

# A Model Study of Cardiac Early Afterdepolarizations

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## Summary

*Since early afterdepolarizations (EADs) have shown to trigger cardiac arrhythmia the purpose of this study is to investigate the mechanisms of their generation process. Hypotheses concerning the mechanisms of EADs which are based on findings from electrophysiological investigations were tested and validated using a computer model of cardiac action potentials. To avoid effects unrelated to this phenomenon the model was specially designed for this purpose. It could be demonstrated that the essential mechanism is the generation of a so-called calcium window during the repolarization phase of the action potential which is due to an alteration of the calcium L-type channel properties caused by  $\beta$ -adrenergic stimulation of the cardiac tissue. Furthermore, it could be concluded that the sarcoplasmic reticulum and the calcium overload-induced calcium release from the junctional sarcoplasmic reticulum are not necessarily involved in the generation mechanism of EADs. A critical consequence of EADs will be a pronounced prolongation of the action potential duration. Hence, the refractory period will be prolonged, too, and may locally induce a functional block of excitation spreading which favors reentrant circuits.*

## Key Words

computer model, cardiac action potential, early afterdepolarizations,  $\beta$ -adrenergic stimulation

## Introduction

Despite the decisive progress in the therapy of various cardiac diseases cardiac arrhythmia still represents a major reason for sudden death. Pharmacological therapies are often based on empirical criteria (arrhythmia classes) which only partially consider the actual mechanisms of the particular arrhythmia [[2]]. However, a detailed diagnosis of cardiac arrhythmia requires a physically underpinned understanding of their generation mechanisms as well as systematically established electrophysiological criteria.

Phenomena contributing to cardiac arrhythmia show a very complex interdependence and act on different structural levels of the myocardium. On the one hand ion channels of the cell membrane are involved, but 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. Endocardial cells, epicardial cells and M-cells show

different electrophysiological behavior and hence,

their responses to external agents will not be the same [[1]]. The presented study focuses on anomalies in the electrophysiological behavior of myocytes which are correlated to cardiac arrhythmia.

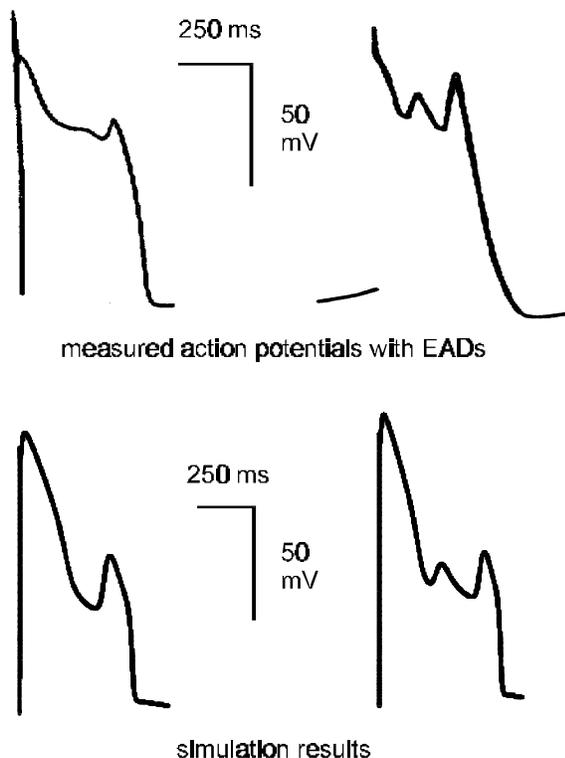
## Methods

For the investigations a computer model of the cardiac muscle cell is used which is mainly based on the Beeler-Reuter model of cardiac action potentials [[4]]. To demonstrate that calcium overload-induced calcium release from the junctional sarcoplasmic reticulum is not necessarily involved in the generation mechanism of EADs the sarcoplasmic reticulum is explicitly not considered in this model. For the reconstruction of normal action potentials in a first step the original mathematical formulations of the ionic currents published in [[4]] were modified based on descriptions from [[18]], [[19]], [[28]] and [[30]].

The dynamic properties of the cell model were adjusted according to findings from recent electrophysiological measurements performed on healthy cells. In a second step modifications were performed aiming at the generation of EADs.

#### *Definition and classification of afterdepolarizations*

The action potential of the healthy cardiac cell is characterized by a continuously and monotonously decreasing double curved course of the plateau and the repolarization phase. However, pathological changes of the ion channel functionality may induce oscillations in the time course of the action potential. That means that the plateau and/or the repolarization phase will not take any more a monotonously course, instead spontaneous depolarizations will occur before or some time after the membrane resting potential is reached. According to descriptions formulated in literature [[7]] afterdepolarizations of the cardiac cell membrane are defined to be oscillations which occur after the begin of the plateau phase and which are preconditioned by the course of the transmembrane potential previous to the afterdepolarization or by other state variables of the dynamic system (fig. 1).



**Figure 1.** Morphologies of cardiac action potentials with EADs. Comparison of measured [[2]] and simulated curves

Depending on the phase within which they arise, afterdepolarizations are subdivided into: early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). While the first occur during the plateau or the repolarization phase, the latter arise from the resting potential level after the repolarization was completed.

In what concerns the impact of EADs on the excitation process of the heart, one realizes that if the magnitude of the membrane potential oscillations go beyond a threshold value they may directly induce triggered beats. On the other hand EADs considerably prolong the action potential duration. Thereby, they entail a significant increase of the refractory period and this in turn will favor functional blocks leading to reentrant circuits. Because EADs may trigger cardiac arrhythmia in two ways, a detailed study of their mechanisms will be presented in the following.

#### *Electrophysiological border conditions*

The connection between EADs and cardiac arrhythmia was observed and experimentally proved in electrophysiological studies where endocardial and epicardial monophasic action potentials (MAP) were recorded synchronously with the ECG signal [[2]]. As stated in literature [[8]], [[11]] and [[30]] the most important findings can be summarized as follows:

EADs are favored by low extracellular potassium concentration and by low stimulation frequencies. They are abolished by an increase of the potassium channel conductivity and by high stimulation frequencies. In contrast DADs are favored by pharmacological agents increasing the intracellular calcium concentration and also by short cycle length. They are abolished by calcium blockers and by medication diminishing the ability of the cell to buffer calcium within the sarcoplasmic reticulum.

With regard to the importance of afterdepolarizations for the arrhythmogenesis the literature supports a clear opinion, but statements concerning the mechanisms of EAD generation are still controversially [[30]]. The main findings which are based on observations from electrophysiological studies are:

- 1) Investigations performed on ventricular myocytes of the ferret have shown, that cesium induced EADs are neither affected by ryanodine nor by

BAPTA [[20]]. Ryanodine diminishes the calcium release from the sarcoplasmic reticulum while BAPTA increases the ability of the cell to buffer calcium. It was concluded that EAD generation does not require high intracellular calcium concentration. Furthermore, calcium release from the sarcoplasmic reticulum is not necessary. The crucial importance is attributed to the inward calcium current which passes the calcium L-type channel during the EAD.

- 2) Results concerning EADs induced by Bay K 8644 in action potentials of the sheep and the rabbit are presented in [[16]]. The (-) isomer of Bay K 8644 is known to act as a calcium L-type channel agonist. When applied to the preparation it enhances the calcium current through the cell membrane by increasing the opening probability of the individual calcium channels [[13]]. Based on observations two main mechanisms were identified: First, an EAD is always preceded by a prolonged plateau phase and second, the activation ability of the calcium L-type channel re-increases during this phase. Hence, after this preconditioning phase the calcium L-type channel can open again. The basic mechanism is therefore, the development of a so-called 'calcium window' during the repolarization phase of the action potential, which is responsible for the depolarizing inward calcium current generating the EAD.
- 3) In contrast to these statements the findings presented in [[22]] lead to the conclusion that EADs and DADs are based on the same mechanism which consists in a spontaneous calcium release from the sarcoplasmic reticulum as a result of a calcium buffer overload. The membrane depolarization is induced by a transient inward current which is triggered by the release process. In the presence of isoproterenol (a  $\beta$ -adrenergic agent) both EADs and DADs can be observed which also are both abolished by ryanodine or by pharmaceuticals deactivating the sodium-calcium exchanger. In [[22]] therefore it was concluded that the spontaneous calcium release from the sarcoplasmic reticulum increases the activity of the sodium-calcium exchanger, which delivers the depolarizing current for both EADs and DADs.
- 4) A comprehensive model study concerning the mechanisms of EADs is presented in [[30]]. It was found that the activation of the sodium-calcium exchanger is decisive only for DADs whereas

EADs have shown to be governed by other mechanisms. The model study was based on the Luo-Rudy model [[18]] which was adapted to simulate the effects of various pharmacological agents [[30]]. The most important findings concerning EADs are summarized as follows:

- The calcium current through the calcium L-type channel is the main carrier of the depolarizing charge forming the EAD.
- Recovery and reactivation of the calcium L-type channel are crucial determinants of EAD generation regardless of the reason by which the EAD was induced (cesium, Bay K 8644 or isoproterenol).
- To elicit an EAD neither an increase of the intracellular calcium concentration nor a calcium release from the sarcoplasmic reticulum are required.
- Although the reactivation of the calcium current represents the most important mechanism, other plateau currents may affect the very sensitive equilibrium of ionic currents prior to the EAD.
- EADs frequently appear at low pacing rates (< 60 bpm) and are unlikely during fast stimulation. This behavior is due to the dependence on the stimulation frequency of the potassium current.

Based on the findings stated above a computer model of cardiac action potentials was developed which takes into account the pathophysiological characteristics of EAD threatened cells. To validate these hypothesis systematically, the model consists only of elements which are strictly required by the emphasized mechanism descriptions.

#### *Requirements on the complexity of the cell model*

First of all, the model must correctly generate the morphology of a normal cardiac action potential. After depolarizing the resting potential by a stimulation impulse up to a threshold value the depolarization has to continue spontaneously and with high velocity. Therefore, the model includes the sodium channel which is known to be responsible for this mechanism. The ionic currents developing the action potential plateau are dominated by the calcium current. In the model this current is considered to pass the calcium L-type channel. Last but not least the repolarization of the action potential is due to the activation of potassium currents. The model considers two types of

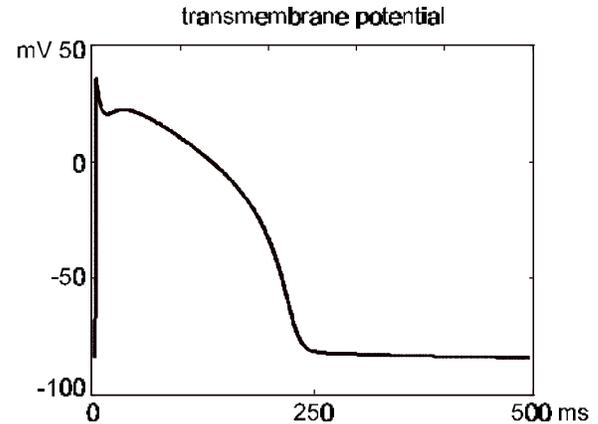
potassium currents: a dynamic one being responsible for the fast repolarization from the plateau potential toward resting potential and a non-dynamic one which mainly controls the resting potential level.

As stated earlier, EADs are correlated only to calcium and potassium channels. Therefore, this minimum component structure of the model is both necessary and sufficient to validate the hypothesis concerning the EAD generation mechanism. The sarcoplasmic reticulum is explicitly omitted from the model to demonstrate that calcium release from this intracellular compartment is not necessarily required for EAD generation.

The skeleton of the cell model corresponds to that of the Beeler-Reuter model [[4]]. The sodium channel, the calcium channel and the dynamic potassium channel are modeled according to the Huxley-Hodgkin formalism. The state variables are the gating variables of the mentioned channels, the calcium concentration and the transmembrane potential. In [[28]] it could be shown that the chlorine current can be neglected. It was also found that the changes in the intracellular concentrations of sodium and potassium are very small. Therefore, these concentrations are considered to be constant during the action potential.

The advantage of a low complexity model, as is the Beeler-Reuter model, mainly consists in its clear structure and its easy manageable size (8<sup>th</sup> order). However, the quantitative description of the Beeler-Reuter had to be reformulated in order to reproduce recent measurements.

The improved formulation of the sodium channel concerns the channel conductivity as well as its dynamics. The conductivity was increased 3-fold becoming  $g_{Na}=12$  mS/cm<sup>2</sup>. In addition the activating variable  $m$  was accelerated twice whereas the inactivating variables  $h$  and  $j$  were accelerated twice and 4-fold, respectively. As a result of this correction the maximum slope of the action potential upstroke becomes  $v_{max}^{\&}=392$  V/s (instead of  $v_{max}^{\&}=115$  V/s in the Beeler-Reuter model). This value is in good agreement with physiological data from literature [[5]]. In [[1]] upstroke velocities within a range of 200-500 V/s are related. The peak magnitude of the sodium current becomes  $394$   $\mu$ A/cm<sup>2</sup> which is very close to  $400$   $\mu$ A/cm<sup>2</sup> published in literature. Fig. 2 displays a normal action potential simulated by the presented model whereas fig. 3 shows details from the upstroke phase and the sodium current during the first 2.5 ms after the stimulus.



**Figure 2.** Normal shape of a cardiac action potential simulated by the presented model

Improvements were also carried out in the description of the calcium L-type channel. Measurements based on the patch-clamp technology [[15]] have revealed that the calcium current activates faster than described in the Beeler-Reuter model. Therefore, the voltage dependent time constant  $\tau_d$  of the gating variable  $d$  was diminished by the factor 1.5, that means that the activation speed of the calcium current was increased 1.5-fold.

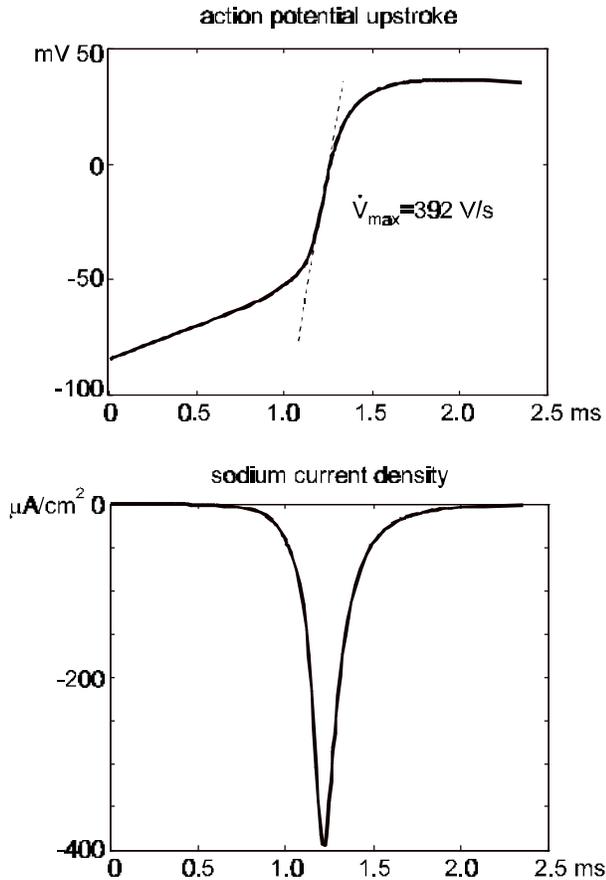
The description of the dynamic potassium channel was also modified as shown in equation (1). The dynamic potassium current is computed using the square value of the gating variable  $x$  in order to reflect experimental results more accurately [[21]]:

$$I_K = x^2 \cdot \frac{3.2 \cdot (e^{0.04(V_m+77)} - 1)}{e^{0.04(V_m+35)}}, \quad (1)$$

with

$$\frac{dx}{dt} = \frac{x - x_{\infty}(V_m)}{\tau_x(V_m)}. \quad (2)$$

The magnitude of the dynamic potassium current was increased 4-fold to reproduce correctly the repolarization velocity of the action potential. At 90% repolarization the action potential shown in fig. 2 has a duration of  $APD_{90}=229$  ms.



**Figure 3.** Details of the action potential upstroke and the peak of the sodium current

## Results

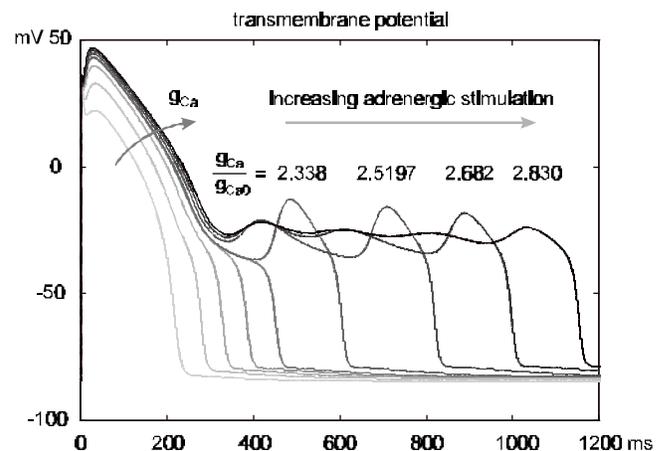
In the following the presented model for the normal action potential is modified and employed to simulate pathophysiological behavior. As demonstrated by electrophysiological investigations EADs show to be correlated to the presence of  $\beta$ -adrenergic agents like isoproterenol which acts comparable to the sympathetic transmitter agent in vivo. On the other hand EADs are known to trigger arrhythmia. Therefore, it is of particular interest to investigate and elucidate these connections.

### Mechanisms and morphologies of myocardial EADs

The presented study goes out from the following example:

In the case of bradycardia the inotropic effect of the sympathetic tone will tend to compensate the chronotropic insufficiency of the patient. As observed

from experiments, if the bradycardia persists, two prerequisites for EAD generation are combined: namely the low stimulation frequency and an overdose of adrenergic agents being released to increase the inotropy. On the other hand it is known from clinical experience that bradycardia may be followed by tachyarrhythmia, a statement which at a first view seems to be contradictory. Elucidating these connections is decisive for the development of reliable therapy methods.



**Figure 4.** Morphologies of simulated action potentials with EADs. The number and the shape of EADs depends on the strength of  $\beta$ -adrenergic stimulation

In fig. 4. various simulated events showing EADs are presented. Dependent on the strength of adrenergic stimulation one or multiple EADs may appear. In this

model study isoproterenol is considered to be the  $\beta$ -adrenergic agent. Actually, isoproterenol is detected by specific receptors of the cell membrane and has a share in various mechanisms. The study focus on those mechanisms which are involved in the EAD generation. They concern the impact of isoproterenol on the calcium L-type channel and the modulation in functionality of the dynamic potassium channel.

In what concerns the calcium L-type channel, the increasing concentration of isoproterenol enhances the channel permeability [[26]]. Single channel recordings have shown that isoproterenol increases the opening duration of the channel and shortens the intervals between two openings. However, the magnitude of the single channel current remains unchanged. Instead, the total number of participating calcium channels is increased several times [[3]].

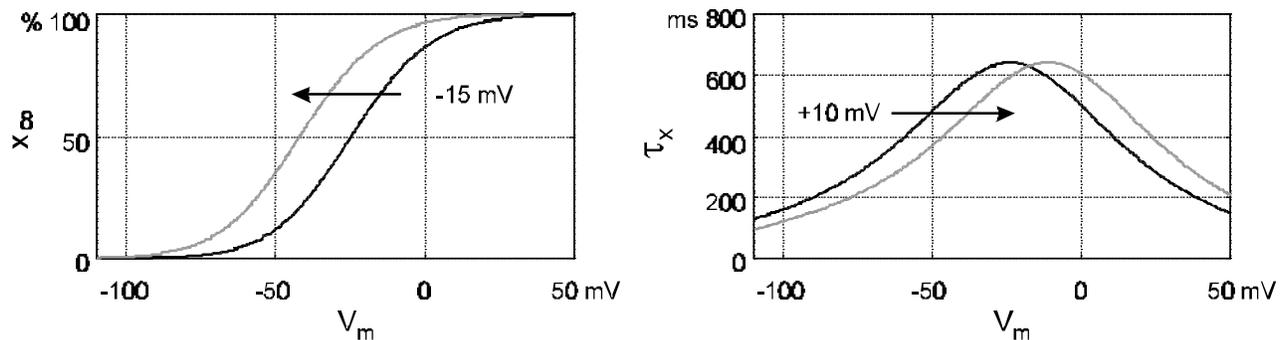
Thereby, the averaged current over the whole cell will be increased, too.

Assuming that  $g_{Ca0}$  is the conductivity of the calcium L-type channel for normal action potentials the ratio  $g_{Ca}/g_{Ca0}$  is a measure for the strength of adrenergic stimulation. The values for this ratio differ for various cell types and are within a range of 1.5-8 [[30]].

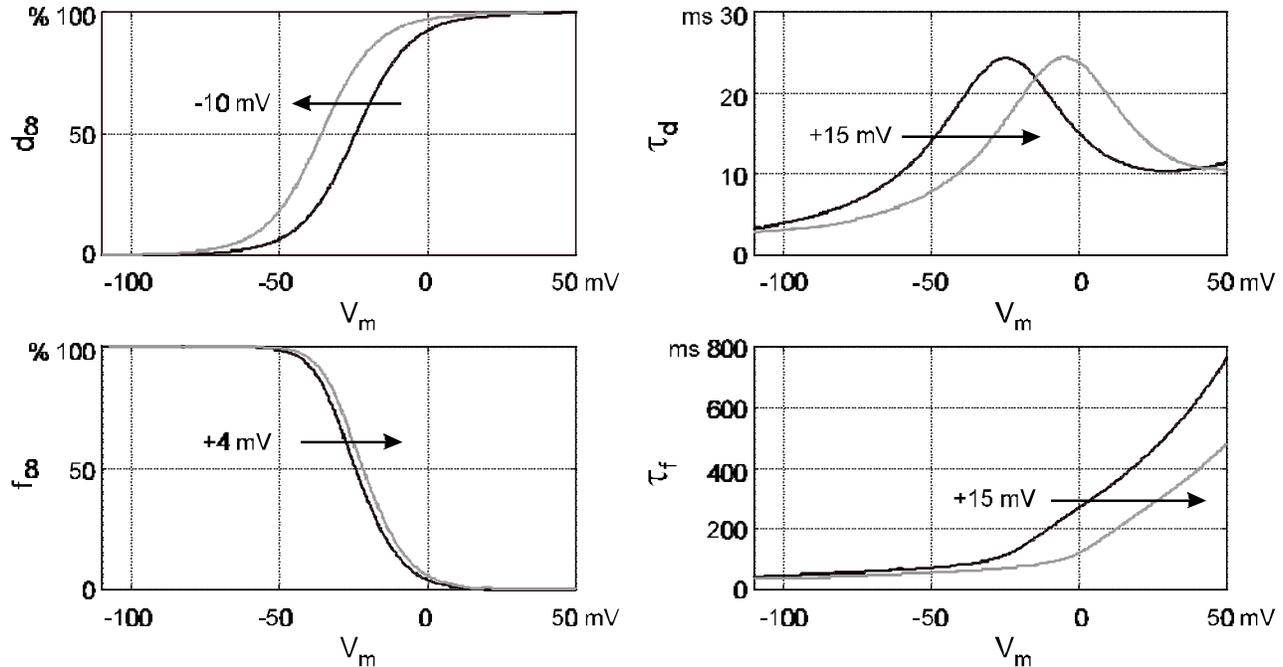
Moreover, experimental findings have shown that the activation and inactivation properties of the calcium L-type channel are also affected by isoproterenol. In [[23]] an isoproterenol induced shift of the activating and inactivating characteristics is related which is depicted in fig. 5. However, this fact is neglected in [[30]], but obviously a shift in opposite directions of the characteristics  $d_{\infty}(V_m)$  (in negative direction of  $V_m$ ) and  $f_{\infty}(V_m)$  (in positive direction of  $V_m$ ) favor the appearance of a calcium window so that the calcium L-type channel is able to be re-opened during the repolarization phase. Therefore, this fact is

considered to be a major determinant for EAD generation and is taken into account in our model. In addition a deceleration of the channel inactivation was observed in [[25]], which is considered in the model by an increase of the inactivation time constant  $\tau_f(V_m)$  by 13%.

Beside the impacts on the calcium L-type channel the dynamic potassium channel is also affected by isoproterenol. According to the present-day knowledge about the cardiac potassium channels,  $\beta$ -adrenergic stimulation enhances the conductivity of the dynamic potassium channel whereas the non-dynamic one is not affected [[24]], [[27]]. However, quantitative descriptions could not yet be found in literature. Comparing measured and simulated events showing EADs (see fig. 1) it was concluded that in the presence of isoproterenol the conductivity of the dynamic potassium channel must increase by about 25%.



**Figure 6.** Impacts of isoproterenol on the activating characteristics of the dynamic potassium channel



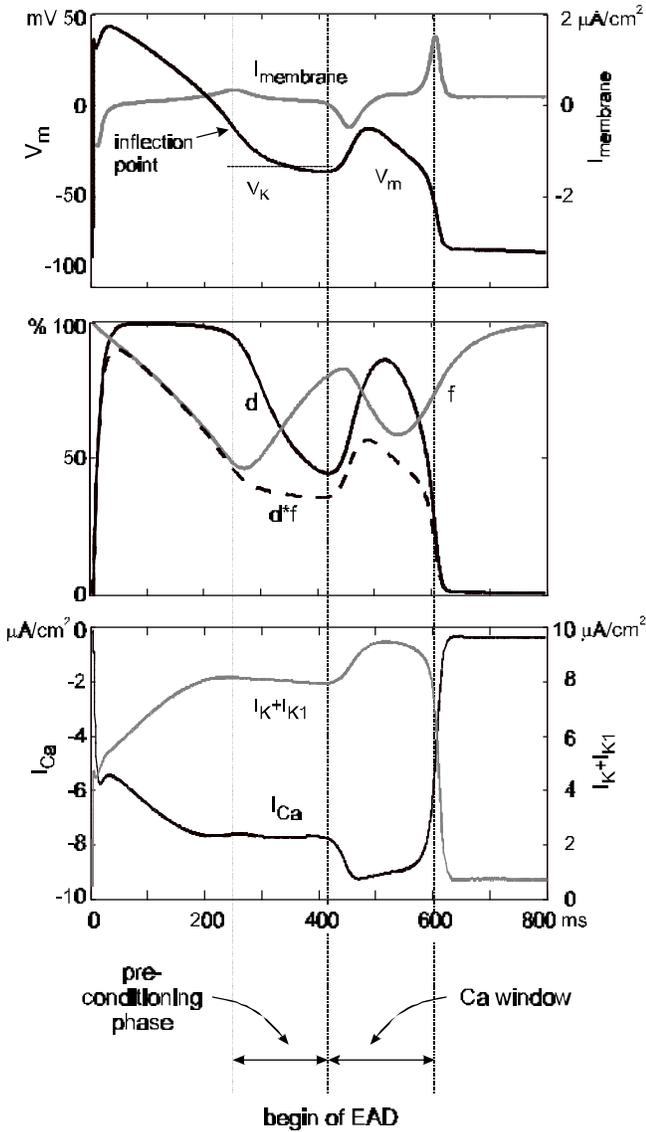
**Figure 5.** Impacts of isoproterenol on the activating and inactivating characteristics of the calcium L-type channel

An isoproterenol induced shifting of the activating characteristic was observed as well. Based on measurements performed in [[10]] and [[12]] in the model a shift by 15 mV in the negative direction of the  $x_{\infty}(V_m)$  curve is considered (fig. 6). The  $\tau_x(V_m)$  curve is shifted by 10 mV in the positive direction, to diminish the values of the x variable time constant for negative values of the transmembrane potential. This fact is important to get a relatively steep repolarization course after the last EAD, as it can also be observed in measurements (see fig. 1).

#### *The preconditioning phase and the calcium window*

Due to the functional changes induced by isoproterenol the coordination of the d, f and x gate is altered. If a certain value of the transmembrane potential is reached during the ongoing repolarization process (the inflection point positions of the  $d_{\infty}(V_m)$ ,  $f_{\infty}(V_m)$  and  $x_{\infty}(V_m)$  curves in fig. 5 and fig. 6 are decisive) an inflection point appears in the course of the transmembrane potential after which the action potential becomes flatter. The repolarization is nearby completely stopped. An intermediate plateau is formed, which has the same effect as if the transmembrane potential would have been clamped on a fixed value  $V_K$ . Starting from this inflection point

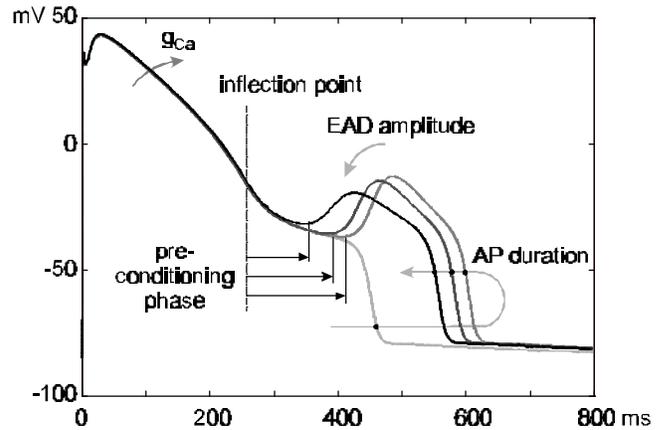
there will be enough time for the d variable to settle to the asymptotic value  $d_{\infty}(V_K)$ . This dynamic process is governed by the time constant  $\tau_x(V_K)$ . In the time course of the d variable a curve fragment appears allowing a horizontal tangent (fig. 7). The range between the inflection point of the transmembrane potential and this horizontal tangent is called the 'preconditioning phase'. Given these border conditions even a very small change of the transmembrane potential can tilt the time course of the d variable towards an increasing trend, re-opening the calcium channel.



**Figure 7.** The mechanism of EAD generation. Preconditioning phase and calcium window

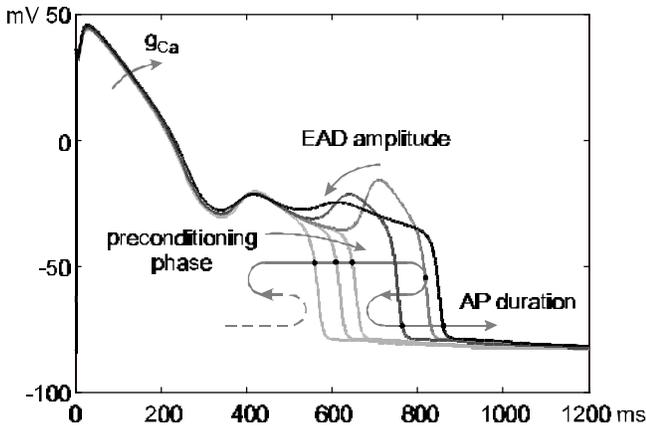
The time course of the transmembrane potential gets flatter and flatter until it is horizontal. A slight disturbance of the sensitive current equilibrium (Ca/K) towards a small net inward current will trigger a new membrane depolarization. The *d* gating variable continues to increase, opening a so-called 'calcium window'. The resulting inward calcium current accelerates itself the depolarization process acting as a positive feedback. This process is comparable with the opening of sodium channels during the action potential upstroke. However, sodium is not involved in this process, because the inactivating gating variables are at 0 at that moment. The sodium

channel gates are closed due to the relatively high transmembrane potential. 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.



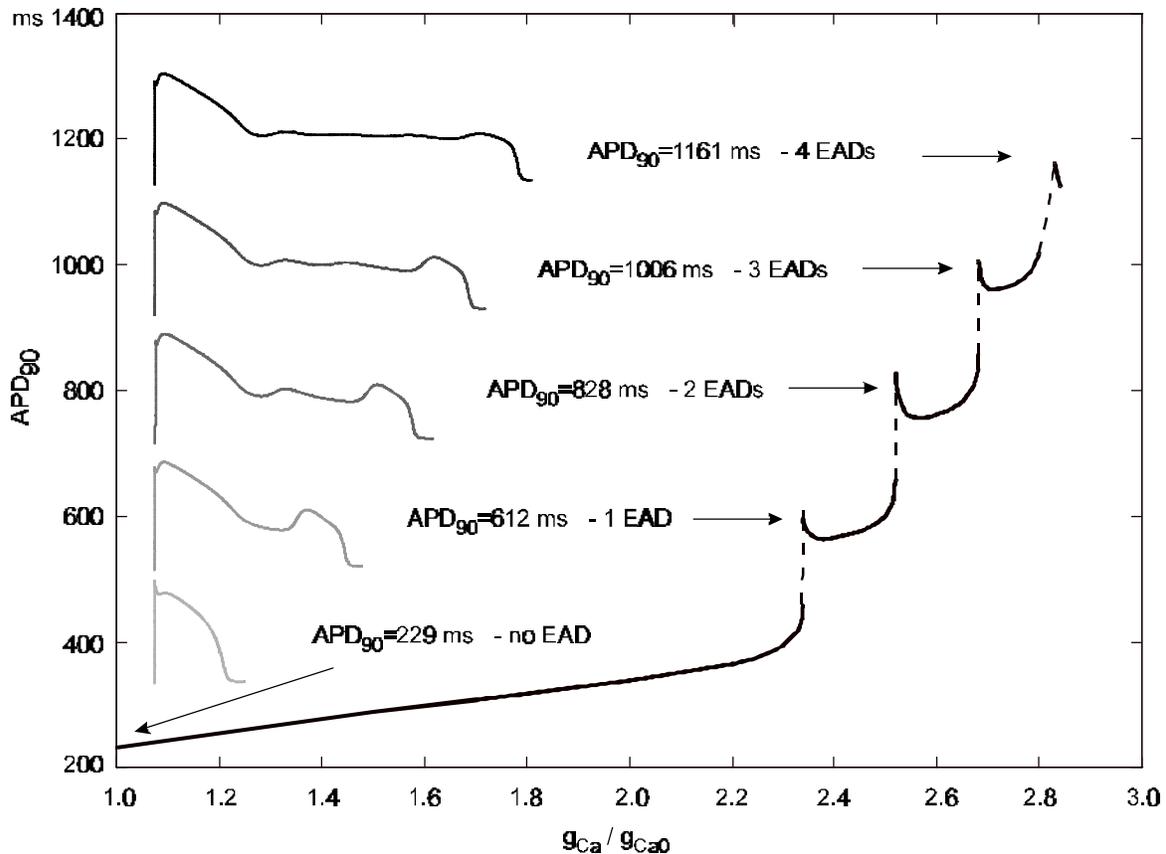
**Figure 8.** Simulated action potentials with one EAD. Modulation of the EAD amplitude and action potential duration by variation of the calcium channel conductivity

At this moment a new preconditioning phase may begin and restart the described mechanism which generates further EADs. When looking at the *x* gating variable one realizes that its local maximums increase with each new EAD within the same action potential. This induces an increase of the potassium current at the begin of each new preconditioning phase. The step like shape of this current can be observed in fig. 7. After a certain number of EADs within the considered action potential the magnitude of the potassium current will be sufficient high to continue the repolarization until the resting potential is reached, instead of starting a new preconditioning phase.



**Figure 9.** Simulated action potentials with two EADs. Modulation of the EAD amplitude and action potential duration by variation of the calcium channel conductivity

Fig. 8 and fig. 9 show that the EAD is the higher the lower the preconditioning plateau is. This can be explained by the fact that for lower (more negative) values of the transmembrane potential the time constant of the  $d$  variable is smaller (fig. 5). Therefore, the slope of the EAD gets steeper and a higher amplitude of the afterdepolarization will be reached. This phenomenon was also observed experimentally [[15]] and was specifically investigated. The investigations were performed using a 2-step voltage-clamp protocol which in the first stage simulates a normal action potential plateau whereas the second stage represents the preconditioning phase for the desired EAD. After this forced preconditioning phase the cell was left to itself and actually a spontaneous depolarization could be observed. The relationship between the voltage level of the preconditioning phase and the EAD amplitudes showed the same trend as does our model.



**Figure 10.** Action potential duration as a function of  $\beta$ -adrenergic stimulation.  $\beta$ -adrenergic stimulation is simulated by variation of the ratio  $g_{Ca}/g_{Ca0}$

A very interesting phenomenon concerns the course of the action potential duration displayed in dependence of the grade of adrenergic stimulation (fig. 10). It is neither continuously nor monotonously. This behavior can also be observed in fig. 8 and fig. 9. The dashed lines in fig. 10 indicate the discontinuity points. Here no APD<sub>90</sub> values can be obtained. That means that the EAD duration cannot fall short of a certain value. The step like course of this parameter is typically for highly nonlinear systems.

### Discussion

The study presents an overview of the hypothesis known from literature concerning the generation mechanism of EADs. To test and validate them a computer model for simulation of the cardiac action potentials was developed. The most important findings elucidating the generation mechanisms of EADs are summarized as follows:

- The depolarizing charge required for EADs is carried through the calcium L-type channel.
- The decisive mechanism of EADs consists in the reactivation of the calcium current through the cell membrane as a result of the development of a calcium window. The reactivation mechanism of the calcium channel does not depend on the type of the agent causing the EAD.
- EAD generation neither requires an increased intracellular calcium concentration nor a calcium release from the sarcoplasmic reticulum.
- EADs are favored by low stimulation frequencies.

It is known from the clinical experience that EADs may induce arrhythmia. This can happen in two ways: first, if EADs occur having high amplitudes they can depolarize a neighboring tissue domain if this one is not refractory. Thereby, an ectopic beat will be triggered. A second and may be more probable mechanism leading to arrhythmogenesis is due to the pronounced prolongation of the action potential duration. This induces a pathologically prolonged refractory period in the tissue regions where EADs occur. These regions represent a local dynamic block for the next excitation front. As a result reentrant circuits may appear surrounding the EAD regions. However, at the current level of the study this argumentation is still hypothetically. Therefore, a detailed study of arrhythmogenesis mechanisms at tissue level has to be performed based on a computer model of cardiac tissue.

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