Investigation of Low-Voltage Defibrillation by Standing Waves in Human Ventricular Tissue Models

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Abstract

Ventricular fibrillation (VF) is one of the main causes of sudden cardiac death. Strong electric shocks remain the only reliable mechanism for successful termination of VF, but often lead to post-injuries. This study aims to explore whether low-voltage shocks at certain frequencies could result in successful defibrillation of human ventricular tissue. 1D and 2D ventricular tissue models were based on the Ten Tusscher et al. myocyte model combined with an extended version of the bidomain model with an external bath, to which the electric shocks were delivered. Sinusoidal low-voltage (10-50 Hz, 20-40 V) shocks were applied at opposite sides of 1D tissue strands and 2D square tissues of variable sizes; in 2D models, VF was induced in form of a single re-entrant wave. In 1D models, standing waves were observed at all frequencies in short ventricular strands (1-2 cm, comparable to the transmural distance in the human ventricles), but not in long strands (5-10 cm). Accordingly, in 2D tissue models of 5-10 cm^2, standing waves failed to form and terminate re-entry; otherwise, electrical waves originating from the shock application sites led to the generation of additional re-entries. In summary, the formation of standing waves due to periodic low-voltage stimulation of human ventricular tissue can lead to defibrillation of transmural re-entrant waves, but not of rotors on the ventricular surface.

1. Introduction

Ventricular fibrillation halts synchronized electrical activation and mechanical contraction of the heart, which can result in the loss of cardiac output and sudden cardiac death [1]. The underlying irregular, self-sustained activity during VF is believed to be produced by propagation of re-entrant waves. The only reliable therapy to prevent such lethal disturbances of cardiac rhythm is defibrillation [2], the delivery of a strong electric shock to the heart, particularly with the implantable cardioverter defibrillator (ICD). However, the strong shocks required for effective defibrillation can have serious adverse effects, including electroporation, various alterations of electrical properties of cardiac tissue and post-shock arrhythmias, as well as psychological effects on patients [3-6].

The adverse effects could be diminished if arrhythmia could be terminated reliably by defibrillation shocks with significantly lower energies. However, low-voltage defibrillation is intrinsically limited due to the fact that changes of the membrane potential in cardiac cells decay exponentially with distance from the electrode, with a space constant of about 1 mm. Attempts to overcome the space constant restriction has been based on the generation of spatially extended "virtual electrodes" arising during defibrillation near tissue heterogeneities [3, 7]. However, such a mechanism of defibrillation is highly dependent on the spatial location of the virtual electrodes that need to coincide with the location of re-entrant waves for this defibrillation method to be effective.

Another mechanism for defibrillation has been proposed based on a combination of animal experiments and computational modelling [8]. Experiments with ex-vivo rabbit hearts showed that stimulation with low-voltage periodic pulses (20-30 V, 5-20 Hz) applied in the bathing solution can result in steady periodic voltage patterns on the heart's epicardial surface – standing waves. Such waves terminated all propagating activity in the cardiac tissue, including re-entry and fibrillation. Mono- or bidomain models of cardiac tissue failed to reproduce these experimental observations, due to the space constant restriction. Extending the bidomain model [9] to account for the existence of a surrounding bathing solution enabled simulation of the standing waves in 1D and 2D tissues [8,9]. Standing waves induced by low-voltage stimulation applied in the bath eliminated re-entry in 2D bidomain ventricular tissues, thus providing a defibrillating effect.

However, such defibrillation was only effective for relatively small rabbit and canine tissues, and it remains unclear if defibrillation via standing waves is possible in the human heart. In this study, we explore a possibility of low-voltage defibrillation by standing waves of variable frequency in human ventricular tissue models.

2. Methods

We use the bidomain model to investigate electrical patterns in variable-sized 1D and 2D human ventricular tissues in response to low-voltage periodic stimulation. To reproduce the standing waves observed experimentally [8], the bidomain equations have been modified to introduce a high-resistive bath as described previously [8,9]. The ionic current in the model was described by the well-known Ten Tusscher *et al*. model [10] for a single ventricular myocyte. Apart from the ionic model, the mathematical formulation and numerical scheme were similar to previous work [9].

Sinusoidal low-voltage (10-50 Hz, 20-40 V) shocks were applied at opposite sides of 1D human ventricular tissue strands and 2D square tissues of variable sizes. In the 2D models, arrhythmic was induced in form of a single re-entrant wave using the standard cross-field protocol.

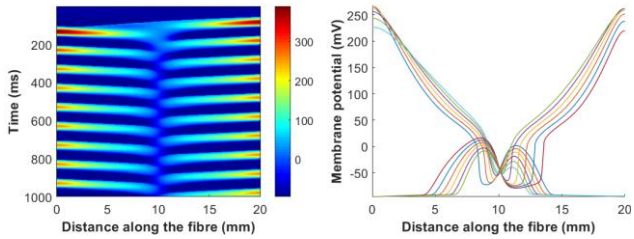

Figure 1. Membrane voltage dynamics in a short 1D human ventricular strand during low-voltage stimulation at 10 Hz, 40 V. Space-time plot (left) and several successive spatial profiles (right) of the membrane potential are shown.

3. Results

Fig. 1 shows results of periodic stimulation of a 20 mm long 1D ventricular tissue strand, with the shocks applied to the external bath. Standing wave patterns emerged for physiologically relevant values of the tissue resistivities [9]. There was no wave propagation in this case, and the standing waves were due to full entrainment of large tissue areas by the external voltage (10 Hz, 40V) applied to the bath at the left and right boundaries. Importantly, the external voltage did not decay away from the boundaries with a classical space constant of 1 mm - instead, the pattern was determined by the second space constant of 20 mm, which emerged due to the presence of the bath [9].

When the length of the 1D tissue strand was increased, only boundary regions of the tissue near the stimulation sites were entrained (Fig. 2). Moreover, in the longest 60 mm stands, local excitations near the boundaries resulted in the generation of action potentials propagating towards centre of the strand (Fig. 2, top); spatial profiles of the membrane voltage clearly showed propagating waves and the lack of a clear node characteristic of standing waves. A mixture of standing and propagating waves was observed in medium-size strands of 40 mm (Fig. 2, bottom). Thus, in these cases, even the longer 20 mm space constant was insufficient for the shocks to entrain the entire tissue.

In 2D human ventricular tissue models of 5-10 cm^2, standing waves failed to form and terminate re-entry at all frequencies (Fig. 3-4). In fact, in some cases electrical waves originating from the shock application sites led to the generation of additional re-entries (Fig. 4), facilitating further development of a fibrillation-like state.

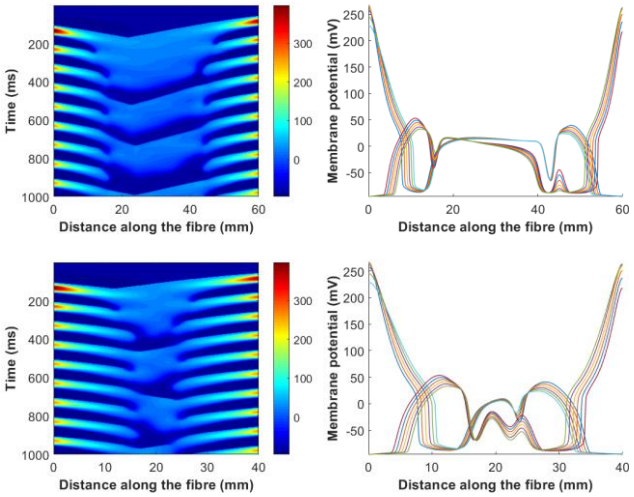

Figure 2. Membrane voltage dynamics in long (top) and medium (bottom) 1D human ventricular stands during low-voltage stimulation at 10 Hz, 40V. Space-time plots (left) and spatial profiles (right) of the voltage are shown. Wave propagating is seen in the middle of the long strands.

4. Discussion

In this study, we used the bidomain model with a bath to investigate electrical patterns arising in variable-sized ventricular tissues in response to low-voltage periodic (10-50 Hz, 20-40 V) stimulation. The model simulations showed that areas 20 mm away from the electrodes can be entrained to form standing waves, which can be sufficient to terminate transmural re-entrant waves within the ventricular walls of 10-20 mm thickness. These results are consistent with previous experimental and modelling studies of smaller animal hearts [8,9]. However, such entrainment is insufficient to terminate surface re-entrant waves in large human ventricular tissues, with dimensions over 20 mm. This can be explained by the existence of two space constants in the bidomain model with a bath, one of 1 mm and another of about 20 mm [9]. The low-voltage stimulation approach could potentially be applied in the atria [11] that have smaller size and wall thickness [12].

The bidomain model also predicts periodic patterns induced by virtual electrodes on epicardial surfaces of the heart, in cases when the cardiac and electrode geometries are such that current enters the epicardium in one region and leaves it in another region [7,13]. Such "surface virtual electrode" patterns can create the appearance of standing waves during cardiac tissue stimulation with the same settings as in the current study. Further studies will be required to explore linked between different bidomain effects arising during low-voltage stimulation and to apply this knowledge to design efficient defibrillation strategies.

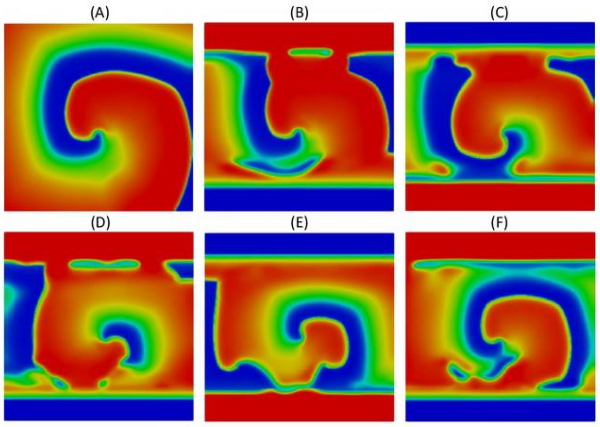

Figure 3. Unsuccessful defibrillation of re-entry in 2D human ventricular tissue (6 x 6 cm^2) during periodic low-voltage stimulation at 20 Hz, 20 V. (A)-(E): 2D voltage distributions are shown for the successive moments.

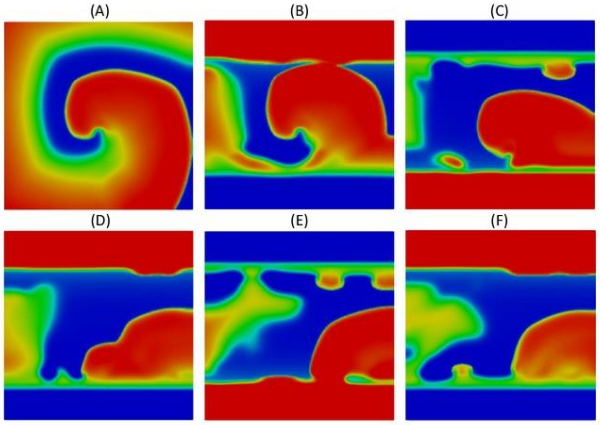

Figure 4. Unsuccessful defibrillation of re-entry in 2D human ventricular tissue (6 x 6 cm^2) during periodic low-voltage stimulation at 10 Hz, 20 V. Wave break-up and the generation of multiple smaller re-entries can be seen.

Acknowledgments

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