Actions of an External Electrical Shock on Human Atrial Excitation – A Computer Model Study

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Abstract. Atrial fibrillation (AF) is one of the most common cardiac diseases that cause morbidity and mortality. One of the most frequently used clinical treatments of AF is to use a large and brief external electrical shock to reset atrial tissue from a disordered fibrillation state to a quiescent state, then the pacemaker of the heart resumes its control of atrial excitation rhythm and thus a defibrillation is achieved. Though widely used in practice, the mechanisms underlying the success of an electrical shock in defibrillation is incompletely understood. In this study, we developed a computer model of human atrial tissue to investigate the actions of an external electrical shock on atrial excitations. Using the model, we computed the defibrillation threshold of the human atrium. We found that due to the supernormal excitability of human atrium, the computed successful defibrillation threshold is much less than the excitation threshold of human atrium in resting state. This study provides some new insights to understand the mechanisms underlying AF defibrillation.

Keywords: External electrical stimulation, defibrillation threshold, bi-domain model of cardiac tissue, reentrant excitation.

1 Introduction

Atrial fibrillation (AF) is the most common cardiac diseases and can cause high risks of sudden cardiac death and disability (Nattel, 2002). Typically AF is characterised by spatio-temporal irregular excitation waves propagating at a high rate (300-500 /min). One of the most frequently used clinical treatments of AF is electrical cardioversion, which uses a brief (0.01-5 ms) and large (0.1-100 KV) external electrical shock to reset atrial tissue from disordered fibrillation to a quiescent state, and then the pacemaker of the heart can resume its control over the rhythm of atrial excitations. This technique is widely used in clinical practice and has dramatically saved the lives of patients with life-threatening cardiac arrhythmias including AF. However, its practical uses are limited by the lack of understanding the underlying mechanisms. A better understanding of these mechanisms will help to refine the design of defibrillation electrodes and the characteristics of stimulation pulse, and to improve the efficiency of defibrillation.

V.G. Duffy (Ed.): Digital Human Modeling, HCII 2007, LNCS 4561, pp. 659–667, 2007.

In this study, we developed a biophysically detailed bi-domain computer model of electrical activity of human atrial tissue. The model considered spatial effects of an external electrical field on a single cell (Biktashev et al., 1997; Zhang & Holden, 2004). Using the model, we studied the excitability and the activation of the atrial tissue by an external stimulation pulse. We found that the human atrial tissue has a feature of supernormal excitability. As a consequence the successful defibrillation threshold was much less than that of human atrial excitation threshold at a resting state and is also less than that predicted by the "upper limit of vulnerability" defibrillation theory (Pumir and Krinsky; 1996; Krinsky and Pumir, 1998).

2 Bi-domain Model of Electrical Activity of Human Atrial Myocytes

In this study, we used the Nygren et al. (1998) model to simulate the electrical action potential (AP) of human atrial myocytes. This is a biophysically detailed model, which was constructed based on a series of voltage clamp experiments on the kinetics of ionic channel of human atrial myocytes. We modified the model to incorporate the actions of an external electrical field, subjected to which a cardiac cell should be taken as a spatially extended object and modelled by a bi-domain model (Biktashev et al., 1997; Zhang & Holden, 2004). In general the modified model takes the form as Equation (1) to Equation (6).

Equation (1) describes the time-dependent rate of membrane potential V(t) of an atrial cell with a total cell membrane capacitance C_m. In the equation, i_j (V,t) is the j_{th} membrane ionic current, $P_j(C_i^m, C_i^n, C_o^m, C_o^n)$ the j_{th} pump/exchanger current, and C_i^m, C_o^m internal and external concentrations of the m_{th} ionic species as described by Nygren et al. (1998). *E* is the external field magnitude, s the index of spatial position of a membrane site with respect to the external field. Equations (3)-(5) specify the general form of voltage and time dependent membrane ionic channel currents.

$$\frac{dv}{dt} = -\frac{1}{C_m}\int\left(\sum_j i_j^s(V^s,t) + \sum_j P_j^s(C_i^m(s), C_i^n(s), C_o^m(s), C_o^n(s), V^s)K(s)sds \right. \tag{1}$$

$$V^s = V + sE(t) \tag{2}$$

$$i_j^s(V^s,t) = (V^s - E_j)G_j^{\max} m_j^{p_j}(V^s)h_j^{q_j} \tag{3}$$

$$\frac{dm_j}{dt} = \alpha_j^m(V^s)(1 - m_j(V^s)) - \beta_j^m m_j(V^s) \tag{4}$$

$$\frac{dh_j}{dt} = \alpha_j^h(V^s)(1 - h_j(V^s)) - \beta_j^h h_j(V^s) \tag{5}$$

$$\frac{dC_i^j(s)}{dt} = -\frac{\sum_j i_j^{iont}(V^s)}{z_j F V_i} \tag{6}$$

K(s) is the spatial dependent weighting function, for which we have Equation (7) as following.

$$\int_s K(s)ds = 1 \tag{7}$$

Equations (1)-(7) can be simplified by using a two-compartment approximation of the integral $\int$ operator following the approaches developed by Biktashev et al. (1997) and Zhang & Holden (2004). Under the action of an external electrical field, a cardiac cell is nearly iso-potential, but it is depolarised in one part, and hyperpolarised in the other part, both by the same amplitude of external stimulation current i_{ext}. These two iso-potential parts are coupled through the intracellular resistance. If we denote the depolarised part by +, and the hyperpolarised part by -, the intracellular conductance by α, then equation (1)-(7) becomes equation (8) -(16).

$$\frac{dV}{dt} = -\frac{1}{2C_m} i_{tot} \tag{8}$$

$$i_j^+(V^+) = (V^+ - E_j)G_j^{\max} m_j^+(V^+)^{p_j} h_j^+(V^+)^{q_j} \tag{9}$$

$$\frac{dm_j^+}{dt} = \alpha_j^m(V^+)(1-m_j^+) - \beta_j^m(V^+)m_j^+ \tag{10}$$

$$\frac{dh_j^+}{dt} = \alpha_j^h(V^+)(1-h_j^+) - \beta_j^m(V^+)h_j^+ \tag{11}$$

$$i_j^-(V^-) = (V^- - E_j)G_j^{\max} m_j^-(V^-)^{p_j} h_j^-(V^-)^{q_j} \tag{12}$$

$$\frac{dm_j^-}{dt} = \alpha_j^m(V^-)(1-m_j^-) - \beta_j^m(V^-)m_j^- \tag{13}$$

$$\frac{dh_j^-}{dt} = \alpha_j^h(V^-)(1-h_j^-) - \beta_j^m(V^-)h_j^- \tag{14}$$

$$\frac{dC_i^+}{dt} = -\sum_j i_j^{tot^+}(V^+)/(z_j F V_i) \tag{15}$$

$$\frac{dC_i^-}{dt} = -\sum_j i_j^{tot^-}(V^-)/(z_j F V_i) \tag{16}$$

where

$$i_{tot} = \sum_j (i_j^+(V^+) + i_j^-(V^-)) + \sum_j (p_j(C_i^{m^+}, C_i^{n^+}, C_o^{m^+}, C_o^{n^+}) + p_j(C_i^{m^+}, C_i^{n^+}, C_o^{m^+}, C_o^{n^+})) \quad (17)$$

$$V^+ = V + \frac{1}{2\alpha} i_{ext} \quad (18)$$

$$V^- = V - \frac{1}{2\alpha} i_{ext} \quad (19)$$

3 Multi-cellular Model of Human Atrial Tissue

A bi-domain model of human atrial tissue is given by a parabolic partial differential equation (PDE) of reaction diffusion type based on the modified Nygren et al. equations, which takes the form as equation (20).

$$\frac{dV}{dt} = \frac{1}{C_m}(-i_{tot} + D\Delta V) \quad (20)$$

D is the diffusion coefficient modelling the extracellular conductance. D is different from the intracellular conductance α. D scales the conduction velocity of a solitary travelling wave solution. Δ is a Laplacian operator. x and y represents spatial coordinates in two dimensions (in *mm*). In the model, the diffusion coefficient D was set to 0.3125cm^2 s^{-1} that gave a plane wave velocity of 32 cm s^{-1}. To solve the equation, we used the explicit Euler method with a 3-node approximation of Laplacian operator for 1D, and 5-node approximation of Laplacian operator for 2D. In numerical simulations, the time step Δt is set to 0.001 ms, and space step ($\Delta x = \Delta y$) is 0.32*mm*. The space step of 0.32 mm is about 1/3 of the space constant of the model and corresponds to the long axis of about 4 cells (the length of a cardiac cell is about 0.08mm). It is sufficiently small for stability of the numerical solution. External electrical stimulation is modelled by a square pulse i_{ext} with a variable magnitude and constant duration of 2 ms. The intracellular conductance α was set to 10 S.

4 Results

4.1 Measuring Excitability of Cardiac Tissue

The excitability of human atria was computed from a 1D bi-domain model of human atrial strand (with a zero-flux boundary condition). The strand is 96 mm in length and discretised by 300 nodes. To measure the excitability of the tissue, the standard S1-S2 stimulus protocol was used. Firstly, a sequence of 5 supra-threshold S1 stimuli was applied to the node-1 of the strand. Each of the stimulus pulse had an amplitude 135 nA and duration 6 ms. The time interval between two successive stimuli is 450 ms, which is large enough for the tissue to recover from its previous excitation before a

new stimulation was delivered. Each of the 5 stimuli evoked an excitation wave propagating from node-1 to node-300. After the 5th stimulus, a test S2 stimulus was delivered to node-100, a time delay δt after the wavefront of the 5th excitation arrived this point (the time defined as dV/dt of the node reaching its maximal value). The test stimulus has a fixed duration 6 ms, but a changeable magnitude of i_{ext}. The excitability of cardiac tissue was determined as the minimal strength of the test stimulus that re-excites the node-100 at a time interval δt after its depolarisation and produces an action potential with an overshoot over -20 mV. Depending on the time interval δt, the S2-evoked excitation can either propagates bi-directionally if δt is sufficiently large such that atrial tissue has recovered its excitability from previous excitation (Figure 1A), or propagates uni-directionally if δt is small such that the excitability of atrial tissue is recovered only in the retrograde direction of previous excitation (Figure 1B), or fails to propagate at all if δt is too small such that the atrial tissue has not yet recovered its excitability from previous excitation (Figure 1C).

The measured excitability of the atrial strand is δt -dependent as shown in Figure 1D. In the figure, the measured minimal stimulus strength is plotted against the time interval δt. With decrease of δt, it is expected that the excitation threshold increases as more energy is required to re-excite less recovered tissue in normal excitable cardiac tissue. However, in the human atrial model, decrease in δt reduces, rather than increases, the excitation threshold when δt is in the range of 220-450 ms. Around δt =220 ms, the tissue reaches a maximal excitability. The excitability of the tissue during the course of repolarisation or immediately after action potential repolarisation is greater than the excitability of the tissue in resting state. This is a typical feature of excitable tissue with supernormal refractory period (Boyett and Fedida, 1984).

In figure 1D, the δt-dependent dynamical behaviour of the S2 evoked excitation wave was also plotted. With decrease of δt, the S2-evoked excitation wave changed from bi-directional conduction (•) to unidirectional conduction (Δ) and then failed to propagate at all (□). The time window during which the S2-evoked excitation wave propagates uni-directionally (the time window marked by Δ) indexes the vulnerable window of the tissue (Starmer at al., 1993; Zhang & Holden, 1997).

4.2 Defibrillation Threshold

Defibrillation threshold can be estimated from the strength-interval curve shown in the figure 1D. According to the theory of "upper limit of vulnerability" (Pumir and Krinsky; 1996; Krinsky and Pumir, 1998), for a successful defibrillation, it is necessary to apply a stimulus pulse large enough to re-excite the part of tissue in its refractory period and the evoked excitation can propagates uni-directionally only in the retrograde direction, not in the anterograde direction of its previous excitation wave. The re-excitation wavefront annihilates with the previous excitation wavefront when they meet leading the tissue quiescent. According to this theory, the minimal strength of an external stimulation for a successful defibrillation should reaches at least the level indicated by the □ in the figure 1D, which is about 155 nA.

4.3 Defibrillation Simulation in a 1D Model of Atrial Strand

Numerical simulations of actions of an external electrical stimulus on the excitation wave of human atria were carried out with a 1D bi-domain model of a ring fibre with circumference of 96 mm. The re-entrant excitation wave was initiated on the strand by a supra-threshold stimulus. After 5 rotations of excitation waves when a steady stable re-entrant excitation was established, a uniform electrical stimulus was applied to the ring strand. The stimulus was with a changeable amplitude i_{ext}, but a fixed duration of 6 ms.

Actions of an external stimulation pulse on re-entrant excitation are shown in Figure 2. In the figure, the propagating action potentials are represented horizontally in space, vertically in time. The time runs from present at the front to the future at the back with a time interval of 10 ms. Stimulation time is indicated by the arrow.

Panel (A) shows the action of an external stimulation pulse with i_{ext}=90 nA. This stimulus is well below the excitation threshold of the tissue in its resting state (110 nA) and the most excitable tissue in its refractory period. This stimulus failed to produce re-excitation in the tissue, and has no effect on the on-going excitation wave. Panel (B) shows the action of an external stimulus with i_{ext}= 102 nA. This stimulus is smaller than the excitation threshold of the tissue in its resting state (110 nA), but is larger than the excitation threshold of the tissue in its most excitable refractory window (101 nA). When this stimulus was applied, most of the ring was not affected, but there were two parts, indexed by P1 and P2, responded. In the part of P1, a pair of excitation waves were generated which propagated in both the retrograde and the anterograde directions of the previous excitation wave. The wave propagating in the retrograde direction annihilated with the wavefront of the previous excitation. The wave propagating in the anterograde direction collides with the wave evoked in the part P2, which propagated only in the retrograde direction. As a result, existing excitation wave dies and a successful defibrillation is achieved. Panel (C) shows the action of an external stimulus with a strength i_{ext}=160 nA. This stimulus is above the defibrillation threshold predicted by the defibrillation theory. This stimulus re-excited most of the tissue and the evoked excitation wavefront did not expand, but shrunk leading to a successful defibrillation. Due to the supernormal excitability of human virtual atria tissue, the successful defibrillation threshold (102 nA) is smaller than the excitation threshold of the tissue in resting state (110 nA) and remarkably less than that predicted by the defibrillation theory (155 nA) of “upper limit of vulnerability” (Pumir and Krinsky; 1996; Krinsky and Pumir, 1998).

4.4 Defibrillation Simulation in a 2D Model of Human Atrial Tissue

In 2D simulations, an external stimulus with a strength of i_{ext}=102 nA (duration of 6 ms) also successfully defibrillated a re-entrant excitation. This is shown in figure 3. In the figure the snapshots of the re-entrant activity before and after application of the pulse stimulation are displayed. Figure 3(A) shows the snapshot 5 ms just before stimulation, figure 3(B) shows the snapshot 10 ms after the stimulation, and figure 3(C) shows the snapshot 100 ms after the stimulation. In figure 3(B), the subthreshold external stimulation generated non-propagating excitation in the parts of tissue in its

refractory period. The non-propagating excitation formed a conduction block to the wavefront of the existing re-entrant excitation, which leads it to termination of re-entrant activity as shown in figure 3(C).

5 Conclusions

In this study we have developed a bi-domain model of human atrial electrical activity based on modification of the Nygren et al. (1998) model to include the actions of an external electrical filed, subjected to which cell membrane potential shows spatial gradient distribution. Using the model, we have quantified the rate-dependent excitability and investigated the effects of a large and rapid external electrical stimulus pulse on human atrial excitation. The significance of this study is that due to the supernormal excitability of human atrial tissue, the successful defibrillation threshold is remarkably lower than the excitation threshold of atrial tissue in a resting state and is also less than that estimated by the "upper limit of vulnerability" theory of defibrillation (Pumir and Krinsky; 1996; Krinsky and Pumir, 1998). This provides new insights to understand the mechanisms underlying the defibrillation by a short and rapid electrical shock.

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Appendix

Figure legends

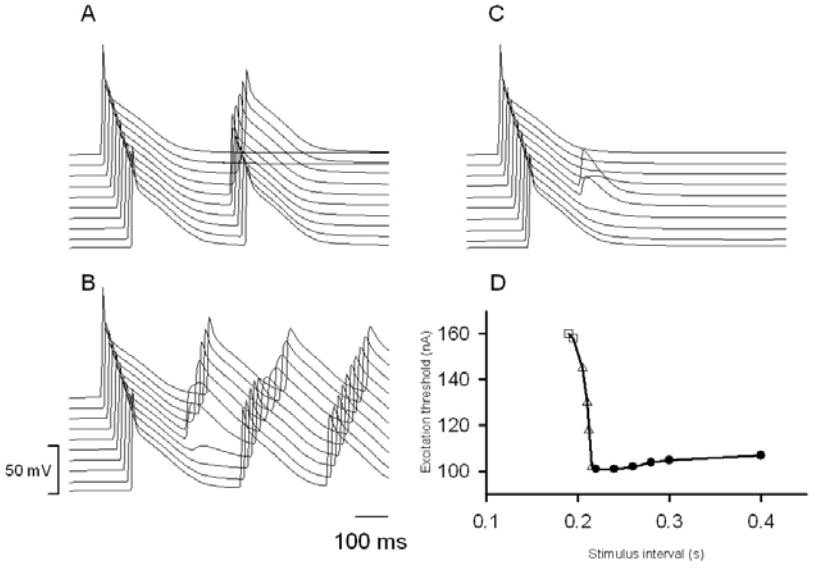

Fig. 1. Time interval (t)-dependent dynamical behaviours of excitation wave evoked by S2 stimulus and the estimated excitation threshold (nA) of human atrial tissue. (A) The re-excitation propagates in both retro- and anterograde directions of a condition wave. (B) The re-excitation propagates only in the retrograde direction of a condition wave. (C) The re-excitation fails to propagate. (D) The estimated excitation threshold against □t, superimposed with the dynamical behaviours of re-excitation (bi-directional conduction: •; unidirectional conduction: Δ; non-propagation: □). Supernormal excitability is illustrated by the biphasic relationship between the excitation threshold and the time interval.

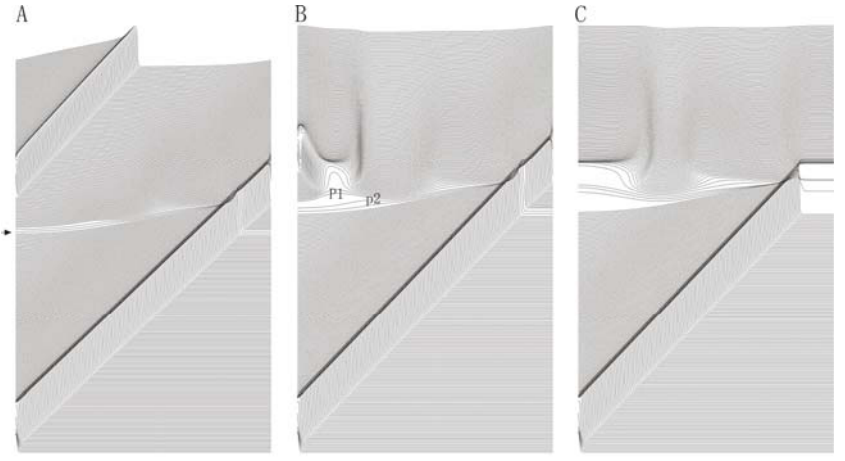

Fig. 2. Actions of an external stimulus on the re-entrant excitation wave in 1D ring fibres. The external stimulus is with different stimulus strengths and a fixed duration (6 ms). Due to the supernormal excitability, the successful defibrillation threshold is much less than that of the normal excitation threshold and that predicted by the defibrillation theory. (A) i_{ext}=90 nA, an unsuccessful defibrillation; (B) i_{ext}=102 nA, a successful defibrillation with an external stimulus strength much less than that predicted by defibrillation theory. (C) i_{ext}=160 nA. A successful defibrillation with an external stimulus strength over the value predicted by defibrillation theory of upper limit of vulnerability.

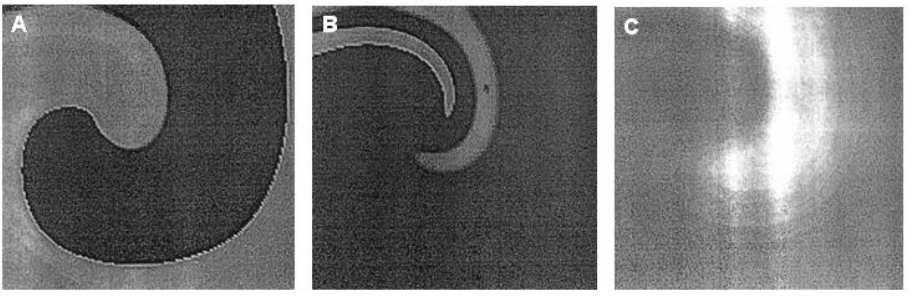

Fig. 3. Defibrillation in a 2D model of human atrium with i_{ext}=102 nA (duration of 6 ms). The part of the tissue with the greatest excitability responds. The evoked excitation propagated in the retrograde direction and collides with the existing reentry wavefront leading to a successful defibrillation. The stimulation strength is 102 nA, which is less than that of a resting tissue and the value predicted by the defibrillation theory of upper limit of vulnerability.