Ionic Mechanisms of Cardiac Arrhythmia

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Summary

In order to achieve optimal therapy results, it is decisive to take into consideration the particular mechanisms of cardiac arrhythmia. Classification and detailed understanding of the underlying mechanisms will therefore establish the basis for successful management of cardiac arrhythmia. Our study focuses on reentry-based arrhythmia triggered by early afterdepolarizations (EAD). Hypotheses concerning the mechanisms of EADs were tested and validated using a computer model of cardiac action potentials. We were able to demonstrate that the essential mechanism consists in the generation of a so-called calcium window during the repolarization phase of the action potential. The generation of the calcium window is caused by an alteration of the calcium L-type channel properties due to excessive ß-adrenergic stimulation of the cardiac tissue. The most critical consequence of EADs is a pronounced prolongation of the action potential duration. This may locally induce a unidirectional transient block of excitation spreading, which favors reentrant circuits. As demonstrated by this study, however, the existence of an excitable gap is required for the reentry to be stable and, thereby, becoming dangerous. Based on findings concerning the prerequisites of reentrant circuits, our study theoretically underpins the strategy of antitachycardia pacing, able to achieve suppression of tachycardia, as a promising alternative to drug therapy.

Key Words

Cardiac arrhythmia, early afterdepolarization, reentry, cell model

Introduction

Despite decisive progress in the therapy of various cardiac diseases, cardiac arrhythmia still represents a major reason for sudden cardiac death. Pharmacological therapies are often based on empirical criteria that only partially consider the actual mechanisms of the particular arrhythmia [1]. However, a detailed diagnosis of cardiac arrhythmia requires a physically underpinned understanding of their generation mechanisms as well as systematically established electrophysiological criteria.

Changes in the electrophysiological substrate contributing to cardiac arrhythmia can be observed at 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. In addition, 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].

As confirmed by clinical experience, the macroscopic phenomenon of reentry is the most common mechanism of cardiac arrhythmia, but the therapeutic strategies for abolishing reentry may differ according to the specific mechanism underlying the arrhythmia. Aiming at the development of antiarrhythmic therapy algorithms, a systematic analysis of cardiac reentry mechanisms and their determinants is an important prerequisite.

In order to analyze the complex interdependencies of the system parameters, a mathematically well-defined model study is performed. The analysis focuses on the mechanisms underlying the electrophysiological anomalies correlated with cardiac arrhythmia. Beyond verifying hypotheses suggested by electrophysiological experiments, the model also serves as a tool for planning clinical studies.

Electrophysiological Background

To establish a systematic foundation of electrophysiological knowledge, mathematical modeling of cardiac tissue will be based on a series of experimental findings, which are summarized in the following. The findings concern changes in the electrophysiological substrate and other observations revealed from experiments that provide an overview of the most important arrhythmogenic mechanisms.

Electrophysiological Substrate of Cardiac Arrhythmia

Early observations concerning cardiac arrhythmia have already confirmed that dispersion of refractoriness is a key factor for arrhythmogenesis and have shown that its increase underlies the arrhythmogenic effect of premature beats [13]. Moreover, interventions such as vagal or sympathetic stimulation, quinidine intoxication, hypothermia, and myocardial ischemia might favor reentrant activity. These can act both by increasing dispersion of refractory periods and by changing conduction velocity and refractory periods such that the minimal length of a circuit in which the impulses can circulate is reduced. From this, the concept of "wavelength" as the product of conduction velocity and refractory period was derived, which permits the length of the reentry circuit to be measured. Modifying the electrophysiological substrate alters not only refractoriness but also the conduction velocity of the excitation impulse. Therefore, a "dynamic dispersion" may exist, which could be modified by physiological or pathological factors favoring reentry and fibrillation.

Abnormalities in myocardial electrophysiology and structure are important for the development of cardiac arrhythmia. Shortened atrial refractoriness and diminution of the rate-dependent change in refractoriness have been associated with a higher vulnerability to fibrillation [2]. For example, changes in the atria of goats have been found to be the result of fibrillation rather than being the cause of it [24]. Also, membrane potential abnormalities leading to impaired conduction have been found in atrial fibers of patients with chronic atrial fibrillation (AF) and extensive degenerative changes.

However, the main finding from clinical practice is that "reentry" is easily induced by increasing dispersion of refractoriness and slowing impulse conduction velocity. In conclusion, an increased dispersion of refractoriness favors the inducibility and persistency of cardiac fibrillation.

Arrhythmogenic Mechanisms

With regard to the basic mechanisms of cardiac arrhythmia, two levels can be distinguished: a cellular and a tissue level (Figure 1).

Mechanisms acting at the cellular level comprise automaticity and triggered activity. The latter has been shown to be related to afterdepolarizations in the membrane potential. However, reentry-based arrhythmia is generated at the tissue level. It is observed most frequently and, therefore, it represents the main topic of this study. Yet, as found in experiments, afterdepolarizations can be decisively involved in the reentry process.

Understanding these mechanisms is essential for successful antitachycardia therapy management. Therefore, the main mechanisms of arrhythmogenesis will be discussed in the following with an emphasis on triggered activity and reentry-based tachycardia.

Automaticity

Automaticity is the ability to generate a spontaneous action potential. All cardiac cells can display this property, but, in a normal heart, most do not. Depending on the location within the heart, therefore, automaticity may be classified as either normal or abnormal.

Cardiac cells with normal automaticity are called pacemaker cells. The dominant pacemaker of the heart is normally the sinus node, but there also exist cells capable of spontaneous diastolic depolarization, such as specialized fibers of the atria, AV junction, and the His-Purkinje system. These secondary pacemakers lie dormant (latent) until the sinus node activity is removed, allowing the latent pacemaker's rhythm to become visible.

A clinical example of abnormal automaticity is accelerated idioventricular rhythm caused by Purkinje cells in an ischemic region after a myocardial infarction. In this arrhythmia, normally quiet Purkinje fibers in the damaged heart muscle suddenly assume control of the heartbeat. Loss of K and uptake of Na (Ca, H and water accumulate as well) within the ischemic cell result in a reduced membrane potential, which can lead to automaticity. However, this arrhythmia caused by abnormal automaticity will not be visible unless the rate of the abnormal focus is greater than that of the dominant pacemaker.

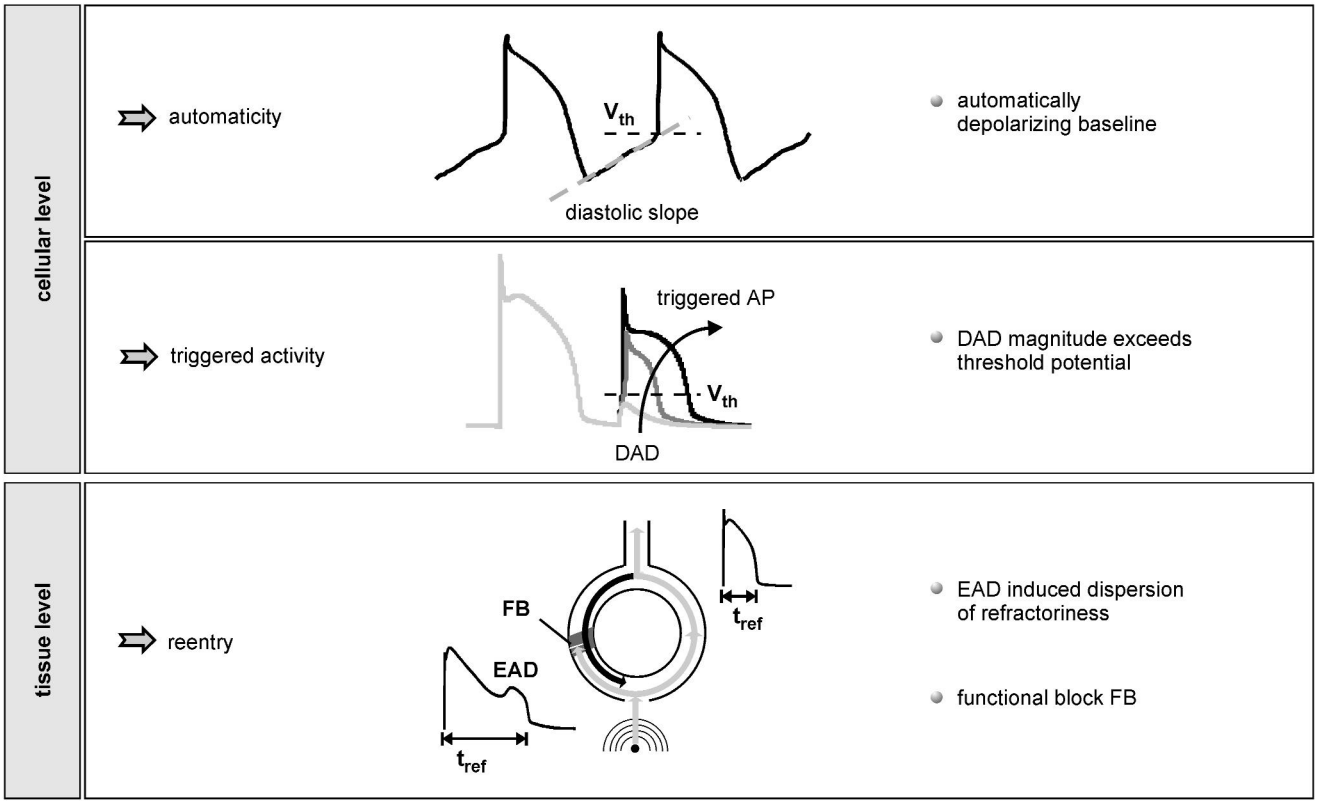

Figure 1. Action levels of cardiac arrhythmogenic mechanisms.

Clinical Evidence of EAD-triggered Arrhythmia

Triggered rhythms are known to be caused by afterdepolarizations, which are oscillations in the membrane potential following an action potential. One mechanism by which triggered activity causes arrhythmia is observed when the afterdepolarization (of either type) is large enough to reach the threshold potential. The resulting action potential is called a triggered action potential. An arrhythmia is induced when impulse initiation shifts from the sinus node to the triggered focus. For this to happen, the rate of triggered impulses must be faster than the rate of the sinus node.

The importance of afterdepolarizations for arrhythmogenesis, however, is also due to a second mechanism that is related to electrophysiological inhomogeneity within the tissue. When EADs occur (predominantly a local phenomenon), the significantly prolonged action potentials give rise to a pronounced dispersion of refractoriness. Therefore, the pathologically changed substrate will alter the normal impulse propagation pattern in a way that the excitation waves may re-excite the tissue. When additional impulses are triggered by delayed afterdepolarizations (DAD) occurring during the vulnerable phase, cardiac activity is likely to become arrhythmic.

Early afterdepolarizations can occur in almost any type of cardiac cell but have been mainly studied in Purkinje fibers and ventricular muscle cells. Early afterdepolarizations often arise from the plateau of an action potential but can also be observed during the rapid repolarization of phase 3 (Figure 2).

The relationship between EADs and cardiac arrhythmia was observed and experimentally proven in electrophysiological studies while recording endocardial and epicardial monophasic action potentials (MAP) synchronously with the ECG signal [1]. Studies have demonstrated that arrhythmias resembling torsade de pointes are induced by agents known also to induce EADs. Therefore, it was hypothesized that naturally occurring torsade de pointes may be caused by EADs [7]. Drugs that prolong the duration of Purkinje-fiber action potentials, such as sotalol and quinidine, were shown to induce EADs and triggered activity. Both drugs block the re-polarizing K current, so the arrhythmia associated with their use may also result from EADs [20].

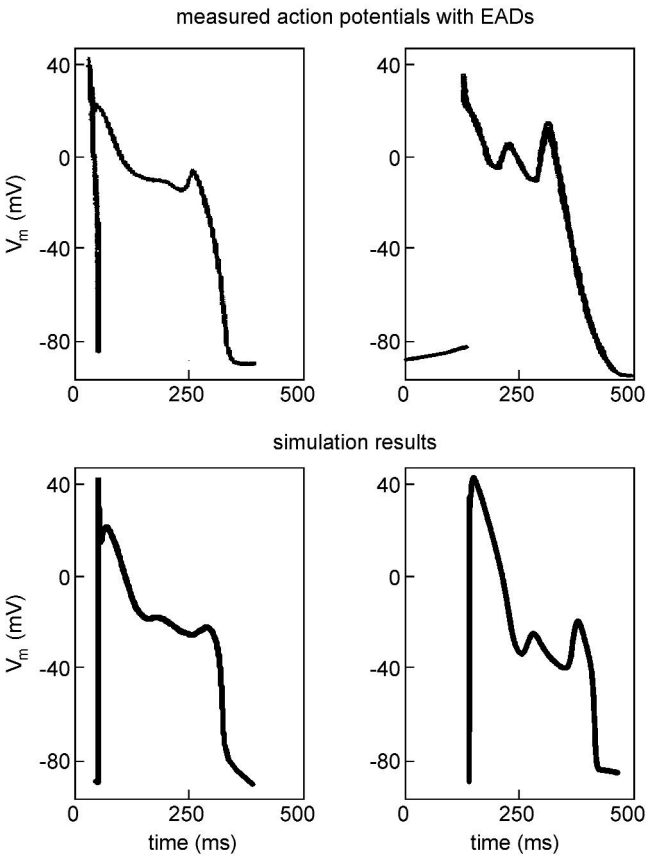

Figure 2. Morphologies of cardiac action potentials with EADs. Comparison of measured [1] and simulated curves [23].

EADs and triggered activity have been produced experimentally under a variety of conditions, most causing marked delays in the repolarization of cardiac cells. Slow heart rate and drug toxicity are two examples [4]. Agents that increase inward current components or decrease outward currents resulted in conditions favorable for EAD generation [25].

Slowed Conduction, Reentry and Unidirectional Block

Aside from defects in impulse formation, abnormalities of impulse conduction represent a second main mechanism of arrhythmogenesis.

As known from experimental studies, conduction delay plays a large role in tachycardia caused by reentry [21]. If extreme delay occurs, the excitation wave is going to be blocked. The block may be bi-directional or unidirectional, the latter being closely tied to the phenomenon of reentry.

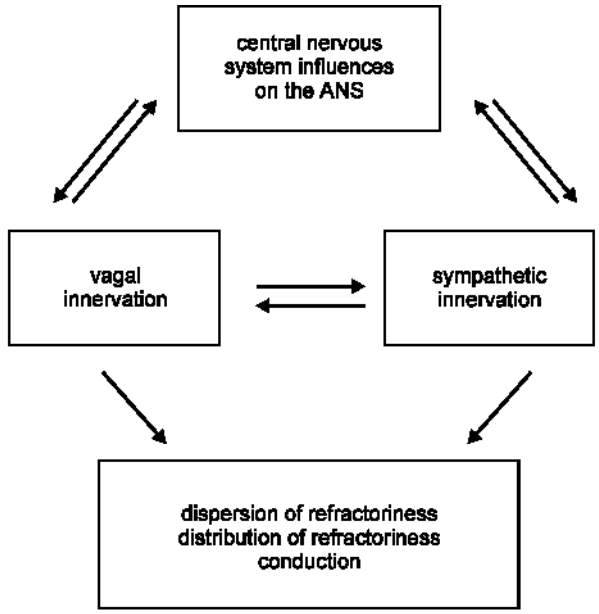

Figure 3. Schematic representation of ANS regulation of atrial electrophysiological properties. Modulation of refractoriness and conduction is not only a dynamic but also a continuous process. Additionally, the vagal-sympathetic balance changes continuously.

Among several causes of slow conduction that may lead to arrhythmias, the following are of main importance [21]:

- changes in membrane current,
- changes in the cable properties of the cell, and
- changes in gap junction resistance.

Normally, the action potential from the sinus node dies out after orderly depolarization of the atria, AV conduction system, and the ventricles. Usually, the impulse does not conduct backwards because the tissue just stimulated is refractory.

Reentry occurs when the action potential does not die out but continues to propagate and reactivate the heart. Almost every clinically important tachyarrhythmia is due to reentry [20]. Reentry can occur almost anywhere in the heart and can assume many sizes and shapes. Experimentally it was first demonstrated in 1906 by Mayer in the excitable ring of a jellyfish [20].

Impacts of the Autonomic Nervous System on Cardiac Arrhythmia

Though the heart has its own control mechanisms, it is additionally controlled by the autonomic nervous sys-

tem (ANS), which constitutes a bridge closing the control loop of the circulatory system.

Because of a variable concentration of nerve endings in the atrial tissue, the effects of vagal stimulation are not uniform across the muscle [6]. Experiments showed that dispersion of refractoriness is increased in the atrium by stimulating vagal nerves. On the other hand, the influence of sympathetic nerves in the atrium is less pronounced than that of the vagus, which is due to the opposite effects of alpha- and beta-receptors on atrial refractoriness.

Summarizing the results of electrophysiological investigations, it can be stated that [6]:

- The ANS may induce less homogeneous behavior of intra-atrial conduction and may change the distribution of refractoriness.
- Vagus and sympathetic nerves may influence each other.
- Vagal and sympathetic effects appear at different times.

All the aforementioned findings stress that the impacts of the ANS on atrial electrophysiological properties are very complex in clinical settings (Figure 3).

Changes in refractoriness may also be caused by other effects that are only mediated by the ANS. It was found experimentally that atrial distension (stretching) is reflected by changes in refractoriness [5]. Distension induces a reflex increase of sympathetic tone that acts inhomogeneously as suggested by pressure measurements performed in both atrial chambers, thus producing an increased dispersion of refractoriness.

Even age should be considered when evaluating the effects of the ANS. Age is linked not only to refractoriness and its dispersion but also to vagal-sympathetic balance [10].

Methods

In order to guarantee accurate reproducibility, the study is performed using a mathematical model of the physical system that is the subject of the investigations. Compared to laboratory experiments, this procedure reveals two important advantages:

- First, when running a protocol several times, the system can be reset to absolutely the same initial conditions. This requirement can never be met during electrophysiological measurements because two individual cells will not necessary behave in the same manner, and even if the same cell is re-used, it will be differently preconditioned by the previous experiment.
- The second and most important advantage is that the construction of the model helps to understand the underlying mechanisms and furthermore, allows tracing inner system variables that are not accessible during electrophysiological measurements.

Model-based Investigation of Cardiac Arrhythmia

Investigating the mechanisms of cardiac arrhythmia, the study is performed in two steps. Microscopic phenomena are investigated at the cellular level, whereas a model description at tissue level is performed to analyze the macroscopic processes.

Arrhythmogenic Mechanisms at the Cellular Level

Since clinical investigations have shown that EADs are mainly involved in arrhythmogenic mechanisms, a detailed analysis of EAD generation was performed using a computer model of cardiac cells. Its basic structure is in accordance with the approaches for modeling cardiac action potentials as postulated by Beeler-Reuter [3] and Luo-Rudy [12]. Moreover, the model is properly designed to take into account the pathological characteristics of EAD-threatened cells [22][23].

In order to validate the hypothesis of EAD generation systematically, the model consists only of elements which are strictly required by the emphasized mechanism descriptions. Therefore, the sarcoplasmic reticulum (SR) is explicitly not considered in this model to demonstrate that calcium overload-induced calcium release from the junctional SR is not necessarily involved in the generation mechanism of EADs.

To induce EADs in the model, the activating and inactivating characteristics of the calcium L-type channel and the dynamic potassium channel were fitted to electrophysiological measurements (Figure 4). Regarding the calcium L-type channel, the increasing concentration of isoproterenol enhances the channel permeability [18]. Assuming that g_{Ca0} is the conductivity of the calcium L-type channel for normal action potentials, the ratio $g_{Ca/gCa0}$ is a measure for the strength of adrenergic stimulation. The values of this ratio differ for various cell types and are within a range of 1.5-8 [26].

Moreover, experimental findings have shown that the activation and inactivation properties of the calcium L-type channel are also affected by isoproterenol. In [14],

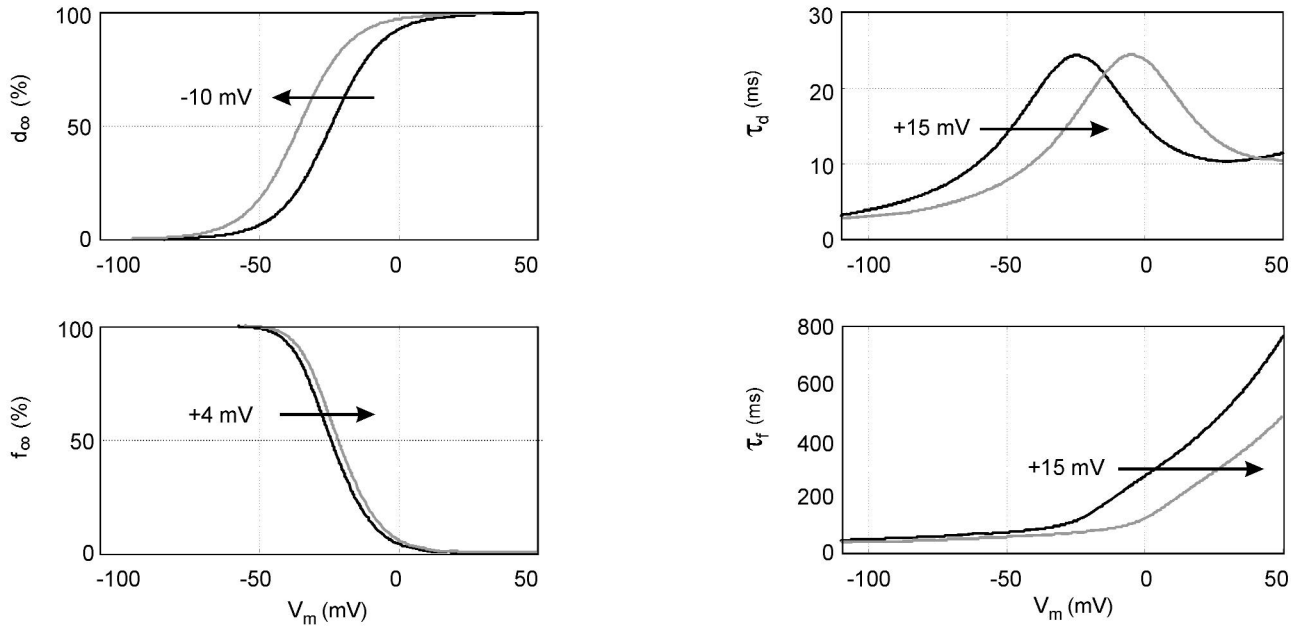

Figure 4. Impacts of isoproterenol on the activating and inactivating characteristics of the calcium L-type channel.

an isoproterenol-induced shift of the activating and inactivating characteristics is described, which is depicted in Figure 4. However, this fact is neglected in [26], 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) favors the appearance of a calcium window. Thus, the calcium L-type channel can be re-opened during the repolarization phase. 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 [17], 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 present knowledge about the cardiac potassium channels, ß-adrenergic stimulation enhances the conductivity of the dynamic potassium channel, whereas the non-dynamic one is not affected [16][19]. However, quantitative descriptions could not yet be found in the literature. Comparing measured and simulated events showing EADs (see Figure 2), it was concluded that the conductivity of the dynamic potassium channel must increase by about 25% in the presence of isoproterenol.

An isoproterenol-induced shifting of the activating characteristic was observed as well. Based on measurements performed in [8] and [11], a shift by 15 mV in the negative direction of the $x_\infty(V_m)$ curve is considered in the model. 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 Figure 2).

According to these findings, isoproterenol will induce functional changes that alter the coordination of the d-, f- and x-gates. If a certain value of the transmembrane potential is reached during the ongoing repolarization, an inflection point appears in the course of the transmembrane potential after which the action potential becomes flatter. The repolarization is nearly completely stopped. An intermediate plateau is formed, which has the same effect as if the transmembrane potential had been clamped on a fixed value VK. 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 (Figure 5). 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

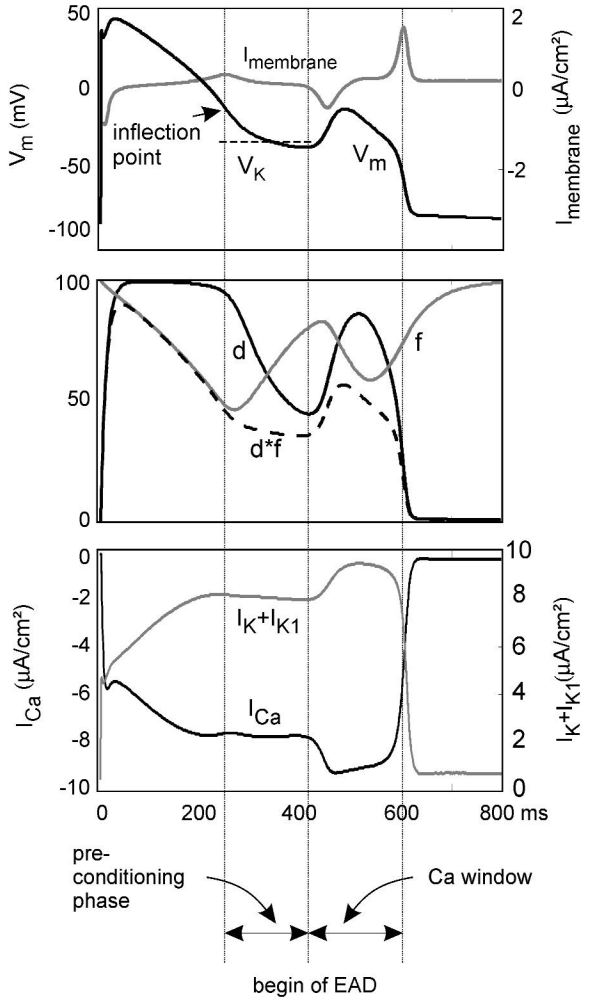

Figure 5. The mechanism of EAD generation. Preconditioning phase and calcium window.

small change of the transmembrane potential can tilt the time course of the d-variable towards an increasing trend, re-opening the calcium channel.

A slight disturbance of the current equilibrium (Ca/K) towards a small net inward current will now be able to trigger a new membrane depolarization. The d-gating variable continues to increase, opening a so-called calcium window. The resulting inward calcium current itself accelerates the depolarization process, acting as a positive feedback. The rapidly increasing transmembrane potential makes the f-gate close again and stops the avalanche-like opening of calcium channels. A new repolarization phase starts closing the calcium window.

Arrhythmogenic Mechanisms at the Tissue Level

In order to investigate the impacts of EADs on the propagation phenomenon, a model of one-dimensional action potential propagation was designed (Figure 6). The fiber is to be built of a chain of cylindrical membrane slices, each is 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 were shown to reduce the propagation velocity if their resistance was increased. A detail of the equivalent electrical network to be analyzed is depicted in Figure 7.

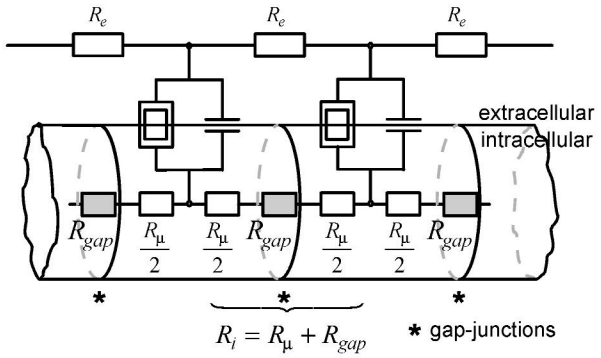

Figure 6. Model of the cardiac muscle fiber. The double-outlined rectangle represents the model of ionic channels. Rm is the myoplasm resistance.

The transmembrane potentials for each of the membrane slices are computed based on a coupled differential equation system (discrete cable equation):

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

where

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

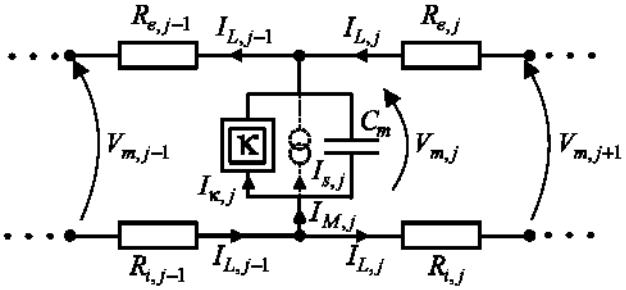

Figure 7. Network elements of the fiber model and definition of current flow directions.

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

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

The geometrical cell dimensions are $\lambda = 10^{-2}$ cm and $r_0 = 10^{-3}$ 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 for 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. 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, such as ischemic regions, gap junctions are known to close, disconnecting the cells electrically. The model could demonstrate that an increase of the gap junction resistance reduces the velocity of action potential propagation. The propagation velocity is modulated by the ratio:

$$\frac{R_i}{R_\mu} = 1 + \frac{R_{gap}}{R_\mu} \tag{4}$$

Frequently reentry-based arrhythmia is observed when regions of the myocardium are temporary or persistently not excitable. For example, an infarcted zone or an operation scar is considered in this study (Figure 8). 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 9), according to the experimental setting used in Mayer's experiment.

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).

Simulation Results

Based on the electrophysiological findings, the computer model for the normal action potential is modified and employed to simulate pathological behavior. As demonstrated by electrophysiological investigations, EADs are correlated to the presence of ß-adrenergic agents like isoproterenol, which act comparable to the sympathetic transmitter agent in vivo. However, EADs are known to trigger arrhythmia. Therefore, it is of particular interest to investigate and elucidate these connections.

In Figure 10, various simulated events showing EADs are presented. Depending on the strength of the adrenergic stimulation, one or multiple EADs may appear. In this model study, isoproterenol is considered to be the ß-adrenergic agent. Actually, isoproterenol is detected by specific receptors of the cell membrane and has a share in various mechanisms. The model study showed

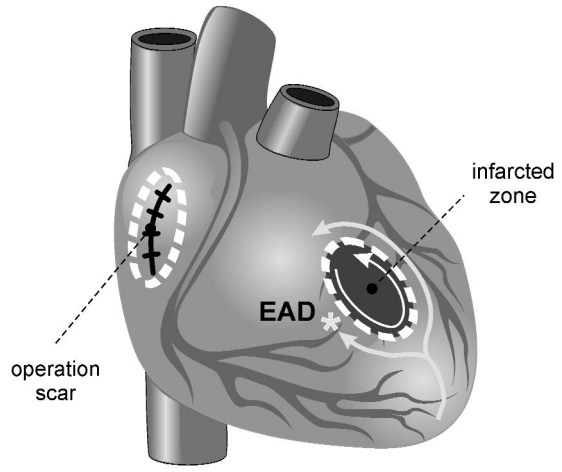

Figure 8. Potential anatomic and functional reentry pathways.

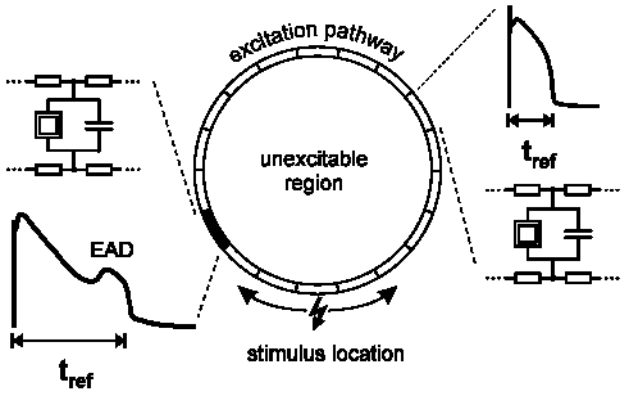

Figure 9. Design of the ring model. EADs are induced within a small segment of the ring-shaped fiber.

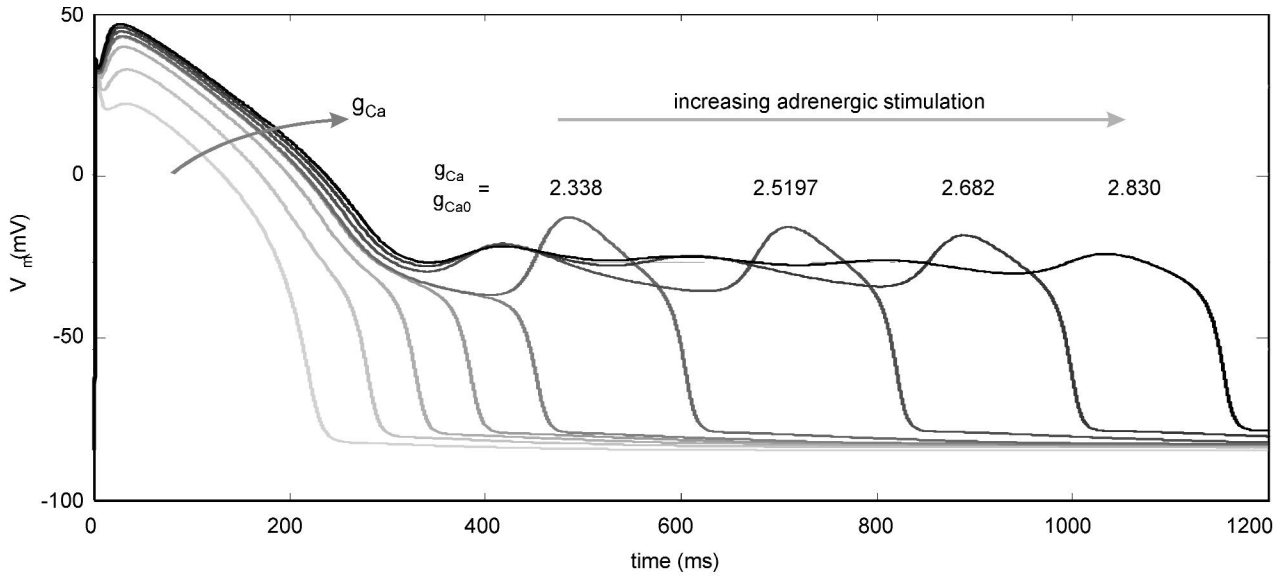

Figure 10. Morphologies of simulated action potentials with EADs. The number and the shape of EADs depend on the strength of ß-adrenergic stimulation.

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.

Simulation of Cardiac Reentry

In the reentry model, EADs were generated by assuming that the ß-adrenergic stimulation increased the Ca channel conductivity 3.33-fold. Figure 9 indicates where EADs were induced. The fiber is stimulated as shown in Figure 11 a (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 extinguish each other. Afterwards, both the left and the right branch repolarize symmetrically (Figure 11 a). The corresponding time course of this process is displayed in Figure 12.

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 11 b). 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 11 c). The excitation propagates normally in the other branch, but it has a longer way to cover and arrives at the opposite side of the cells affected by EADs. Meanwhile these cells have become fully or almost fully repolarized (see arrow in Figure 11 d 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 only possible 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 $R_{gap} = 8*R_m$. The action potential wavelength corresponding to the APD_{90} parameter resulted as 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

The study presents an overview of the hypotheses stated in literature concerning the generation mechanisms

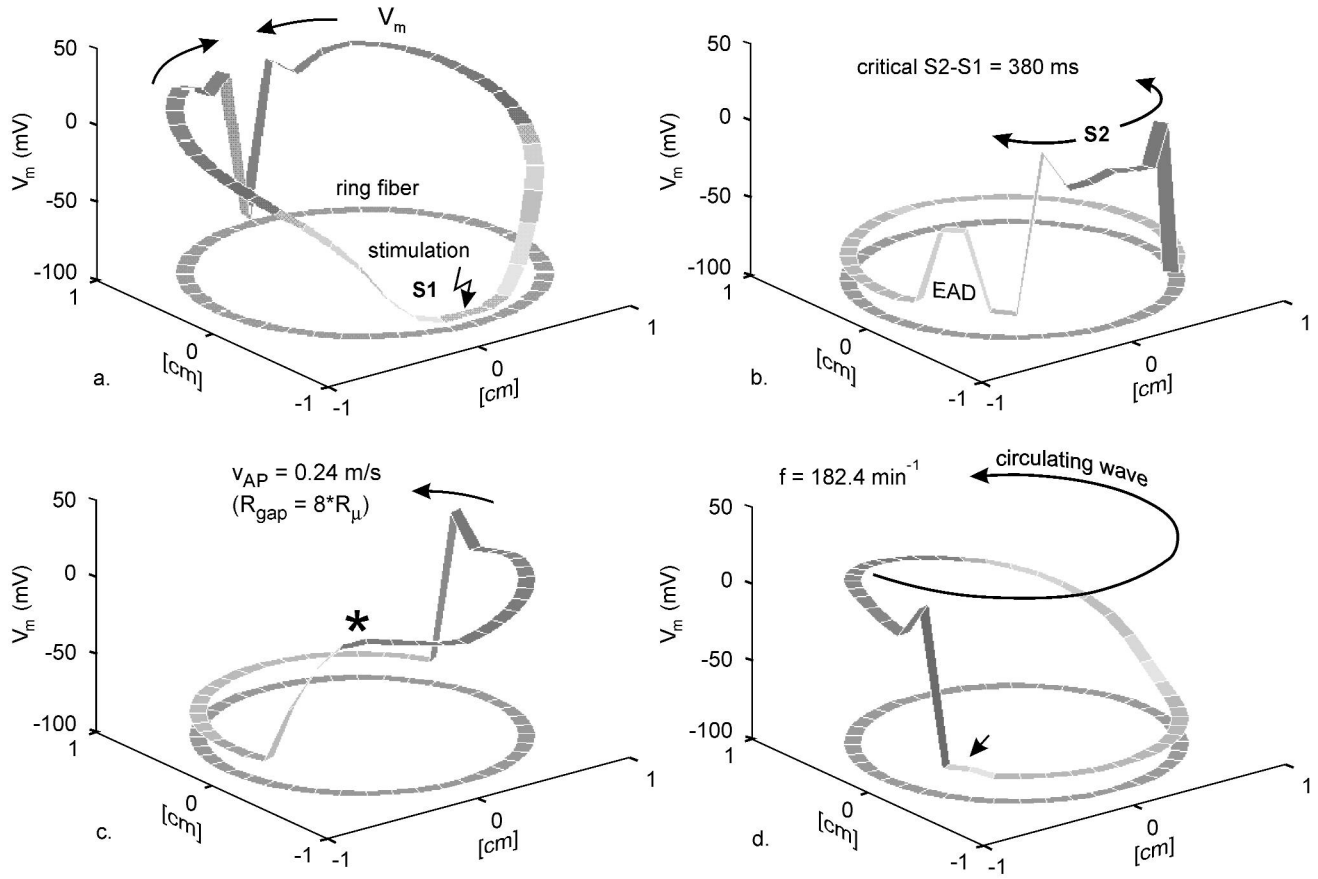

Figure 11. Simulation results of cardiac reentry. Spatial distribution of the transmembrane potential.

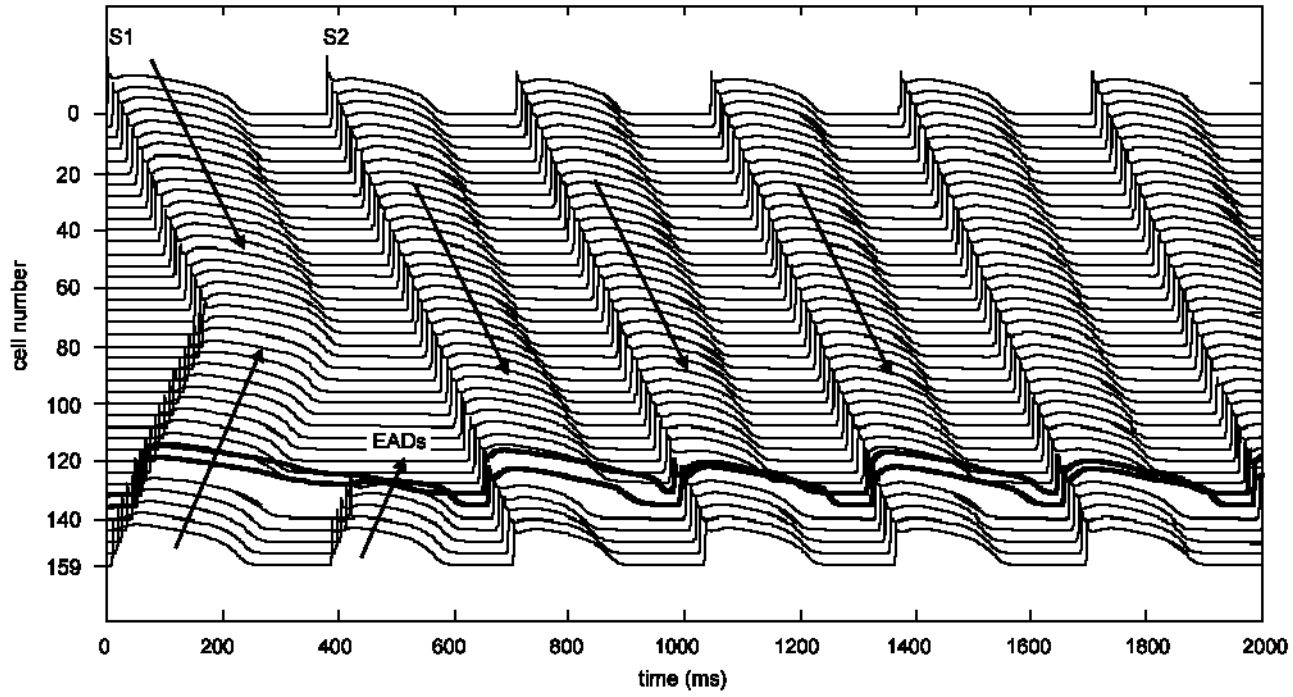

Figure 12. Time course of the simulated reentry process.

of cardiac arrhythmia with an emphasis on the contribution of EADs to arrhythmogenesis. To test and validate these assumptions, a properly designed computer model was developed and used to simulate cardiac action potentials in isolated cells as well as in cardiac tissue.

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 agent causing the EAD.
- EAD generation neither requires an increased intracellular calcium concentration nor a calcium release from the SR.
- EADs are favored by low stimulation rates and are abolished by high stimulation rates.

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. In general, the following prerequisites have to be satisfied [21]:

- Reentry requires a suitable region of heart with electrical characteristics capable of supporting reentry. Additionally, for random reentry, the path must contain a critical mass of cardiac tissue to sustain the several simultaneously circulating reentrant wavefronts.
- The excitation wavefront must encounter unidirectional block. In order for the unidirectional block to occur, a premature impulse must arise in a region with a short effective refractory period so that it occurs before the action potentials in one of the pathways have repolarized.
- The activation wave must be able to circulate around a central area of block.
- Tissue initially activated must have sufficient time to recover excitability. There must always be a gap of excitable (either fully or partially) tissue ahead of the circulating wave.
- Reentry requires an initiating trigger which brings one or more of the conditions to a critical state. The trigger beat may be unrelated to the reentrant tachycardia and may occur by any mechanism (e.g. due to DADs).
- Regional differences in refractory period may cause conduction of an appropriately timed premature impulse to be blocked in the region with the longest refractory period.

Stable reentry, however, is achieved only if the recovery wavelength is less than the circumference of the ring. This fundamental finding revealed by both experimental and model studies led to the so-called wavelength concept underlying the theory of cardiac fibrillation.

Outcomes for Antitachycardia Electrotherapy

Recent observations of AF demonstrated that such an excitable gap actually does exist while the model study has revealed its importance for the stability of reentrant circuits. These findings give evidence that if reentry persists, an excitable gap has also to exist. That means that antitachycardia pacing within this gap enables control of reentry. The discussion of tachycardia theory pertains to the underlying mechanisms of those arrhythmia deemed treatable by antitachycardia pacing. Factors influencing termination success by antitachycardia pacing include [15]:

- the refractory period and conduction velocity of the stimulation site, reentrant circuit, and intervening myocardium,
- the number of entry routes into the reentrant circuit,
- the relative locations of the stimulation site and the circuit,
- the rate of the tachycardia,
- stimulus pulse timing and number,
- pharmacological factors, and
- the disease process or substrate.

Among these influencing factors, clinical studies have established three antitachycardia pacemaker parameters as being most important for successful termination. These are:

- the number of stimulation pulses,
- the stimulation pulse timing, and
- the site of stimulation.

Determining the optimal number of pulse stimuli is the first step towards termination success. In some tachycardias, two or more stimuli are often more effective than a single stimulus. The first pulse compresses the length of the refractory tissue in the reentrant circuit when it collides with and slows the encircling wave momentarily. The resultant wider excitable gap allows the second pulsed wave to reach the reentrant circuit early enough to fully interrupt the circulating wave.

The most important clinical parameter for determining tachycardia termination success is the site of stimulation. Studies have shown that reentrant circuits can be terminated by fewer pulses when the stimulation site is located in the normal myocardial tissue proximal to the slow conduction zone [9]. The optimal site for success would be the ischemic zone itself, close to the proximal side of the slow zone. However, here the tissue excitability may be reduced due to the ischemia and, thus, a higher stimulation current would be required.
Noninvasive techniques for determining the precise location of a reentrant circuit, particularly its slow zone of reentry and the direction of the wave front in this zone, are topics of future research. Though restrictions on mapping reentrant circuits currently still exist in clinical practice, the outcomes of both experimental and model studies should be emphasized because they are yielding strategies to be pursued for successful antiarrhythmic therapy.

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