Mechanisms of Afterdepolarization Induced Cardiac Arrhythmia

I. WEISS, A. URBASZEK, M. SCHALDACH
Department of Biomedical Engineering, University of Erlangen-Nuremberg, Germany

Summary

Since early afterdepolarizations (EADs) have shown to trigger cardiac arrhythmia the purpose of this model study is to investigate the mechanisms of their generation process and furthermore to elucidate the mechanisms of EAD-induced reentry circuits. EADs are generated due to the reactivation of the calcium L-type channel during the repolarization phase of the action potential. The most critical consequence of EADs is the pronounced prolongation of the action potential duration, which increases the dispersion of refractoriness. This may locally induce an unidirectional transient block of excitation spreading which favors reentrant circuits.

Key Words

Cardiac arrhythmia, early afterdepolarizations, cardiac reentry, computer model

Introduction

Despite the decisive progress in the therapy of various cardiac diseases cardiac arrhythmia still represents a major reason for sudden death. Phenomena contributing to cardiac arrhythmia show a very complex interdependence and act on different structural levels of the myocardium. Automaticity and triggered activity are known to be arrhythmogenic mechanisms acting at the cellular level, where the ion channels of the cell membrane are involved. On the other hand the interaction between cells, the spatial orientation of muscle fibers and the heterogeneous composition of the myocardium also contribute to the generation of arrhythmia [1]. The clinical experience showed that the macroscopic phenomenon of reentry is the most common mechanism of cardiac arrhythmia. Aiming at the development of antiarrhythmic therapy algorithms a systematic model based analysis of cardiac reentry mechanisms and their determinants is an important prerequisite.

Methods

Hypotheses concerning the mechanisms of EADs which are based on findings from electrophysiological investigations were tested and validated using a computer model of the cardiac action potential. The complexity of the membrane model (based on the Beeler-Reuter [2] and the Luo-Rudy models [7]), was strictly limited to the main components required by these hypotheses for two reasons: first, to avoid effects unrelated to the EAD mechanism and second to minimize the computation expense required by the model of action potential propagation.

As demonstrated by electrophysiological investigations EADs show to be correlated to the presence of ß-adrenergic agents like isoproterenol which acts comparable to the sympathetic transmitter agent in vivo. The properties of the calcium L-type channel are affected by isoproterenol resulting in a shift of the activating and inactivating characteristics [3]. In addition a deceleration of the channel inactivation was observed in [5], which is considered in the model by an increase of the inactivation time constant $\tau_f(V_m)$ by 13 %. However the main effect of ß-adrenergic stimulation on the calcium L-type channel is a pronounced increase of the Ca channel conductivity.

Beside the impacts on the calcium L-type channel the dynamic potassium channel is also affected by isoproterenol. ß-adrenergic stimulation enhances the conductivity of the dynamic potassium channel (in the model the conductivity was increased by 25 %) whereas the non-dynamic one is not affected [4][6].

characteristic	shifted by
$d_\infty(V_m)$	-10 mV
$\tau_d(V_m)$	+15 mV
$f_\infty(V_m)$	+4 mV
$\tau_f(V_m)$	+15 mV
$x_\infty(V_m)$	-15 mV
$\tau_x(V_m)$	+10 mV

Tab. 1. Impacts of isoproterenol on the gating variables.

To induce EADs in the model the activating and inactivating characteristics of the calcium L-type channel and the dynamic potassium channel were shifted as indicated in table 1.

Due to the functional changes induced by isoproterenol the coordination of the d, f and x gate is altered. An inflection point appears in the course of the transmembrane potential after which the action potential becomes flatter and the repolarization is nearby completely stopped. A slight disturbance of the sensitive current equilibrium (Ca/K) towards a small net inward current will trigger a new membrane depolarization. The d gating variable continues to increase, opening a so-called 'calcium window' (figure 1). The resulting inward calcium current accelerates itself the depolarization process acting as a positive feedback. The rapidly increasing transmembrane potential conditions that the f gate begins to close again and stops the avalanche like opening of calcium channels. A new repolarization phase starts closing the calcium window.

To investigate the impacts of EADs on the propagation phenomenon a model of one dimensional action potential propagation was designed (figure 2).

The fiber is considered to be build up of a chain of cylindrical membrane slices each being represented by a membrane model. These models are interconnected by resistors representing the intracellular (R_i) and the extracellular (R_e) space. Gap junctions were taken into account which showed to reduce the propagation velocity if their resistance is increased. A detail of the equivalent electrical network to be analyzed is depicted in figure 3. The transmembrane potentials for each of the

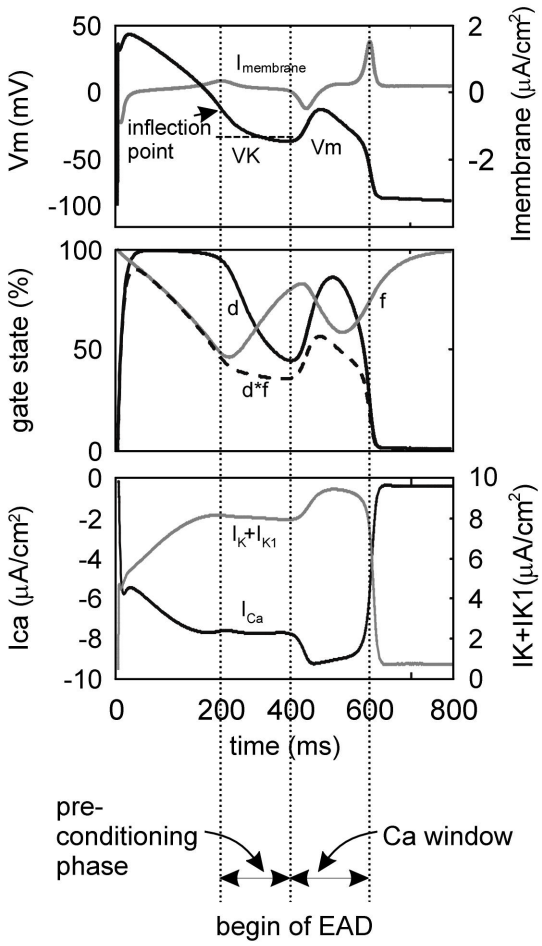

Figure 1. The mechanism of EAD generation. Preconditioning phase and calcium window.

membrane slices are computed based on a coupled differential equation system (discrete cable equation):

$$C_m \frac{dV_{m,j}}{dt} = \frac{1}{R_{i,j-1} + R_{e,j-1}} V_{m,j-1} - \left[\frac{1}{R_{i,j-1} + R_{e,j-1}} + \frac{1}{R_{i,j} + R_{e,j}} \right] V_{m,j} + \frac{1}{R_{i,j} + R_{e,j}} V_{m,j+1} - I_{k,j} - I_{s,j} \quad (1)$$

$$C_m = c_m \cdot 2\pi r_0 \cdot \lambda \quad (2)$$

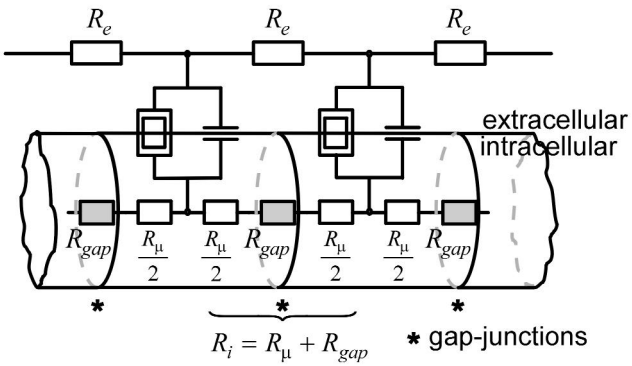

Figure 2. Model of the cardiac muscle fiber. The double outlined rectangle represents the model of ionic channels. R_m is the myoplasm resistance.

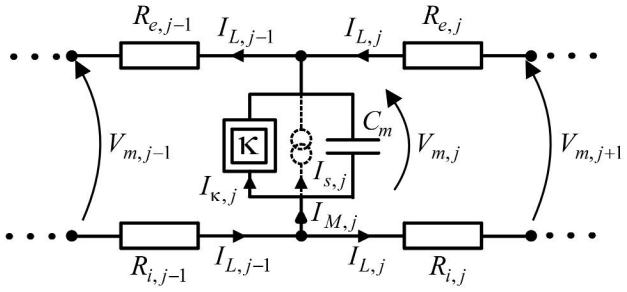

Figure 3. Network elements of the fiber model and definition of current flow directions.

In the model study it is assumed that the volume including the main part of the extracellular current flow is comparable to the intracellular volume, hence:

$$R = R_{e,j} = R_{\mu,j} = \frac{\lambda}{g \cdot r_0^2 \cdot \pi}, \quad j = 1..N \qquad (3)$$

The geometrical cell dimensions are $l = 10^{-2}$ cm, $r_0 = 10^{-3}$ cm whereas the electrical characteristics are $g = 6.7$ mS/cm for the electrolyte conductivity and $c_m = 1\ \mu F/cm^2$ for the specific membrane capacitance. Except of diseased regions the muscle fiber is considered to be homogeneous.

The propagation phenomenon was investigated for both, a model of a linear and a ring shaped muscle fiber. It is assumed that only a fraction of the total membrane area is effectively contributes to the membrane capacitance. To reduce the computation expense one excitable element of the model was considered to represent 5 cells. To adjust the normal propagation velocity under these border conditions to 1 m/s the fraction of active membrane was chosen to be 85 % ($c_{m,eff} = 0.85\ \mu F/cm^2$). A number of N=160 excitable elements corresponding to 800 was considered. For normal spread of excitation (propagation velocity 1 m/s) gap junctions were considered to be fully opened ($R_{gap} = 0$ Ohm). In diseased tissue like ischemic regions gap junctions are known to close disconnecting the cells electrically. It could be shown in the model that an increase of the gap junction resistance reduces the velocity of action potential propagation. The propagation velocity is modulated by the ratio:

$$\frac{R_i}{R_\mu} = 1 + \frac{R_{gap}}{R_\mu} \qquad (4)$$

Frequently reentry-based arrhythmia is observed when regions of the myocardium are temporary or persistent unexcitable. For example an infarcted zone or an operation scar is considered (figure 4).

The excitation wave has to pass around the damaged tissue following a ring shaped pathway. Based on this observation the reentry phenomenon is investigated in a model of a ring shaped muscle fiber (figure 5).

EADs were induced within a small segment of the ring model by modifying the model parameters of some of the membrane slices. The resulting very pronounced dispersion of refractoriness favors the start-up of a reentry circuit which could be initiated by two consecutive stimuli (S1,S2).

Results

The model study showed that EADs are generated due to the appearance of a so-called calcium window during the repolarization phase of the action potential. The calcium window results because of an alteration of the calcium L-type channel properties caused by ß-adrenergic stimulation of cardiac tissue. In the reentry model EADs were generated by assuming that the ß-adrenergic stimulation increased the Ca channel con-

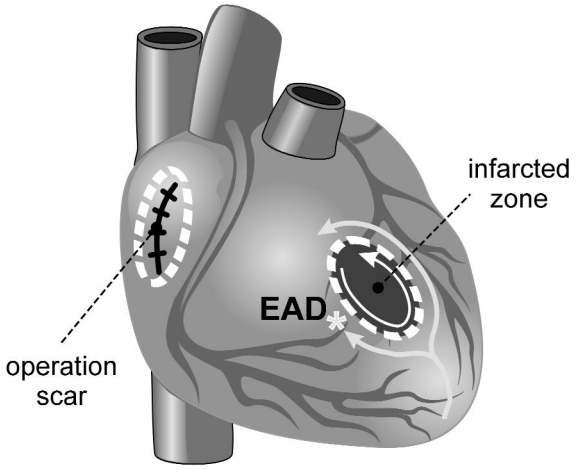

Figure 4. Potential anatomic and functional reentry pathways.

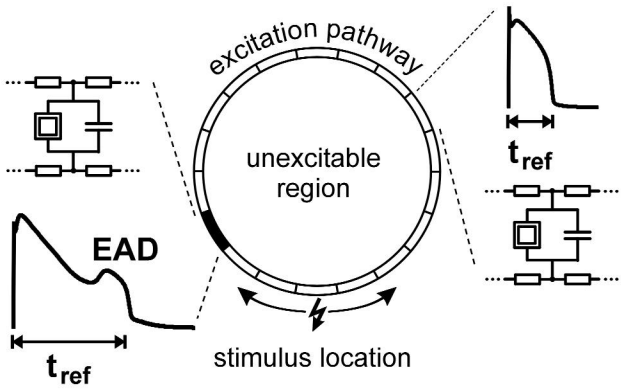

Figure 5. Design of the ring model. EADs are induced within a small segment of the ring-shaped fiber.

ductivity 3.33-fold. The figure 5 indicates where EADs are induced. The activating and inactivating characteristics of the calcium L-type channel and the dynamic potassium channel were shifted as indicated in table 1. The fiber is stimulated as shown in figure 6a (stimulus S1 at t = 0 ms). In the case of normal propagation the excitation spread takes place symmetrically in both branches of the ring model. The wavefronts meet at the diametrically opposite point of the stimulus location and efface each other. Afterwards both the left and the right branch repolarize symmetrically (figure 6a).

In the case of diseased tissue a region of the ring fiber remains depolarized due to the occurrence of EADs. The stimulus S2 is elicited 380 ms after S1 and propagates normally until the EAD region is reached (figure 6b). As a consequence of the significantly prolonged action potential duration the excitation wave originating from the S2-stimulus is blocked in the branch of the ring fiber where EADs appeared (figure 6c). The excitation propagates normally in the other branch but has a longer way to cover and arrives at the opposite side of the cells affected by EADs. Meanwhile these cells have got fully or almost fully repolarized (see arrow in figure 6d indicating the rise in the baseline) and therefore the excitation wave can pass through this domain reentering into the region where it initially started.

However, stable reentry is possible only if the wavelength corresponding to the refractory period of the propagated action potential is less than the circumference of the ring fiber. It is called the recovery wavelength because it is associated to the time required by the sodium channel to recover from inactivation. In the model the ring diameter was considered to be 2.55 cm (8 cm circumference) and the propagation velocity was reduced to 0.24 m/s by setting the gap junction resistance to $R_{gap}=8*R_{\mu}$. The action potential wave length corresponding to the APD_{90} parameter resulted to be 4.6 cm. The coupling interval S2-S1 was 380 ms resulting in a stable reentry tachyarrhythmia corresponding to a cycle length of 329 ms (182.4 min^{-1}).

Discussion

In what concerns the EAD generation mechanism it could be concluded that the sarcoplasmic reticulum and the calcium overload-induced release from the junctional sarcoplasmic reticulum are not necessarily involved in this process. A critical consequence of EADs is the pronounced prolongation of the action potential duration which contributes to the generation of a local functional block of excitation spreading favoring reentrant circuits. The initiation of the reentrant circuit depends on the relationship between the propagation velocity, the longest way between the stimulus location and the EAD zone and the coupling interval S2-S1. Whether the reentry wave circulates clockwise or counterclockwise depends on the location of the EAD zone. The counterclockwise direction of rotation is achieved if the EAD zone is placed in the left branch as shown in the discussed example. If the EAD zone is placed exactly diametrically opposite to

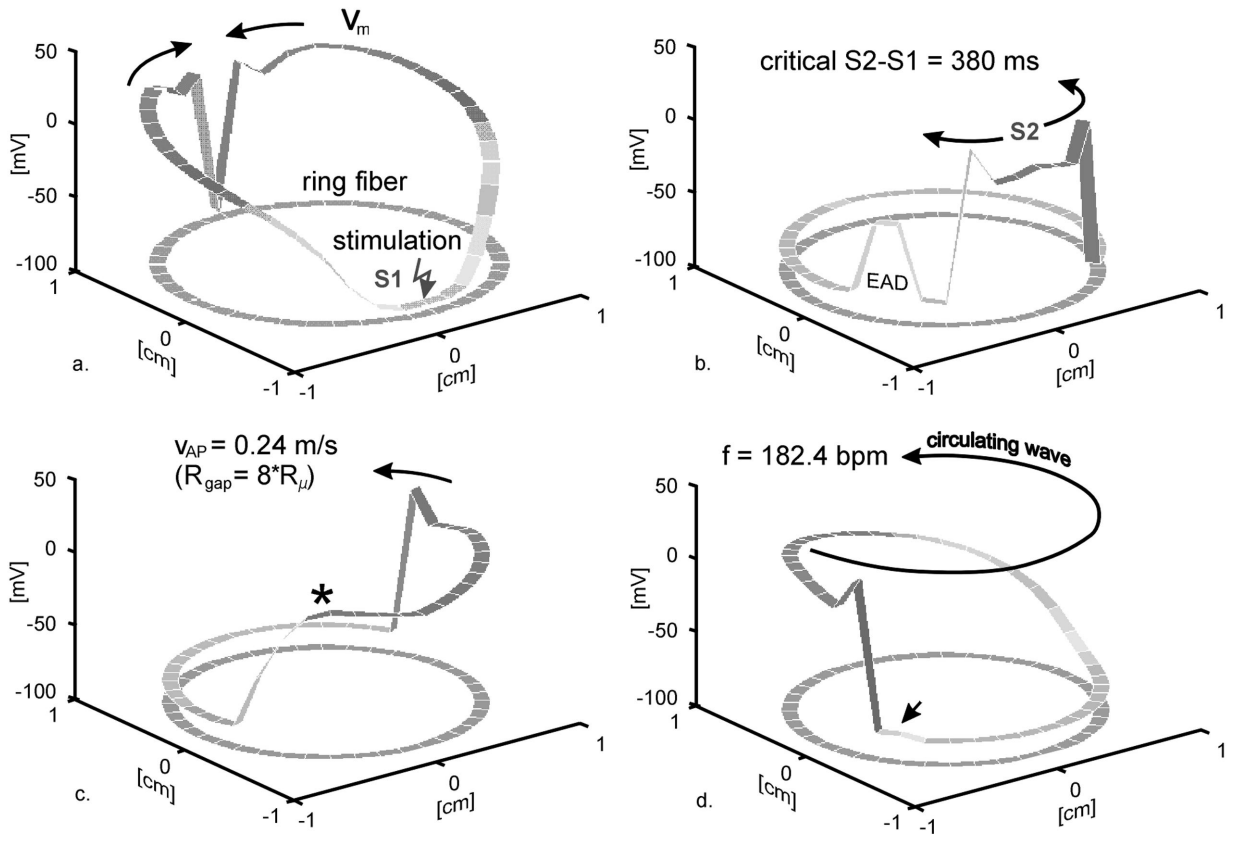

Figure 6. Simulation results of cardiac reentry.

the stimulus location no reentry will occur. Stable reentry, however, is achieved only if the recovery wavelength is less than the circumference of the ring.
Out of this also the main finding results giving evidence that if reentry persists an excitable gap exists which allows the reentry to be suppressed by precisely timed antitachycardia stimulation.

References

[1] Antzelevitch C, Sicouri S. Clinical relevance of cardiac arrhythmias generated by afterdepolarizations. Role of M cells in the generation of U waves, triggered activity and torsade de pointes. JACC. 1994; 23:259-77.

[2] Beeler GW, Reuter H. Reconstruction of the Action Potential of Ventricular Myocardial Fibers. J. Physiol.; 1977; 268:177-210.

[3] Rosen MR. The concept of afterdepolarizations. In: Rosen MR, Janse MJ, Wit AL, Cardiac Electrophysiology: A Textbook. Mount Kisco (NY): Futura 1990 pp. 267-271.

[4] Szabo G, Otero AS. G protein mediated regulation of K+ channels in heart. Annu. Rev. Physiol, 1990; 52:293-305.

[5] Tiaho F, Richard S, Lory P, Nerbonne JM, Nargeot J. Cyclic-AMP-dependent phosphorylation modulates the stereospecific activation of cardiac Ca channels by Bay K 8644. Pflügers Arch, 1990; 417:58-66.

[6] Tseng G, Robinson RB, Hoffmann BF. Passive properties and membran currents of canine ventricular myocytes. J. Gen. Physiol, 1987; 90:671-701.

[7] Zeng J, Rudy Y. Early afterdepolarizations in cardiac myocytes: mechanism and rate dependence. Biophysical Journal, 1995; 68:949-964.