CREATIVE CONCEPTS

Decreased repolarization reserve increases defibrillation threshold by favoring early afterdepolarizations in an *in silico* model of human ventricular tissue

Nele Vandersickel, PhD,[*] Ivan V. Kazbanov, MS,[*] Arne Defauw, PhD,[*] Daniël A. Pijnappels, PhD,[†] Alexander V. Panfilov, PhD[*‡]

From the [*]Department of Physics and Astronomy, Ghent University, Ghent, Belgium, [†]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands, and [‡]Laboratory of Mathematical Modeling in Physiology and Medicine, Ural Federal University, Ekaterinburg, Russia.

Introduction

Sudden cardiac death due to ventricular fibrillation is the largest cause of death in the industrialized world.[1] The most effective way for terminating ventricular fibrillation is electrical defibrillation, which is the application of a strong electrical shock to the heart via a set of electrodes placed on the body surface or directly in the heart itself (implantable devices). Because such a shock is painful and can damage the tissue, it is of paramount importance to understand the factors determining the defibrillation threshold (DFT) and how these factors relate to the underlying type of arrhythmia and the affected cardiac tissue. Therefore, several experimental, theoretical, and clinical investigations have been performed to determine DFT.[2]

One of the important findings was that defibrillation can fail in some cases, and DFT is increased substantially.[3] However, the mechanisms of defibrillation failure and success are still poorly understood. The principal difficulty, as shown in experiments and confirmed by classic cable theory, is that the changes in transmembrane potential, induced by an electric field, decay exponentially with increasing distance from the electrodes.[4] These surface polarizations, occurring near the electrodes, create areas of hyperpolarization and depolarization. A typical example is the famous dog-bone configuration when point sources are applied.[5–7] However, during defibrillation, tissue far from the electrodes also becomes excited. Several mechanisms have been proposed for this "far-field" stimulation, which can be due to large-scale or small scale effects.[8] The large-scale effects are caused by some kind of heterogeneity in the tissue architecture.[4,9–11] These heterogeneities can be due to larger-scale nonuniformities, such as fiber orientation,[12,13] or other obstructions, such as fibrosis, blood vessels, branching structures, or other structural inhomogeneities.[14–16] The small-scale effects can be caused by microheterogeneities at the cell level; they also can cause far-field tissue excitations.[8,14,17,18] Some modeling studies have shown that DFT decreases with decreasing complexity of the wave pattern.[8,19]

There are several mechanisms by which cardiac arrhythmias are maintained.[20] One important class is arrhythmias, which are maintained by the appearance of early afterdepolarizations (EADs). EADs occur in a single cell when the RR is reduced to such an extent that reversal of the normal repolarization of the action potential can occur (eg, by reactivating the L-type Ca channel).[21] EADs are likely to occur because of genetic defects such as the long QT syndrome[22] or as a result of drug-induced cardiotoxicity.[23] However, they also are found in patients with other conditions, e.g. with increased Na/Ca exchanger activity as seen in cardiac hypertrophy and heart failure.[24,25] At the tissue level, EADs seem to play an important role in the life-threatening arrhythmia torsades de pointes (TdP).[26,27] However, TdP remains incompletely understood. Only recently have *in silico* studies started to explore arrhythmias that can occur as a result of EADs.[21,28–30]

In a recent *in silico* study by our group, we classified different types of fibrillation due to EADs in 2-dimensional (2D) tissue slabs.[30] Our simulations showed that by gradually decreasing the RR in 2D tissue (by increasing the conductance of the L-type Ca current and decreasing the conductance of I_{Kr}), arrhythmias that are maintained by the existence of EADs at the single cell level are possible.[30] By gradually decreasing the RR, we characterized 3 different types of such arrhythmias. First, we found a fibrillatory pattern, namely, spiral fibrillation type b (SFb), which is characterized by the coexistence of Na-mediated waves with Ca-mediated waves (biexcitability).[31] In this pattern we very often observed only short-living rotors,

KEYWORDS Early afterdepolarization; Ventricular fibrillation; Defibrillation threshold; *In silico*

ABBREVIATIONS 2D = 2-dimensional; **DFT** = defibrillation threshold; **EAD** = early afterdepolarization; **SFa** = spiral fibrillation type a; **SFb** = spiral fibrillation type b; **SR** = sarcoplasmic reticulum; **TdP** = torsades de pointes (Heart Rhythm 2015;0:1–9)

Dr. Vandersickel and Ivan Kazbanov are supported by the Research Foundation-Flanders. **Address reprint requests and correspondence:** Dr. Nele Vandersickel, Department of Physics and Astronomy, Krijgslaan 281, S9, 9000 Gent, Belgium. E-mail address: Nele.Vandersickel@ugent.be.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2015.01.033

and this pattern has a very chaotic nature.[30] Second, reducing the RR further, we found a second fibrillatory pattern, called spiral fibrillation type a (SFa). There, we clearly observed spiral waves; however, they are purely maintained by Ca-mediated waves, whereas no Na current was present anymore. This was in contrast to spiral patterns induced in simulations by altered properties of the restitution curve with standard parameters, which were always maintained by the Na current.[32,33] Finally, reducing the RR to such an extent that the single cells in the 2D tissue no longer repolarize to their resting state, we found that in 2D tissue this manifests itself as an oscillatory fibrillation type that consists out of phase waves.

Arrhythmias caused by a reduced RR might react differently to electroshock therapy in terminating fibrillatory activity in the heart. Indeed, as the tissue is depolarized simultaneously, one might expect difficulties in repolarization because of the appearance of EADs. Therefore, the aim of this study was to determine whether and how this reduction of RR may affect DFT. We performed an extensive and systematic study to determine DFT for a wide range of parameters. In addition, we investigated the effect of blocking certain currents right after the shock.

Methods

Bidomain and monodomain computer modeling

For our defibrillation study, we chose to follow a protocol similar to that reported by Plank et al.[8] The defibrillation simulations were performed using the bidomain model,[34–36] which is widely used for simulation of electric activity in cardiac tissue. It is an extension of the monodomain model, which is mostly used for simulation of the electrical heart. It has been shown that during normal activity of the heart, the monodomain equations and bidomain equations differ only slightly.[37] However, a bidomain model is necessary to study defibrillation-related phenomena.

The bidomain equations consist of a parabolic and an elliptic equation[38]:

$$\frac{\partial V_m}{\partial t}=\frac{-I_{ion}+I_{stim}-G(V_m,t)}{C_m}+\frac{1}{C_m\beta}(\nabla(\sigma_i\nabla V_m)+\nabla(\sigma_i\nabla\phi_e))$$
$$\nabla(\sigma_i+\sigma_e)\nabla\phi_e+\nabla(\sigma_i\nabla V_m)=0 \quad \nabla(\sigma_b)\nabla\phi_e=-I_e \tag{1}$$

where V_m is the transmembrane potential, and ϕ_e is the extracellular potential. The relationship between V_m and ϕ_e is given by $V_m=\phi_i-\phi_e$, where ϕ_i is the intracellular potential. C_m is the cell capacitance per unit surface area, and β is the surface-to-volume ratio. We took $\beta\times C_m=1\frac{\mu F}{mm}$.[37] I_{ion} is the sum of the following ionic currents:

$$I_{ion}=I_{\mathrm{Na}}+I_{\mathrm{K1}}+I_{\mathrm{to}}+I_{\mathrm{Kr}}+I_{\mathrm{ks}}+I_{\mathrm{CaL}}+I_{\mathrm{NaCa}}+I_{\mathrm{NaK}}+I_{\mathrm{pCa}}+I_{\mathrm{pK}}+I_{\mathrm{bCa}}+I_{\mathrm{bNa}}, \tag{2}$$

where I_{stim} is an externally applied stimulus for initiating a wave. The dynamics of these ionic currents are taken from the TNNP-TP06 mathematical model for human ventricular tissue.[39,40] G represents the electroporation function,[22] and σ_i and σ_e are the intracellular and the extracellular conductivity tensors. The following values are taken[18]:

$$\sigma_{iT}=0.03\frac{S}{m}$$
$$\sigma_{iL}=0.03\frac{S}{m}$$
$$\sigma_{eT}=0.12\frac{S}{m}$$
$$\sigma_{eL}=0.30\frac{S}{m} \tag{3}$$

We set the intracellular conductivities to randomly fluctuate in the following fashion[8]:

$$\sigma_i=\overline{\sigma}_i(1+F\eta), \tag{4}$$

where F is fixed to 0.5, and $\eta\in[-1,1]$ and the average values are given by Equation (3). The tissue is surrounded by a conductive bath of $\sigma_b=1S/m$ from where we apply an external shock with strength I_e.[8]

We solved these bidomain equations with the operator splitting method. First, we solved the parabolic Equation (1) with the explicit Euler integration scheme. From this equation, V_m^{next} can be found. We used a time step of 0.02 ms and a space step of 0.25 mm in both x and y directions. Second, this value was used to compute ϕ_e^{next} by solving this equation with a forward Euler scheme:

$$\nabla[(\sigma_i+\sigma_e)\nabla\phi_e]+\nabla(\sigma_i\nabla V_m)=\frac{\partial\phi_e}{\partial t}, \tag{5}$$

until we reached convergence,

$$\frac{\sum_{i,j}\left|\phi_{e,ij}^{t}-\phi_{e,ij}^{t+\delta t}\right|}{\tau}<tolerance\times\left(\sum_{i,j}\left|\nabla(\sigma_i\nabla V_m)\right|\right), \tag{6}$$

where i and j represent the grid coordinates. We took a tolerance of 10^{-6} [41] and a time step of 0.01 ms. As boundary conditions, we used Neumann boundary conditions. At the tissue bath interface, continuity of normal component of the extracellular current and continuity of the extracellular potentials were enforced.

When no electrical shocks are applied, monodomain and bidomain descriptions yield very similar results[37]; therefore, we used a monodomain description for creating the EAD patterns. Of note, 10 ms before the start of a shock, we switched to the bidomain description, and 10 ms after the end of the shock, we switched back to the monodomain model. The monodomain description can be obtained from the bidomain description by assuming σ_i to be a constant. In this case, Equation (1) reduces to 1 equation:

$$\frac{\partial V_m}{\partial t}=\frac{-I_{ion}+I_{stim}-G(V_m,t)V_m}{C_m}+\frac{1}{C_m\beta}\underbrace{\frac{\sigma_i\sigma_e}{\sigma_e+\sigma_i}}_{\sigma}\nabla^2V_m, \tag{7}$$

so we found

$$\frac{\sigma_T}{\beta C_m}=0.024\frac{mm^2}{ms}$$
$$\frac{\sigma_L}{\beta C_m}=0.15\frac{mm^2}{ms}. \tag{8}$$