Role of spiral wave pinning in inhomogeneous active media in the termination of atrial fibrillation by electrical cardioversion

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Abstract

Atrial fibrillation is the most common type of arrhythmia to affect humans. One of the treatment modalities for atrial fibrillation is an electrical cardioversion. Electrical cardioversion can result in one of three outcomes: an immediate termination of arrhythmic activity, a delayed termination or unsuccessful termination. The mechanism of delayed termination is unknown. Here we present a model of an atrial fibrillation as a coexistence of several spiral waves pinned to the inhomogeneities in active media. We show that in inhomogeneous system delayed termination can be explained as the unpinning of a spiral wave from inhomogeneities and its termination after collision with the edge of the system.

Keywords: excitable media, spiral wave pinning, electrical cardioversion, atrial fibrillation, arrhythmia mechanisms
Introduction

Atrial fibrillation is the most common type of arrhythmia to affect humans. The underlying mechanism is still not clear despite extensive experimental and theoretical studies aiming to characterize the spatiotemporal organization of electrical activity during this type of arrhythmia. Several mechanisms have been proposed. However, three dominate: a coexistence of multiple spiral waves (multiple wavelets hypothesis) [1], a stationary, high frequency spiral wave (mother wavelet hypothesis) [2] and a point sources of periodic activity [3]. One of the treatments for atrial fibrillation is electrical cardioversion. During this procedure, a monophasic or biphasic electrical shock is applied to the chest to reset the abnormal forms of electrical activity within the atria and restore spontaneous sinus rhythm [4]. Several studies have previously investigated the effect of cardioversion on the electrophysiology of myocardial cells with evidence supporting alteration of cell membrane potential [5], a prolongation of the repolarization time [6] and a heterogeneous distribution of the electrical field within muscle [7].

Electrical cardioversion is a frequently used technique to restore sinus rhythm. It can result in one of three outcomes: an immediate, delayed or unsuccessful termination. However, despite significant research devoted to the explanation and characterization of electrical cardioversion, its effect on the spatiotemporal organization of activation waves is not fully understood. Two mechanisms have been proposed to explain the ability of electrical cardioversion to terminate atrial fibrillation: the depolarization of a critical mass of the myocardium [8] and a prolongation of the action potential duration leading to an increase in the wave size, causing a termination of the fibrillation due to the resultant decrease in the spatial area available for wave propagation [9].

One of the unexplained phenomena occurring in clinical practice is the delayed termination of electrical activity following the application of the cardioversion shock. In this phenomenon, electrical cardioversion does not terminate all abnormal activity but, instead, renders it unstable before leading to a spontaneous termination. The details of this instability and the resulting delayed termination are not known. An understanding of this phenomenon may give insight into the mechanism of atrial fibrillation itself and provide new ideas for its treatment.

A hypothesis providing a mechanism of the delayed termination was proposed by Zemlin et al. [10]. Using a mathematical model, they showed how a three-dimensional scroll wave self-terminates within a few cycles after the application of the electric shock. However, their result is only applicable to 3D systems (the ventricular wall) since such self-termination is driven by filament curvature dynamics, negligible in the thin atrial muscle.

An important hypothesis for the 2D system was provided by Pumir and Krinsky in [11] where authors showed an unpinning of the spiral wave from a heterogeneity in the active media after the application of an external electrical field and postulated its role.
in arrhythmia cardioversion. Their model was later supported by experimental observation of the pinning of the spiral wave to millimeter sized obstacles in heart tissue [12]. However, their work was focused on the detailed mechanism of unpinning and the more statistical properties of unpinning, which could be linked with clinical observations, were not assessed. Additionally, authors investigated the transition between an anatomical reentry wave (a wave circulating around a non-conducting area) and free spiral wave. However, pinning of the spiral wave to a non-conducting area is only one mechanism of wave anchoring. Inhomogeneity of the tissue may also act as an anchor for spiral waves resulting in a different behavior of the wave during cardioversion and after unpinning.

Here, we develop the hypothesis of Pumir and Krinsky and propose an explanation of the phenomenon of delayed termination in a two-dimensional model of the atrial muscle in presence of the tissue inhomogeneity. We assume that the fibrillation is driven by a stationary spiral wave (the “mother rotor” hypothesis [2]) pinned to a local inhomogeneity. During electrical cardioversion, we hypothesize that the center of rotation (spiral wave tip) of the mother rotor shifts and that this displacement results in an unpinning and a drift of the wave as was shown for the case of pinning to heterogeneities [11]. If the drifting wave should collide with an inexcitable boundary or obstacle, the mother rotor will terminate. The set of activations obtained following the electrical cardioversion corresponds to the activity of the drifting mother rotor before termination. However, should the drifting mother rotor enter a region at which it would again be anchored, atrial fibrillation would resume and this case would be classified as an unsuccessful cardioversion.

Methods

There are several models of heart cell electrochemical activity with varying levels of complexity (see [13] for a comprehensive overview of the mathematical modeling of the heart). The most widely used formalism is based on partial differential equations in the following form:

\[
\frac{\partial v(r,t)}{\partial t} = -I_{ion}(v, w)/C + \nabla \cdot (D \cdot \nabla v)
\]

\[
\frac{\partial w(r,t)}{\partial t} = G(v, w)
\]

where \( v \) denotes a distribution of the electrical potential across cell membranes. \( w \) denotes the distribution of the states of the ion channels, ion exchangers and ion pumps regulating the dynamics of the current flowing through the cell membrane \( (I_{ion}) \). \( C \) is the membrane capacity and \( D \) denotes the distribution of the diffusion coefficients related to the electrical coupling of the cells. Different models vary in the number of variables describing the states of the ion channels, pumps and exchangers resulting in the dynamics of \( I_{ion} \) current. The most simple models use only one variable to describe this current. In our study, we used such simplified model, namely the FitzHugh-Nagumo model (FHN) [14]. The FHN model is widely used to investigate wave
phenomena in excitable media (such as the heart tissue) due to its simplicity and well
known properties. For an in depth discussion of model properties see [15].

The FHN model is composed of two partial differential equations:

$$\frac{\partial v}{\partial t} = \frac{1}{\mu} (v - \frac{1}{3}v^3 - w) + \nabla \hat{D} \nabla v$$  \hspace{1cm} (3) \\
$$\frac{\partial w}{\partial t} = \mu (v + \beta - \gamma w)$$  \hspace{1cm} (4)

where $v$ is the transmembrane voltage, $w$ is the total slow current, $\gamma = 0.5$, $\mu = 0.3$. Computations were carried out on a two-dimensional, 100x100 rectangular grid. The Euler integration scheme was used with a time step $\Delta t=0.05$ and the spatial step $\Delta x=0.4$. Since we were not aiming to quantitatively reconstruct physiological phenomena, we used dimensionless units in our study. We used zero-flux boundary conditions at the sample borders. Border of the sample corresponds anatomically with areas in the heart where excitable tissue is in contact with inexcitable structures: e.g. orifices of the valves or edges of the scar tissue. Optical mapping studies showed spiral waves terminating at such borders between excitable and inexcitable tissue [16].

In order to include the effect of tissue anisotropy, we introduced two diffusion coupling coefficients $D$: the horizontal and the vertical diffusion coefficient. Calculations for different ratios of the horizontal and vertical coefficients did not show any qualitative difference in mechanism presented here (results not shown). Therefore, due to lack of consensus in the literature (published coupling coefficients ratio range from 1:1 to 9:1) [17][18] we set the diffusion coefficient to 0.5 in the horizontal direction and to 0.2 in the perpendicular direction.

There are several types of tissue inhomogeneity, ranging from structural (e.g. inhomogeneous fibrosis of the muscle) to functional (e.g. inhomogeneity of the action potential duration). Natural inhomogeneity is increased in pathological state predisposing heart for arrhythmia occurrence. In our work we investigated inhomogeneity of the current inhibition. This inhomogeneity was introduced into our system as a spatial dependence of the kinetic parameter $\beta$ (responsible for current inhibition) on the spatial position and was performed in two steps. Firstly, a horizontal gradient of $\beta$ was introduced (from 0.85 at the left edge of sample to 0.75 at the right edge) to induce a drift of the spiral wave towards the left edge of the system [19]. Next, to introduce regions which could anchor the spiral waves, a random, local decrease of $\beta$ was superimposed in the following way: for each node of the simulation grid, with a probability $p$, the value of $\beta$ was decreased within an area of radius $R$. The magnitude of the decrease depended on the distance from the node. The decrease of the $\beta$ was determined by coefficient $I$ (referred further as inhomogeneity intensity) according to following equation:

$$\beta \rightarrow \beta - I (1 - \frac{r}{R})$$  \hspace{1cm} (5)
where \( r \) is the distance from the center of the node. Because \( \theta \) is responsible for current inhibition and for a small \( \theta \) the system depolarizes spontaneously, the condition \( \theta > \theta_{\text{min}} \) was introduced to avoid the formation of spontaneously firing regions. For low values of the probability \( p \), only a few sites were created. For larger \( p \), the sites merged forming large patches with constant values of \( \theta \) and acting as anchoring sites (Fig. 1). For values of \( \theta \) smaller than 0.64, the system became oscillatory due to a very low current inhibition. For \( \theta \) greater than 0.85, the size of the meandering pattern of the spiral wave exceeded the size of the sample leading to a spontaneous termination of the wave. Therefore, we set the initial gradient to 0.85 at one edge and 0.75 at the other edge of the sample. Introduction of the inhomogeneity in the form of a random decrease in the \( \theta \) parameter spatial distribution, lowered the average value of \( \theta \) far below 0.85. Therefore, addition of the condition \( \theta > 0.75 \) prevents the system from reaching the self-oscillatory regime.

Spiral waves were initiated in the system by setting the spatial distribution of \( v \) and \( w \) to the distribution within a propagating spiral wave: for each element of the simulation grid, its phase was calculated as:

\[
\theta = \frac{r - k\varphi - 2\pi kn}{2\pi k}
\]

where \( r \) and \( \varphi \) are polar coordinates of a given point with respect to the center of the spiral wave, \( k \) is its winding number and \( n \) is an integer set so as to obtain a phase between 0 and 1. Values of \( v \) and \( w \) for a given element of the grid were set depending on the phase. \( \vartheta = 0 \) corresponded to the resting state and \( \vartheta = 1 \) corresponded to the wave front depolarization. All intermediate values of the variables were copied from the stationary distribution of the variables within the action potential cycle. This approach was applied four times, to each quarter of the system.

Spiral waves either drifted towards the left edge and terminated or anchored to areas with a relatively constant, low value of \( \theta \). For further analysis, we only selected the cases with at least one anchored spiral wave. In order to find the characteristic simulation time after which a spiral wave could be considered anchored, we calculated a distribution of the termination times for 1000 simulations \((R=3.2, I=0.02, A=0.65 \text{ and } p=0.02)\) with the duration of the simulation \( T_{\text{max}}=1500 \). In 439 of them, activity was still detected after \( T_{\text{max}} \). In the remaining cases, the spiral waves terminated. The distribution of the termination times is shown on Fig. 2. Most of the spiral waves terminated for time between 90 and 540. Consequently, the checking time for spiral wave stability was set to 600: if, after \( t=600 \), activity was detected in the system, it was assumed that the spiral wave was anchored.

Note that, in general, a spiral wave in an inhomogeneous system should be almost always not stationary and ultimately terminate after a collision with the edge of the system (which may occur for short observation times). This non-stationarity is visible as a long tail in the distribution (Fig. 2). Due to this effect, our results partially depend on the cutoff value we picked for the checking time. However, because of the statistical method we used to fix the checking time, this dependence is not crucial.
There are two methods of electrical cardioversion used in clinical practice: monophasic and biphasic cardioversion. In both methods a short pulse (or two consecutive pulses of opposite sign for biphasic cardioversion) of electrical current is passed through the thorax [20]. This current alters the voltage of the cell membranes and the propagation of activation waves, leading to their termination if sufficient current amplitude is applied. Several studies have shown that structural inhomogeneities of the myocardial tissue cause an inhomogeneous distribution of the electrical field during electrical cardioversion [5][21]. However, irrespective of the spatial distribution of current amplitude or whether the change in transmembrane voltage is positive or negative, a cardioversion shock will either terminate a spiral wave or shift its position [22]. Since, in our study, we focused on the dynamics of spiral wave after this shift, we used a simplified effect of electrical cardioversion, that is a homogeneous, global increase of the variable $v$ in the FHN model ($v$ corresponds to the transmembrane voltage). Another reason for simplified cardioversion is sensitivity of the spiral waves on inhomogeneity of the variable $v$, which would be introduced using more realistic model (e.g. Pumir and Krynski [23]). Since in our work we wanted to focus on impact of tissue function inhomogeneity we had to minimize influence of inhomogeneity introduced by cardioversion. Combined effect of both types of inhomogeneity will be addressed in future research.

Due to the stochastic nature of inhomogeneity generation, we conducted a series of simulations for different probabilities (500 repetitions for each value of $p$). Each simulation comprised the following steps:

1. Generation of the inhomogeneity for the given value of the parameter $p$.
2. Initiation of the spiral waves.
3. Simulation for the time $T_{\text{max}}$. Simulation at each iteration was continued only if spiral waves were found to be anchored after $T_{\text{max}}$.
4. Cardioversion: a global increase of the $v$ variable
5. Simulation for the time $T_{\text{max}}$.

If, after step 5, there was no activity in the system, the case was considered a successful termination. In addition, the number of cycles and the average cycle length before and after cardioversion was calculated.

To assess the effect of the model parameters on spiral wave unpinning, we varied the following parameters: the radius of the inhomogeneity $R$, the intensity of the inhomogeneity $I$ and the stimulation amplitude $A$. Initially, we set the parameters to: $R=8$, $I=0.02$, $A=0.65$ and varied each of the parameters in the range in which spiral wave unpinning and drift occurs. The radius of the inhomogeneity $R$ was varied between 4 and 12. For $R<4$ due to the small size of the inhomogeneity in relation to the wave width (between 7 and 9, depending on the local $\beta$ value), spiral waves were not able to anchor to a single inhomogeneity. Spiral wave pinning was still observed in the case of several inhomogeneities generated in a close proximity effectively forming a bigger cluster. However, such an effect was very rare (maximally in 3% cases for $R=3$ and 2% for $R=2$) requiring large numbers of iteration which exceeded the available computational resources. The intensity of the inhomogeneity $I$ was varied between
0.01 and 0.04. For $I<0.01$, the gradient of $\beta$ introduced by a single inhomogeneity was too weak to anchor the spiral wave. Spiral wave pinning was still observed when several inhomogeneities overlapped (thus introducing effectively a larger gradient). However, similarly to the case of small $R$, the effect was obtained very rarely. Increasing $I$ above 0.04 did not result in any significant change in the results obtained. The stimulation amplitude $A$ was varied between 0.1 and 0.85. For $A<0.1$, the shift of the spiral wave position caused by a stimulation was usually insufficient to induce unpinning. For $A>0.85$, stimulation caused the termination of all activity in the sample.

Fibrillatory cycle length was measured at the left-upper corner of the sample. Local activation time was recorded when the value of the potential (the variable $v$) crossed 50% of the local action potential amplitude. The cycle length was defined as the difference between consecutive local activation times.

**Results**

In the system with unperturbed initial conditions (linear gradient of parameter $\theta$), all initiated spiral waves drifted toward the left edge of the system and terminated. However, after inhomogeneity generation with a non-zero probability $p$, patches of low $\beta$ value were able to act as stabilizing areas for spiral waves. Cardioversion applied in these cases resulted in either a successful or an unsuccessful termination of the spiral waves.

Examples of an unsuccessful and a successful termination are shown on Fig.3 and 4, respectively. In both cases, of all the spiral waves induced initially, only one remained anchored. Cardioversion shock induced a drift of the remaining spiral wave. In the case shown in Fig.3, however, the drifting spiral wave entered an area in which it was able to re-anchor. In the case shown in Fig. 4, the spiral wave continued to drift until it collided with the edge of the system and terminated. Termination occurred after 6 cycles in this example.

The results for the base parameters ($R=3.2$, $I=0.02$, $A=0.65$) are shown in Fig.5. The number of successful terminations after cardioversion is shown on Fig. 5a. To obtain the cardioversion success rate, this value has to be divided by the number of stable cases where spiral waves anchored on inhomogeneities (Fig.5.b). The maximum success rate of 100% was obtained for the lowest probability ($p=0.02$). The average spiral wave cycle length was significantly larger after cardioversion than before it (paired t-test passed with $p<0.0001$) (Fig.5.c). Additionally, the average cycle length before and after cardioversion decreases as a function of the probability of inhomogeneity generation (Fig.5.d). Cardioversion success rate increases with the average cycle length of the spiral wave (Fig.5.d). This relationship is a superposition of dependences shown in Fig. 5.b and Fig.5.c - the cardioversion success rate decreases with the parameter $p$, which is also related with decrease of the cycle length.

Effect of the radius of the inhomogeneity $R$ on cardioversion success rate is shown in Fig.6.a. The highest success rate was obtained for $R=1.2$. With increasing $R$, cardioversion success rate decreased. A decrease was greater for low $R$ and high $p$.  


values. Similar characteristic was obtained for varying value of the inhomogeneity intensity $I$ (Fig.6.b) with the highest success rates for $I=0.02$. Increase of the stimulation amplitude caused more uniform increase of the success rate (Fig.6.c) except for $A=0.45$ and $A=0.65$ for which success rate was only slightly different in comparison with differences for other values.

A relation between cardioversion success rate and average cycle length for varying values of the radius of the inhomogeneity, the stimulation amplitude and the inhomogeneity intensity is shown in Fig.7. All results show a correlation between the cardioversion success rate and the average cycle length. We performed linear regression obtaining $R^2$ between 0.53 and 0.94 when varying the radius of the inhomogeneity, 0.64 to 0.94 when varying the stimulation amplitude and 0.87 to 0.95 when varying the inhomogeneity intensity (see Fig.7 for detailed values for each parameter). The minimum cycle length and minimum success rate varied for different values of parameter $R$. With increasing $R$, both the average cycle length and success ratio dropped from 13.2 and 0.85 for $R=1.6$ to 8.3 and 0.24 for $R=4.8$ for average cycle length and success ratio respectively (Fig.7.a-b). The minimum values did not change with a changing stimulation amplitude (Fig.7.c). When the inhomogeneity intensity was changed, only for $I=0.01$, the minimum values were significantly higher.

**Discussion**

Our model of electrical cardioversion in an inhomogeneous active media reproduces the clinically observed features of the electrical cardioversion of atrial fibrillation. It demonstrates the characteristics of the immediate and of the delayed cardioversion as well as the features observed in clinical setting. We obtained:

- delayed termination,
- the probabilistic nature of cardioversion success,
- a dependence of the success rate on the amount of tissue damage,
- an increased cycle length after cardioversion.

The delay of the termination in our model resulted from the drift of the spiral wave between the cardioversion event and its collision with the boundary of the system which resulted in the termination. Delayed termination has previously been shown in a 3D system of the ventricular wall with scroll wave [10], where scroll wave filaments became unstable after cardioversion and collided with the boundary of the system. However, this model is inappropriate to explain the termination of spiral waves in the atria due to the small wall thickness of the atria and thus a very short filament (1-3 mm, much smaller than the wave size which is of the order of centimeters).

The probabilistic nature of cardioversion success can be explained by the stochastic nature of the spatial distribution of the inhomogeneity which forms anchoring sites. Because the trajectory of the drift is affected by the inhomogeneities in the system, its ultimate fate (either re-anchoring at a new site or a delayed termination) will also be of a stochastic nature. Since the spatial distribution of the electrical remodeling of the
atrial muscle appears to be random (there are no studies claiming otherwise so far), our stochastic approach for the modeling of the inhomogeneity in the system was the most reasonable approach we could use.

The dependence of the termination success rate on the amount of tissue damage is reflected in our results by the decrease in cardioversion success rate with an increase in the probability of inhomogeneity generation. (Fig. 5.b). The cardioversion success rate in our model depends on the amount of anchoring areas in the system (i.e. areas with a relatively homogeneous value of $\theta$). In cases, for which there are large areas capable of such anchoring, it is unlikely that the shifting of the position of the spiral wave tip will cause it to drift and terminate by colliding with the edge of the sample. This is also consistent with the clinical observation that cardioversion is more likely to be unsuccessful in patients with an extensive electrical remodeling of the atria due to an atrial fibrillation lasting many years [24].

A relation between fibrillation cycle length and cardioversion success rate (Fig. 6.b) is due to a dependency of the conduction properties on the parameter $\theta$. For higher values of $\theta$, the spiral wave core is larger and the conduction is slower (due to an increase in the inhibition of the $v$ variable; see Eq.3 and 4). The slower conduction results in an increase in of the cycle length. In addition, an increase in the spiral wave core increases the probability of a collision with the sample edge and termination (simply because the spiral wave tip moves further). Combined, those properties result in a positive correlation between the cycle length and the probability of a successful cardioversion. This relationship was recently observed in a clinical setting during the cardioversion of patients undergoing an ablation procedure [25]. In this study, it was shown that the patients who responded successfully to electrical cardioversion also exhibited a longer atrial fibrillation cycle length, suggesting that the cycle length may serve as an indicator of an immediate cardioversion success. However, this relationship was observed only for short term success (immediate success of the cardioversion) and is not extended to long term restoration of sinus rhythm, which remains not clear - as is reported in [26][27].

The increased cycle length after cardioversion in our model is caused by the inhomogeneity of parameter $\theta$. Areas of low $\theta$ and thus shorter cycle length acted as anchoring sites for spiral waves. In all successful cases, cardioversion caused spiral wave shift and drift due to the inhomogeneity of $\theta$. Since the drift was caused by a spatial change of $\theta$ and the drift occurred in the direction of large $\theta$, the spiral wave cycle also increased with increasing $\theta$. Unfortunately, due to technological difficulties, there is no research data available suggesting whether pinned reentry has shorter cycle length than unpinned one in live, atrial tissue. Further research is needed to address this issue. This effect is caused by the dependence of the spiral wave cycle length on the parameter $\theta$ (the cycle length increases with parameter $\theta$). Spiral waves unpinned from the areas of small $\theta$ ($\theta=\theta_{min}$) drifted toward areas a larger $\theta$ (at the left edge of the system), thus increasing their cycle length.

Simulations for varying values of the parameters: the radius of inhomogeneity $R$, inhomogeneity intensity $I$ and stimulation amplitude $A$ (Fig.6-7) showed similar
patterns: a decrease of the cardioversion success rate as a function of the probability of inhomogeneity generation and its positive correlation with the average cycle length before cardioversion. This similarity is to be expected due to the nature of the postulated mechanism of the termination of the spiral wave (detachment from the inhomogeneity, the drift and collision with the sample edge). With an increasing level of the inhomogeneity, the spiral wave drift towards the sample edge is less probable (due to a possibility of re-attachment) ultimately decreasing the probability of the termination. A positive correlation between the cardioversion success rate and the average cycle length is also expected to be independent of the model parameters – the spiral wave core will be always greater in areas with a higher \( \beta \) value (causing both an increase of the cycle length and a more probable termination) irrespectively of the specific distribution of the inhomogeneity (parameters \( R \) and \( I \)) and the stimulation amplitude.

An increase in the radius of the inhomogeneity (parameter \( R \)) caused a decrease of the cardioversion success rate (Fig.6.a) with the highest success rate for \( R=1.2 \). This is caused by a more probable detachment of the spiral wave from a smaller inhomogeneity. A similar drop was obtained when the inhomogeneity intensity was increased (Fig.6.b). For low intensities, the gradient of the parameter \( \beta \) is small and the attracting force pinning the spiral wave is therefore smaller. A spiral wave pinned by a small gradient of \( \beta \) can be more easily detached by global stimulation. Thus, the lower intensity of the inhomogeneity, the higher the probability of detachment. An increase in stimulation amplitude (parameter \( A \)) caused an increase in the cardioversion success rate. This is expected due to an increase of the shift of the spiral wave spatial position with an increasing \( A \). A larger shift of the position results in more probable detachment of the wave from the inhomogeneity.

We used the following simplifications in our model of cardioversion:

- FitzHugh-Nagumo model of the electrical activity of the heart tissue (which is very simplified with respect to the complex behavior of ionic channels),
- simplified geometry of the system (two dimensional flat rectangle),
- we investigated only the effect of the inhomogeneity of the tissue excitability as an example of one of the modes of the electrical remodeling of the heart muscle,
- the effect of the electrical cardioversion was introduced as a uniform change of the variable \( v \) across the whole system.

The essential features of the mechanism presented in this study comprise:

- pinning of the spiral wave to tissue inhomogeneity,
- unpinning of the wave by electric cardioversion,
- drift of the spiral wave,
- termination by collision with non-excitable area.

In order to assess whether our simplifications have an effect on the results obtained in this paper, we discuss them in the context of the mechanism features listed above.

Spiral wave drift caused by the tissue inhomogeneity was shown to be a generic property of excitable media [19][28]. In an inhomogeneous system, spiral wave
pining may be explained as the existence of the regions, to which the inhomogeneity induced drift leads spiral waves from all surrounding directions. Therefore, pinning and drift may take place also in more detailed models and for such other types of inhomogeneities which are able to induce a drift of the spiral wave. Unpinning of the wave by a global stimulus is caused by a shift of the spiral wave tip beyond the attracting region of the inhomogeneity. Both mono-phasic (as we used in this study) and bi-phasic stimuli causes such a shift of the spiral wave position (due to the excitation of the area in front of the wave [29]) which, if the shift is large enough, is the only requirement for the wave unpinning to occur. Termination of the spiral wave by collision with a non-excitable region is also a generic property of the excitable media not depending on the model details and on the geometry of the system. In summary, the mechanism presented in this study is based on the basic properties of excitable media and it is not related with specific kinetics of the model used, the type of inhomogeneity or on the properties of the cardioversion stimulus. In [11], the Authors performed a detailed comparison of the wave dynamics during the unpinning of a spiral wave at a non-conducting area caused by cardioversion using models with a different level of detail and found no significant qualitative difference in the results.

The applicability of the mechanism presented here in the context of the different types of atrial fibrillation mechanisms (the coexistence of multiple spiral waves [1], the stationary, high frequency spiral wave [2] and the existence of a focal sources of periodic activity [3]) depends on whether a pinned spiral wave exists in the system. The effect of the cardioversion on a focal sources of depolarization is beyond the scope of this work. In the case of the multiple wave hypothesis, in which atrial fibrillation is presented as a random propagation and collision of multiple wavelets, our mechanism probably is not applicable, since a shift of the wavelets spatial positions should not promote termination of the arrhythmia. However, electrophysiological studies indicated that there are critical locations in the atria responsible for maintenance of atrial fibrillation and of which ablation terminated an arrhythmia [30]. Numerous animal (e.g. [31][32]) and clinical (e.g. [33][34]) studies further identified and described stable, high-frequency sources as important elements of atrial fibrillation maintenance, “driving” rest of the atria. Such sources of high-frequency activity may be of ectopic or reentrant nature. In case such a “driver” of atrial fibrillation is of reentrant nature, our results may be applicable, since cardioversion could destabilize the reentry wave and induce its drift away from area able to sustain high frequency of rotation and promote its termination. In a case of the mother wavelet hypothesis (a macro reentrant wave anchored by a non-excitable area or tissue inhomogeneity) our mechanism could be also applicable. The detachment of the mother reentry wave and its termination by collision with a non-excitable area (as shown above) would explain the delayed termination of arrhythmia, and mother wave unpinning failure or re-attachment would correspond to cardioversion failure.

**Summary**

Our hypothesis about the mechanism of the delayed cardioversion can be generalized in the following concept: a healthy heart muscle has the ability to spontaneously terminate a spiral wave, unlike disease-remodeled heart muscle which lacks this
ability. Pathological areas of the heart muscle provide a substrate for the anchoring and persistent rotation of spiral waves. Electrical cardioversion may terminate all activity (immediate termination) or shift the centers of rotation of the spiral waves. When such a shift occurs, spiral tips may shift to other pathological pinning areas (unsuccessful termination), or may collide with an inexcitable area or shift to areas of healthy muscle, in which case they terminate (successful, delayed termination). This general concept leaves room for other mechanisms of self-termination than the one we proposed.

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Bibliography


Figure Legend

Fig. 1 Example of a spatial distributions of the parameter $\beta$ corresponding to the total current inhibition for a low probability ($p = 0.002$, $R = 8$, $I = 0.02$) (a) and a larger probability ($p = 0.015$, $R = 8$, $I = 0.02$) (b). The global gradient of $\beta$ (visible as a horizontal gradient in the shading of the background) causes a spiral wave to drift toward left edge of the system (not shown). However, areas with a low value of $\beta$ (dark gray patches) may stop this drift acting as anchoring sites for spiral wave (see text for details).

Fig. 2 Distribution of termination times obtained from 1000 simulations for $R=3.2$, $I=0.02, A=0.65$ and $p=0.02$. Most of the spiral waves terminated for time between 90 and 540. Consequently, the checking time for spiral wave stability was set to 600.

Fig. 3 Example of an unsuccessful cardioversion in a system with inhomogeneity generated for $p=0.02$, $R=8$, $I=0.02$, $A=0.65$. The position of the spiral wave tip is denoted by a star. Initially, the spiral wave was anchored in the area with a low and relatively homogeneous value of $\beta$: (a) After cardioversion (at $t=270$, see Part (c)) the tip of the wave drifted to the right and re-anchored. (b): The shift of position is marked by the arrow. (c): Action potential measured at the left upper corner of the system as a function of the time, with the potential change due to cardioversion marked by the vertical arrow.

Fig. 4 Example of a successful cardioversion in a system with inhomogeneity generated for $p=0.02$, $R=8$, $I=0.02$, $A=0.65$. The position of the spiral wave tip is denoted by a star. Initially, the spiral wave was anchored in a patchy area with a low value of $\beta$ (a). After cardioversion (for $t=250$, vertical arrow in (c)) the wave drifted toward the upper edge of the sample where it terminated (b). The shift of position is marked by the arrow. The termination occurred after 6 cycles after the cardioversion. The approximate trajectory of the wave tip is marked by the white dashed line. (c): Action potential measured at the left upper corner of the system as a function of the time, with the potential change due to cardioversion marked by the vertical arrow.

Fig. 5 Results of the simulations for base parameters: radius of the inhomogeneity $R=3.2$, intensity of the inhomogeneity $I=0.02$ and stimulation amplitude $A=0.65$. Number of cases resulting in anchored spiral waves and the number of successful termination cases as a function of the probability of inhomogeneity generation $p$ (a). Cardioversion success rate defined as the ratio of the number of cases with a successful termination to the number of cases with anchored spiral waves (b). Average cycle length measured before and after cardioversion for cases with a successful termination (c). Relation between cardioversion success rate and average cycle length (d). Linear regression resulted in $R^2=0.89$.

Fig. 6 Ratio of the successful cardioversions as a function of the probability of inhomogeneity generation $p$ for varying values of radius of the inhomogeneity $R$ (a), inhomogeneity intensity $I$ (c) and stimulation amplitude $A$ (b).
Fig. 7 A relation between cardioversion success rate and average cycle length for varying values of radius of the inhomogeneity $R$ (a-b) (results separated into two plots for clarity), stimulation amplitude $A$ (c) and inhomogeneity intensity $I$ (d). For each set data points corresponding with given parameter value, linear regression was performed with $R^2$ displayed at right side of the label.
Fig. 2

Distribution of termination times

cases number

termination time [a.u.]

Fig. 3

(a) $t=220$

(b) $t=450$

(c) $t$-cardioversion

18
Fig. 6
Fig. 7