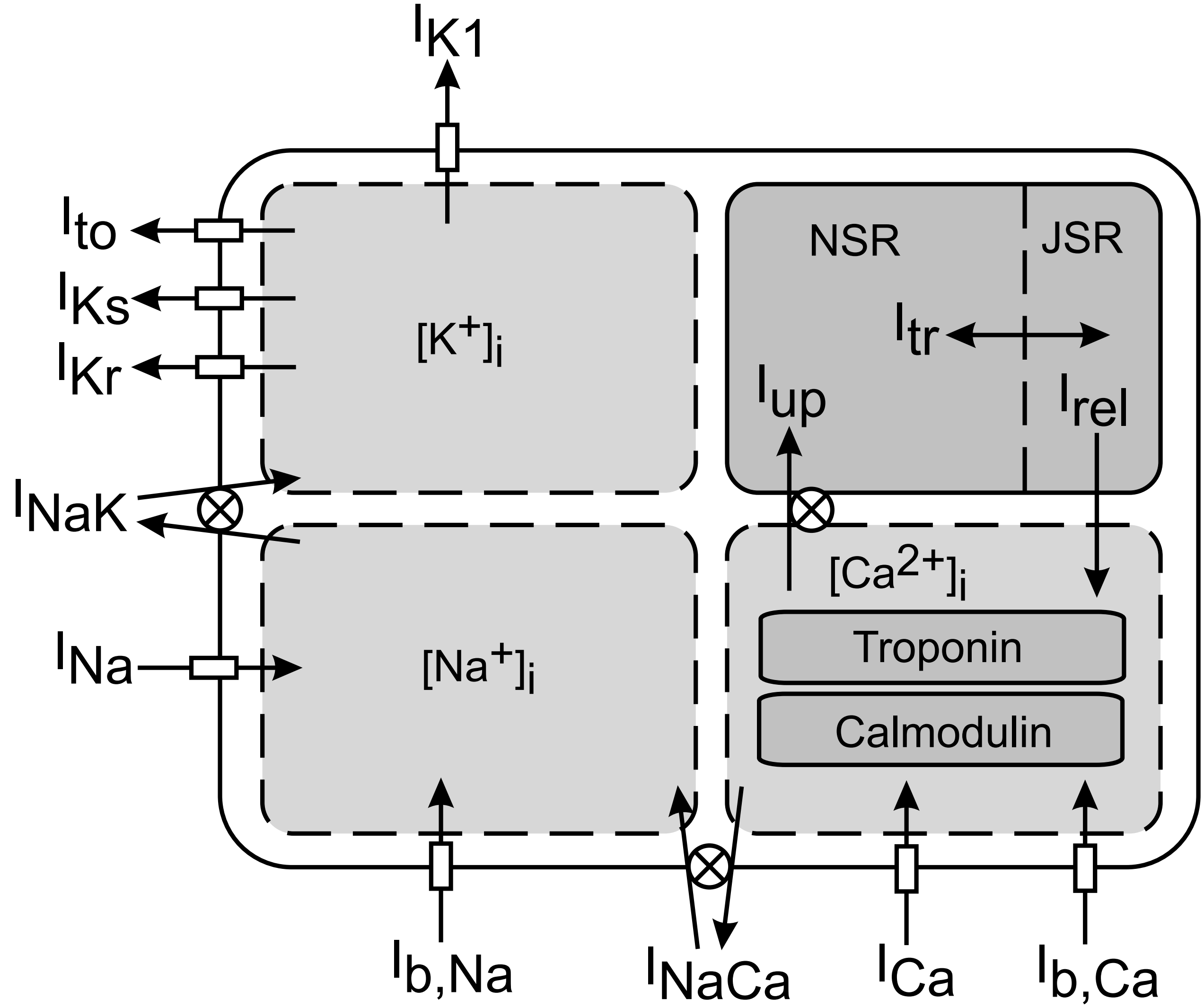

Figure 2
Priebe-Beuckelmann cell model.

The current transition from the cardiac tissue to the monodomain bath region is done with the fulfillment of specific boundary conditions. At the frontier the normal component of current between a bidomain and monodomain tissue is continuous in the extracellular space, the normal component of current between a bidomain and monodomain tissue is zero in the intracellular space, and the extracellular potential and the monodomain potential are continuous [10].

Simulation parameters
Sixty simulations were done with a three-dimensional virtual wedge of cardiac tissue. Its size was fixed at the value $1 \times 1 \times 2$ cm^3. It was generated using cubic voxels with 0.2 mm side lengths, which constituted the grid of the model. The realistic fiber twist was implemented using a rule based method. According to the studied situation the simulations used a model with or without cleavage planes (see fig. 3).

Two types of electrodes, characterized by different geometric forms, were the source of the electric signal. In both cases they were fixed at the ends of the longest axis ($z = 0$, $z = 2$ cm). In case of quadratic planar electrodes (1×1 cm^2 in size), they were placed in bath medium. Because of the chosen conditions, the applied electric signal had to cross

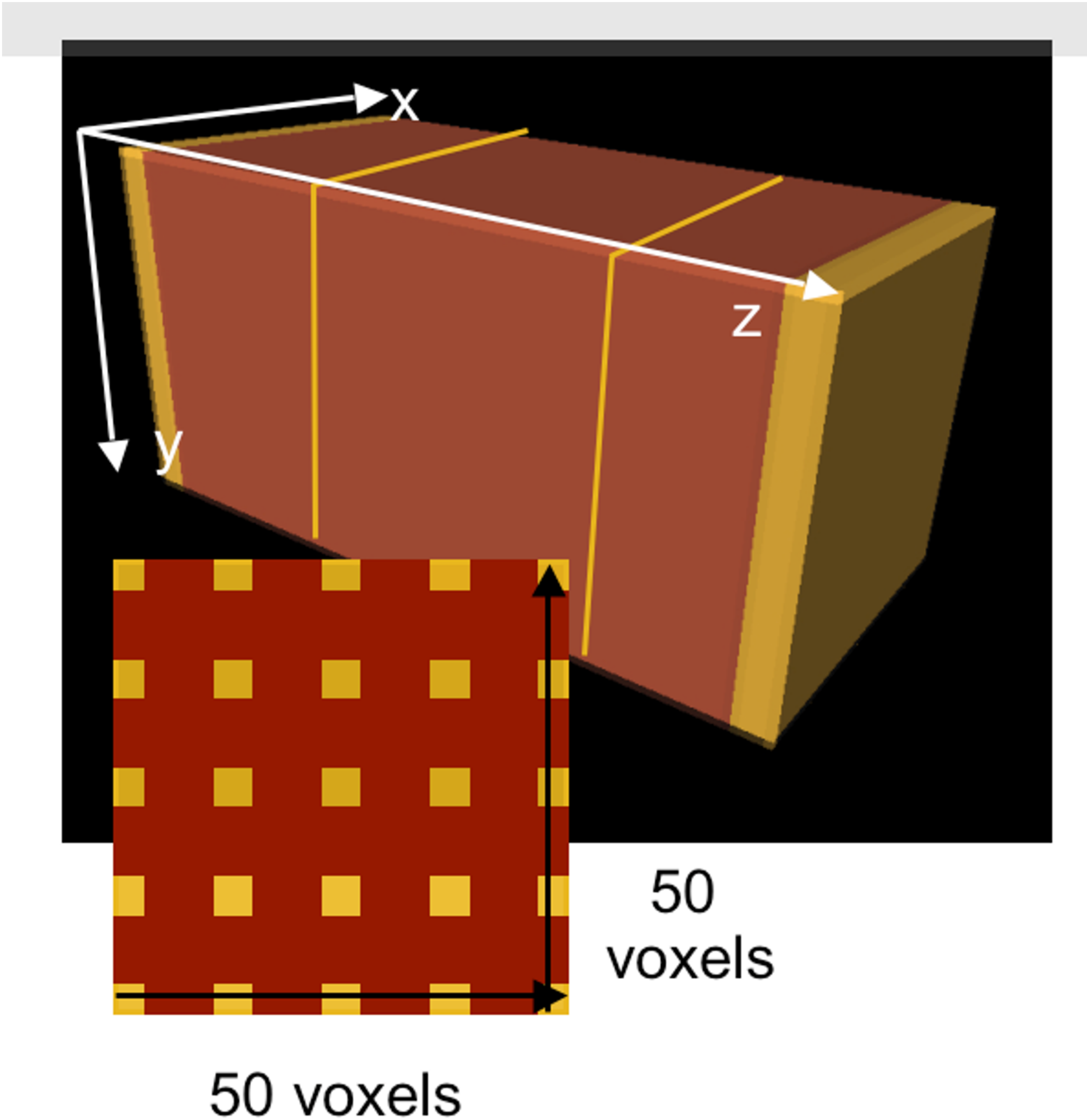

Figure 3
The model of the wedge of myocardium, which contains cleavage planes and is incorporated in bath is represented.

1 mm of the bath medium before entering the myocardial area. In this way the extracellular potential was homogeneously distributed to the myocytes placed on the boundary surfaces. The second type of electrodes had a ring shape. Their outside diameters were 1 cm and their inside diameters were 0.98 cm. The ring electrodes were

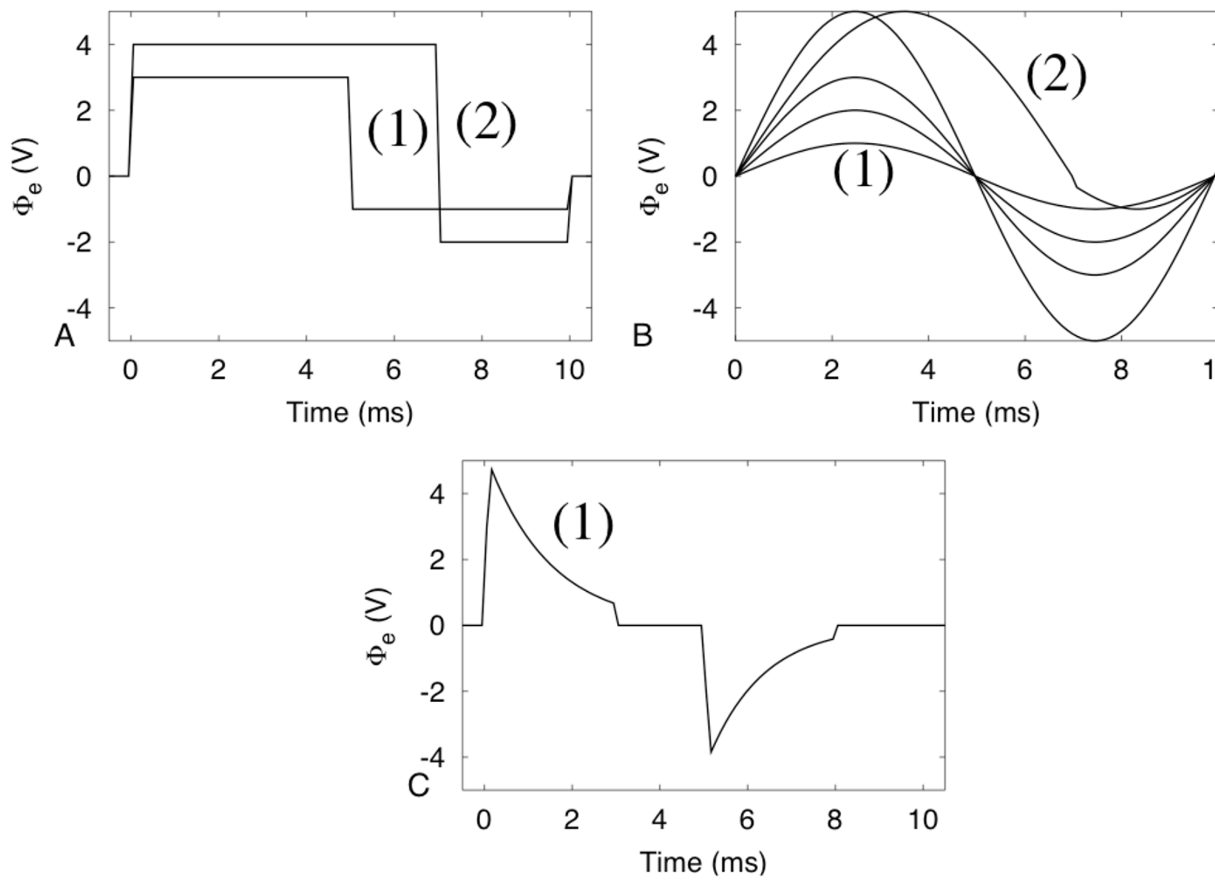

Figure 4
The applied biphasic electric signal for defibrillating the myocardium: A) rectangular, B) sinusoidal, C) exponentially truncated.

directly attached to the myocardium. Through them both monophasic and biphasic electric impulses were delivered. The calculation time step was 10 μs. The simulations were done with a Power Mac G5. The machine had 2 GHz CPU speed. The average time needed for each computation was 10 hours.

Results

The first objective was to study the cardiac tissue reaction to different types of biphasic signals given by planar electrodes. Past studies revealed that cleavage planes are drastically reducing the time needed for the entire tissue to be depolarized after an electrical shock [11]. Firstly a cardiac wedge, which was not fragmentized by cleavage planes was used. In this way the differences between the obtained results were enhanced. A continuous medium needs more time for passing from one phase to another, especially when the depolarization front is planar.

Considering experimental data we decided to do the simulations using exponentially decaying, sinusoidal and rectangular signals with magnitudes varying from 0.1 to 5 V. The two phases of the applied electric signal were temporally symmetric and equal to 5 ms (see the lines denoted by (l) in fig. 4). Simulations done with electrical impulses with equal signal characteristics, but distributed along 7 and 3 ms (see the lines denoted by (2) in fig. 4) presented negligible differences.

The first reaction of the myocardium after the biphasic impulse was the appearance of depolarization fronts at both ends. The most interesting feature of this phase was the magnitude of the transmembrane voltage near to the

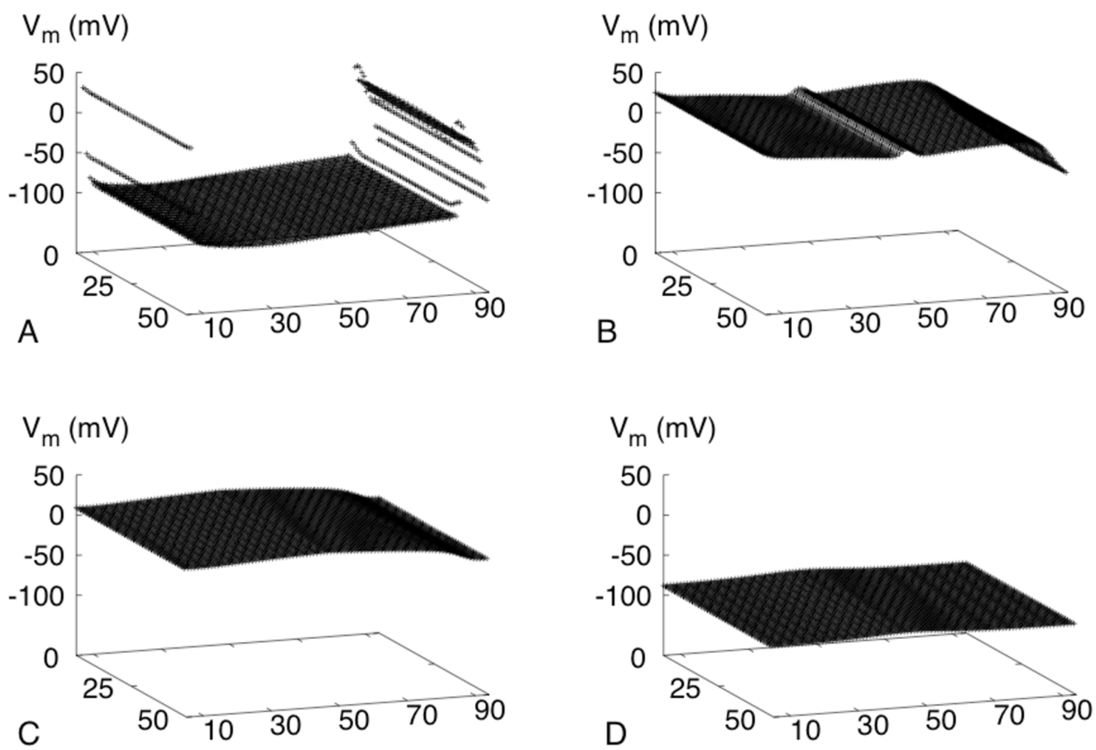

Figure 5
The temporal evolution of the electrical behavior of a 3D continuous model of the human myocardium, stimulated with (± 5 V, ± 5 V) biphasic sinusoidal electrical signal is shown. Planar electrodes were used. For an easier visualization of the variation of V_m along the axis of interest (z axis, measured in voxels) a slice of the cardiac tissue (middle of y axis) is presented. Because of symmetry reasons all the planes intersecting the y axis give the same information. The cardiac behavior at certain moments (A) 1 ms, B) 70 ms, C) 140 ms, D) 435 ms) after the electrical stimulation is reflected.

border of the bath medium. A strongly hyperpolarized region was induced in the cases in which the magnitude of the second phase of the applied electric signal was too high (fig. 5). The depolarization front was not able to annihilate it. In the other cases the tissue reached the isopotential state after approximatively 150 ms. The time course of the transmembrane voltage was followed until complete repolarization. For identifying further differences between various signals, the time needed in each case for the tissue to get from one state (resting, depolarized, repolarized) to another was measured and compared. From the temporal point of view, the intervals corresponding to complete depolarization and total repolarization brought the most valuable information. These data can give a measure whether a defibrillation shock will be successful or not.

For sinusoidal and exponentially decaying signals always less time was needed for achieving complete depolarization and total repolarization in comparison to the rectangular ones. The time intervals could be further decreased by increasing the ratio between the magnitudes of the first

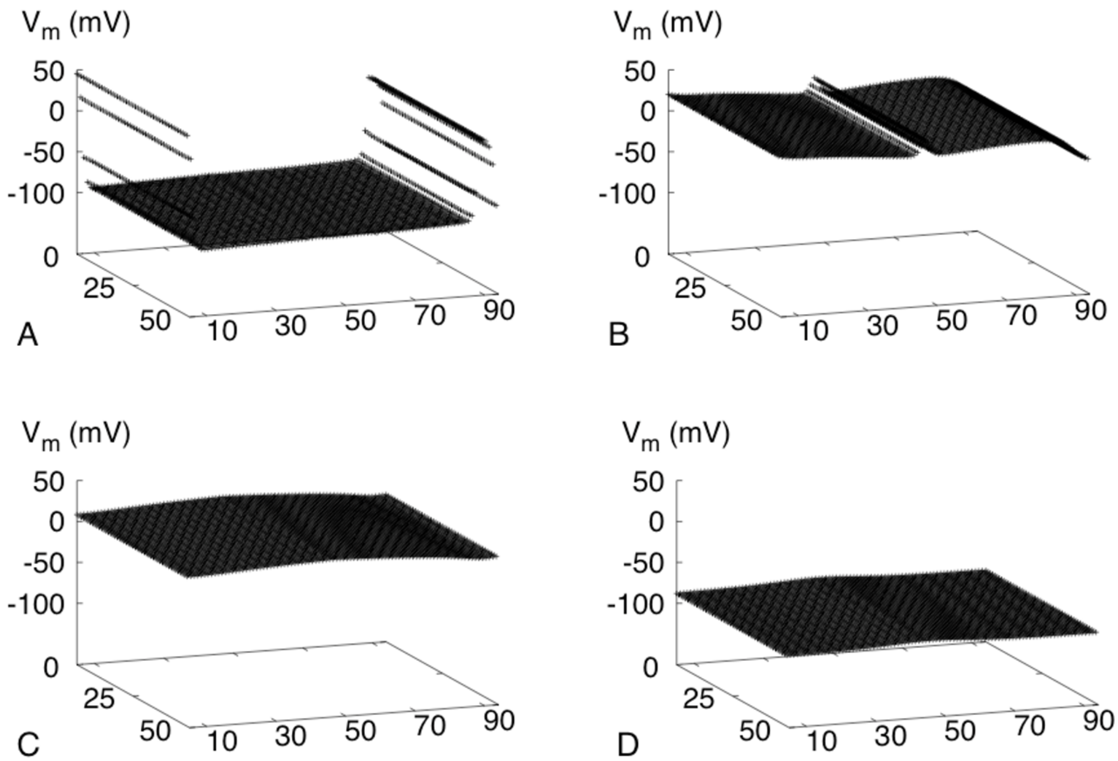

Figure 6
The temporal evolution of the electrical behavior of a 3D continuous model of the human myocardium, stimulated with (± 3 V, ± 1 V) biphasic exponentially decaying electrical signal is shown. Planar electrodes were used. For an easier visualization of the variation of V_m along the axis of interest (z axis, measured in voxels) a slice of the cardiac tissue (middle of y axis) is presented. Because of symmetry reasons all the planes intersecting the y axis give the same information. The cardiac behavior at certain moments (A) 1 ms. B) 72 ms, C) 140 ms, D) 430 ms) after the electrical stimulation is reflected.

and second phase of the electric signal. For example, a rectangular signal of ± 1 *V* in both phases induced the complete depolarization in 90 ms and total repolarization in 450 ms. A rectangular signal of ± 2 *V* in first phase and ± 1 *V* in the second one induced the complete depolarization in 85 ms and total repolarization in 440 ms. The most successful signal was the exponentially decaying one with the magnitudes maxima fixed at ± 3 *V* and ± 1 *V* (fig. 6).

The second objective of the study was to understand the phenomena related to tissue discontinuities. For this, a model, which included interlaminar clefts between layers of cardiomyocytes was used. The virtual wedge had a tissue with realistic fiber orientation that was twice intersected by isolating half filled grids (see fig. 3). While the extracellular domain remains continuous, the intracellular domain contains two planes with a chessboard pattern of voxels with zero intracellular conductivity. The used geometrical pattern is showing that cardiac cleavages are intersecting each other. In this way we obtained a schematic description of the structure of the heart.

The simulation showed that- when the electrodes were rectangular- the depolarization front was continuous (movie 1 [see additional file 1]). For this case the

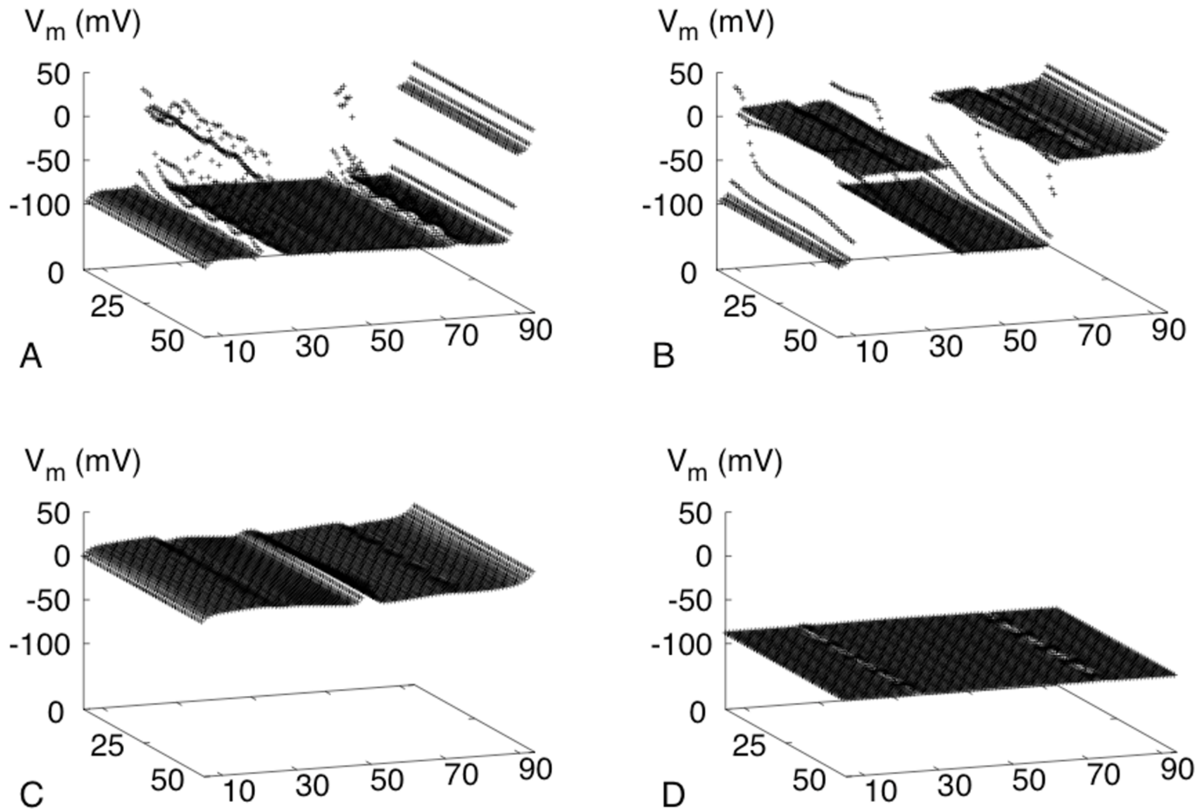

Figure 7
The temporal evolution of the electrical behavior of a 3D model of the human myocardium, which contains cleavage planes, stimulated with ± 2 V monophasic electrical signal is shown. Planar electrodes were used. For an easier visualization of the variation of V_m along the axis of interest (z axis, measured in voxels) a slice of the cardiac tissue (middle of y axis) is presented. Because of symmetry reasons all the planes intersecting the y axis give the same information. The cardiac behavior at certain moments (A) 1 ms, B) 20 ms, C) 45 ms, D) 410 ms) after the electrical stimulation is reflected.

intramural myocardium was depolarized by secondary sources created near to the cleavage planes. The side area closest to the anode was depolarized, while the opposite one was hyperpolarized. When the extracellular potential was strong enough to produce a depolarization front from the depolarized region that was near to the cathode, also the cleavage planes were inducing depolarization fronts.

The biphasic electric signal created depolarization fronts at both ends of the tissue. The cleavage planes created depolarization fronts during the first 5 ms of the signal. A comparison with a monophasic impulse showed that their behavior is identical in both cases. Changing the polarity of the electrical impulse did not change the electric behavior in the intramural region. The difference that can be seen is the time needed to depolarize the region between the electrodes and the nearest cleavage planes. This difference is illustrated in the fig. 7B and 8B.

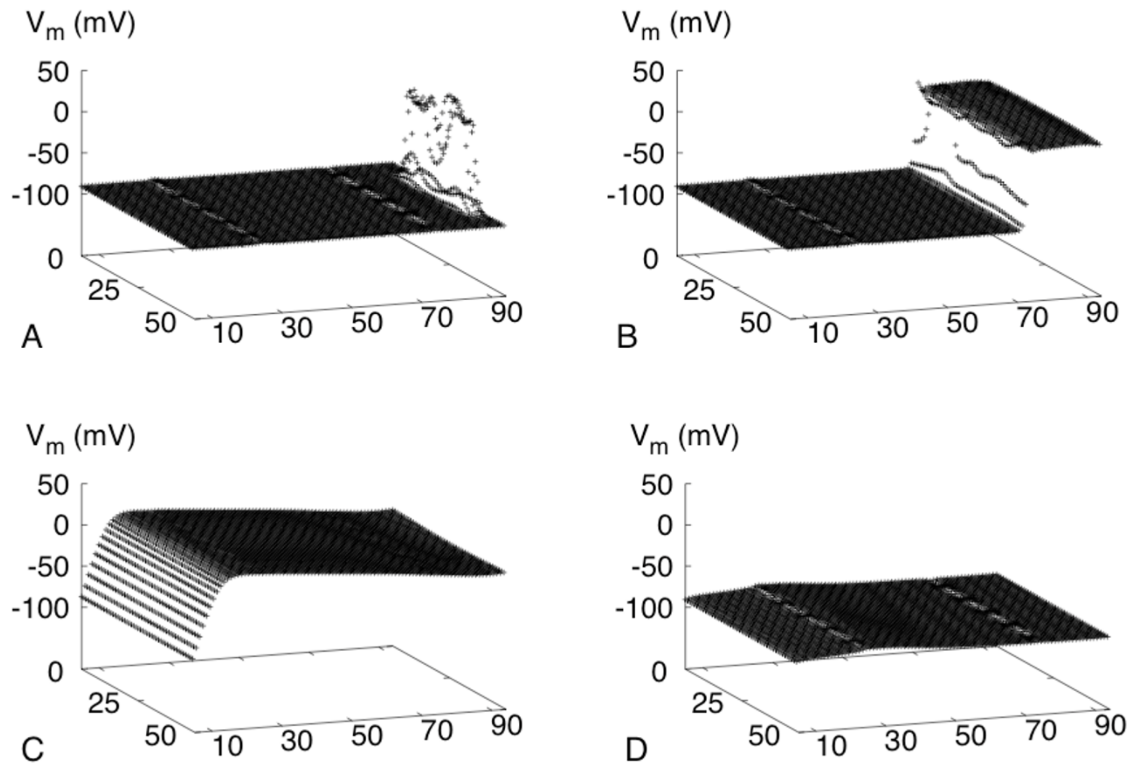

Figure 8
The temporal evolution of the electrical behavior of a 3D model of the human myocardium, which contains cleavage planes, stimulated with (± 2 V, ± 1 V) biphasic exponentially decaying electrical signal is shown. Planar electrodes were used. For an easier visualization of the variation of V_m along the axis of interest (z axis, measured in voxels) a slice of the cardiac tissue (middle of y axis) is presented. Because of symmetry reasons all the planes intersecting the y axis give the same information. The cardiac behavior at certain moments (A) 1 ms, B) 20 ms, C) 50 ms, D) 400 ms) after the electrical stimulation is reflected.

The comparison between monophasic and biphasic electrical impulses was done also for the ring electrode case (fig. 9 and 10). They were applied directly on the myocardium. The electrodes were not incorporated in a bath medium to maintain the big corresponding gradient of the extracellular potential spatial distribution. A cardiac tissue fragmented by cleavage planes was considered. The simulation of the reaction of the myocardial tissue bulk, after a monophasic electric impulse (±0.2 V) was applied for 10 ms, showed that both rings produced a depolarization of the neighboring tissue. The directly induced depolarization, the one produced by the cathode, was too weak for creating a depolarization front. The one correlated to the virtual cathode constituted the source of a depolarization front. The same type of behavior appeared when the biphasic electric shock (± 0.2 V, ±0.1 V) was applied for 5 ms for each phase (movie 2 [see additional file 2]). In both situations, the cleavage planes did not induce the appearance of secondary sources, so the tissue reacted as it would have been continuous. The explanation of the non-activation of the area neighboring the cleavage planes is that the depolarization front never achieved a spatially uniform distribution. This drastically enlarged the limit of the needed extracellular potential gradient along the z axis

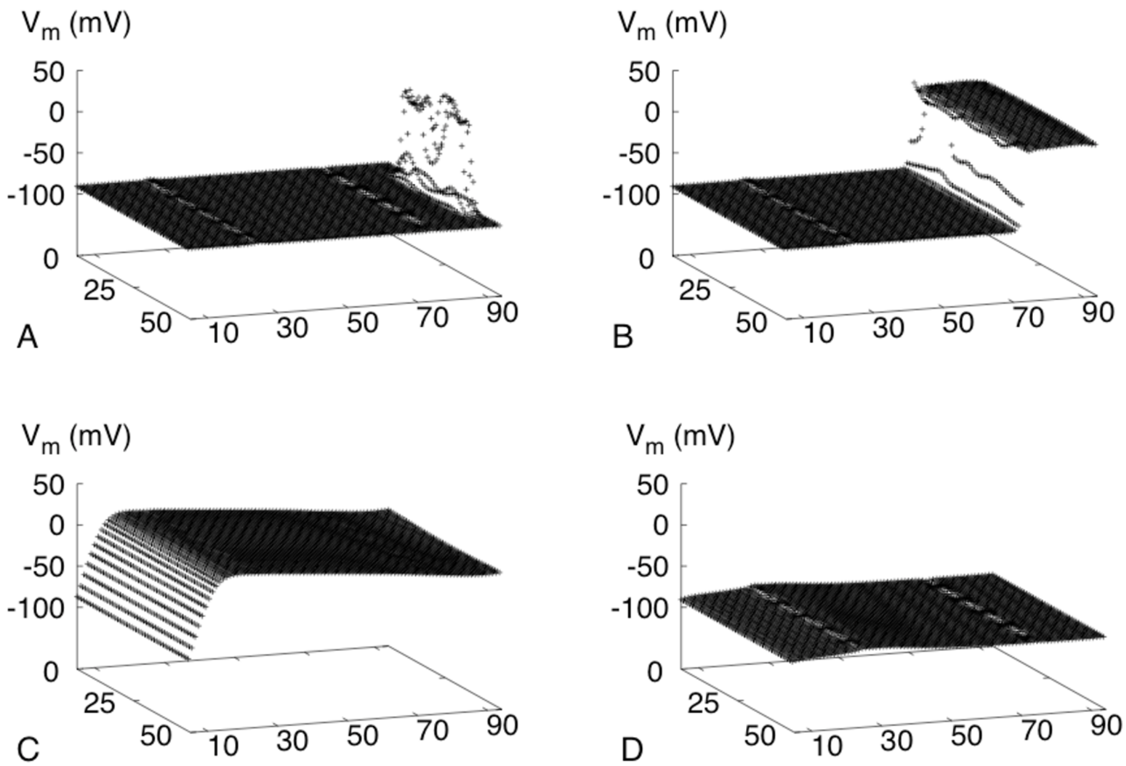

Figure 9
The temporal evolution of the electrical behavior of a 3D model of the human myocardium, which contains cleavage planes, stimulated with ± 0.2 V monophasic electrical signal is shown. Ring electrodes were used. For an easier visualization of the variation of V_m along the axis of interest (z axis, measured in voxels) a slice of the cardiac tissue (middle of y axis) is presented. Because of symmetry reasons all the planes intersecting the y axis give the same information. The cardiac behavior at certain moments (A) 10 ms, B) 40 ms, C) 240 ms, D) 470 ms) after the electrical stimulation is reflected.

in the areas which bordered the clefts. The results of the simulations done with ring electrodes provided two characteristics that would make one to incline in the favor of biphasic electrical shocks. First, when the myocardium was monophasically activated the real cathode depolarized only a small part of the neighboring area. The tissue in that region was not ulterior excitable. Since the depolarization front, produced at the opposite end did not induce a depolarization in that region, the goal of complete tissue depolarization failed (see fig. 9C). Second, the biphasic shock reduced very much the time needed for the tissue to pass from one phase to another. The largest amount of depolarized tissue was achieved 240 ms after the monophasic shock was applied, while only 85 ms were needed by the whole tissue to be depolarized after a biphasic impulse was given.

Disscusion

The presentation of our work started with a comparison between different types of biphasic electric shock, which are used in practice for treating a fibrillating human heart. All along the study the reaction of resting tissue to an electrical shock was shown. This reflects the way healthy tissue reacts, so it is helpful for getting a general fundamental

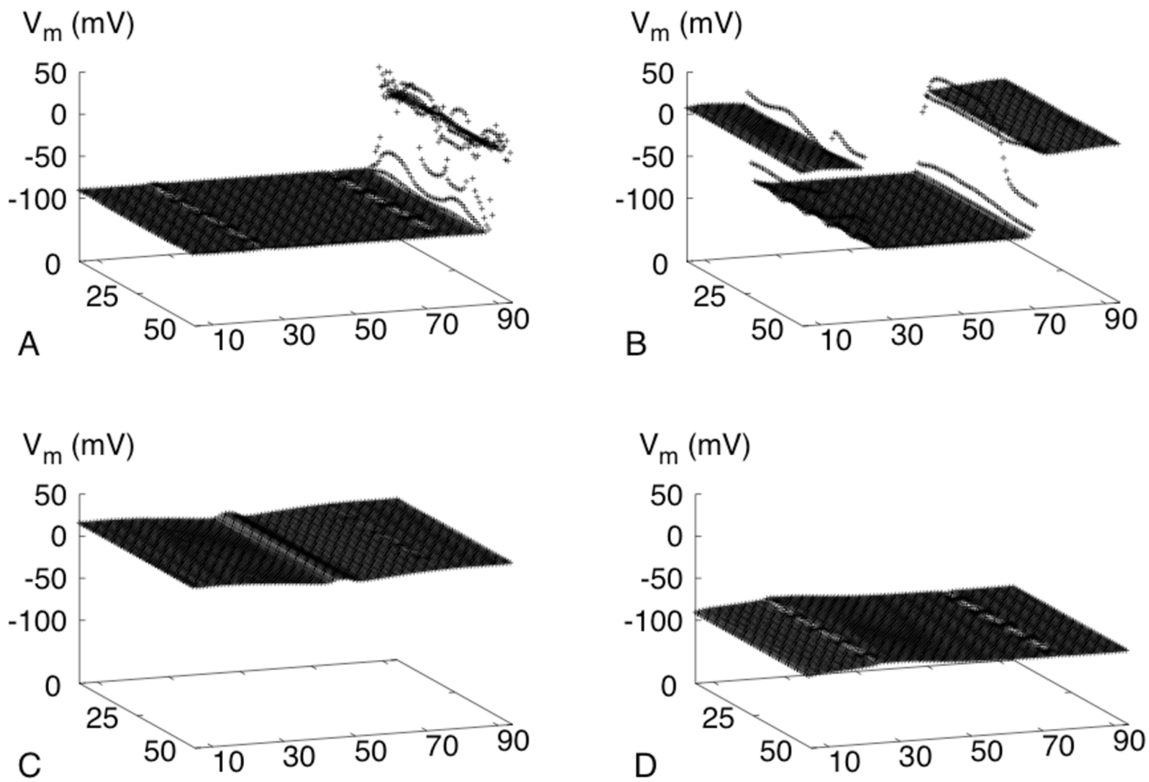

Figure 10
The temporal evolution of the electrical behavior of a 3D model of the human myocardium, which contains cleavage planes, stimulated with (± 0.2 V, ± 0.1 V) biphasic exponentially decaying electrical signal is shown. Ring electrodes were used. For an easier visualization of the variation of V_m along the axis of interest (z axis, measured in voxels) a slice of the cardiac tissue (middle of y axis) is presented. Because of symmetry reasons all the planes intersecting the y axis give the same information. The cardiac behavior at certain moments (A) 10 ms, B) 40 ms, C) 85 ms, D) 430 ms) after the electrical stimulation is reflected.

understanding of the phenomena. Information gathered in this work will be used in future studies, which will present the effects of the electrical shocks on fibrillating tissue. The data obtained from our simulations showed that the sinusoidal and the exponentially decaying signals were more efficient in exciting a tissue than the rectangular ones. It was observed that a very strong hyperpolarization induced through the second phase of the electrical shock may lead to the failure of the therapy. This result indicates that the magnitude of the second phase of the electrical shock has to be smaller than the magnitude of its first phase. Nevertheless this magnitude has to be high enough to produce depolarization fronts.

The present article shows the importance of biphasic signals over monophasic ones for ring and planar electrodes. The given comparisons with monophasic impulses is reflecting some of the causes that can lead to the failure of complete depolarization. For example, monophasic shocks of same temporal length and magnitude as biphasic ones, applied through ring electrodes can produce a non excitable area which will stop the depolarization front. Comparing the results it was concluded that it is recommended to create depolarization fronts uniformly distributed in space for producing secondary electrical sources in the intramural region. A planar depolarizating front is activating the areas near to the cleavage planes much easier, so high voltages are not requested. In this way the clefts induce the appearance of secondary electric sources, which will start depolarizing the cardiac inner wall simultaneously with the primary sources. Another reason which sustains the bigger efficiency of the biphasic defibrillating shocks, compared to the monophasic ones, is the fact that a fibrillating tissue has already some refractory regions, so a depolarization produced at both ends (as was the presented reaction of the myocardium to the biphasic electrical impulse) would increase the chance of the entire tissue to be depolarized.

Conclusions

The simulations were done in three-dimensional human ventricular myocardium, which included a realistic fiber orientation and also cleavage planes. All these features, put together form a very complex representation of the cardiac muscle. The clefts constitute one of the most important features of the model, since they have been poorly studied from the electrical point of view in the past [5]. Considering this it proves to be of high importance to understand their basic role. If a fibrillation would be ongoing in the virtual myocardium an electrically chaotic behavior would be present. In such circumstances it would be very difficult to identify the exact influence of the cleavage planes. This information is needed in order to take a good decision if the clefts should or not be included in the defibrillation simulation of the fibrillating cardiac human heart.

The chances of the defibrillation success depend on many factors. This is why the article does not exclusively address the total excitation time of the modeled tissue. On contrary, it is also focused on identifying the depolarization sources. These two combined information give a measure of how fast the myocardium can be brought in an electrically equivalent state. The affirmations related to the activation of the-cleavage planes, were the results of the statistics done with many computer experiments. At present we are developing a mathematical theory in order to explain the statistics.

Competing interests

None declared.

Authors' contributions

IMP had the idea to do the study, performed the simulations, the data analysis and wrote the manuscript. GS engineered the software needed for describing the bidomain model and electrophysiological behavior. OD was responsible for supervision of the project. All authors have read and approved the final manuscript.

Additional material

Additional File 1

Temporal evolution of transmembrane voltage V_m *(see colors code on the right corner) in a cardiac tissue containing cleavage planes after (± 3 V, ± 1 V) biphasic exponentially decaying electrical signal is applied through planar electrodes. Depolarization fronts appear at both ends of the tissue. First it appears on the right side (z = 100) and after inverting the polarity of the electrical signal it is induced on the left end (z = 0). In the 4th ms secondary electrical sources appear near to the left cleavage plane (z = 25) and in the 7th ms secondary electrical sources appear near to the right cleavage plane (z = 75). Notice that after the tissue is completely depolarized (55th ms) all its parts are passing from one state to another in the same time.*
Click here for file
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Additional File 2

Temporal evolution of transmembrane voltage V_m *(see colors code on the right corner) in a cardiac tissue containing cleavage planes after (± 0.2 V, ± 0.1 V) biphasic sinusoidal electric signal is applied through ring electrodes. Notice that both real and virtual circular cathodes (z = 0, respectively z = 100) are depolarizing the region around them (1st ms). In the first 5 ms the depolarization is spread only from the virtual cathode (right end of the tissue) and after inverting the polarity of the electrical signal a depolarization front is spreading also from the left end of the tissue (z = 0). No secondary electrical sources can be observed in the intramural region, even though cleavage planes were integrated in the model. Notice that after the tissue is completely depolarized (90th ms) all its parts are passing from one state to another in the same time.*
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