Ischemic Modulation of Vulnerable Period and the Effects of Pharmacological Treatment of Ischemia Induced Arrhythmias. Simulation Study

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Abstract-- **First identified in the '30s [1][2], the concept of vulnerability applies perfectly to biological oscillators. We can safely say that vulnerability is an inherent property of any excitable media. The duration of vulnerable period (the time interval during which single stimuli can initiate self-sustaining propagation) is sensitive to medium properties and stimulus parameters (stimulus field, timing behind the conditioning wave and stimulus amplitude). Apart from medium properties and stimulus characteristics, heart vulnerability is affected by any intervention targeting the excitatory and recovery process. Therefore we can expect that any pathological condition disturbing heart excitation or tissue recovery will most probably alter the duration of vulnerable period (VP). In this paper we shall explore the implications of ischemia and one of the arrhythmia counteracting methods widely used in clinical practice - antiarrhythmic drugs - in changing the boundaries of VP.**

The Cardiac Arrhythmia Suppression Trial (CAST) studies, as well as classification based on functional characteristics, revealed the arrhythmogenic potential of both class I and class III agents, but failed to identify the proarrhythmic mechanisms. This study presents results from a mathematical model [3] of the ventricle based on Luo-Rudy cellular formulation [4] modified for studying the ischemic modulation of vulnerable period and the effects of pharmacological treatment of ischemia-induced arrhythmia. Simulations revealed the link between the cellular antiarrhythmic properties and the proarrhythmic effect at the multicellular level in the case of Na^+ channel blockade. Na^+ channel blockade delayed recovery of cellular excitability, but also introduced a non-uniform dispersion of refractoriness along the cardiac fiber that can serve as a substrate for initiating a new arrhythmia. Our initial analysis proved that fast unbinding rates are essential in reducing the proarrhythmic potential of class I drugs. However, further investigations led us to believe that binding properties are equally important. An antiarrhythmic drug with high affinity for drug-channel complex formation elicits a higher level of blockade per time unit. Under this light we hypothesize that even the modern, fast unbinding drugs are not necessarily safe.

Index terms-- antiarrhythmic drugs, sodium blockade, ischemia, vulnerable period, reentry.

I. Introduction

PROLONGATION of cardiac vulnerability - a time window during which single stimuli elicit self-sustaining propagation - is the precursor of serious, life-threatening arrhythmias. The CAST studies [5][6] have demonstrated that post infarction patients display an increased risk of sudden cardiac death after using drugs with Na^+ channel blocking properties. The main problem resides in the initial classification of antiarrhythmic drugs, primarily based on their effects on electrophysiological characteristics of isolated, normal cardiac cells. Multicellular analysis and/or diseased conditions where arrhythmias are likely to occur were ignored, in part for pure practical reasons, from the classification procedures. Simply put, the catastrophic clinical results where nothing short than the display of lack of knowledge about the whole palette of drug action. As a result the antiarrhythmic drugs remain one of the most controversial pharmacological treatment in the medicine of our days.

In the last years technology offered an alternative to medication in the form of advanced implantable devices for sensing, identifying and control cardiac rhythm disorders. Although these advances paralleled the accumulating evidence of proarrhythmic potential of antiarrhythmic drugs, the clinical practice did not abandon the pharmacological means in favor of electronic devices for certain reasons, in which maybe cost and intervention time play a significant role. The Antiarrhythmics vs. Implantable Defibrillators (AVID) Clinical Trial [7] showed that

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implantable devices not only stop arrhythmias and restore normal heart rhythm, but they also improve overall survival in patients with coronary disease. However, a recent experimental study [8] on vulnerable period has showed that electrical methods can induce themselves reentry, generating self-sustaining forms of arrhythmias. Both CAST studies made the medical community aware of proarrhythmic properties of class I drugs, but failed to give a clear explanation of the problem origin. Further more, tests were conducted only on post infarction patients ignoring the ones under ischemic attack or other pathologic conditions inducing arrhythmia. Or, it is known that acute coronary diseases are the basis for two types (type 1a and type 1b) [9] of dangerous ischemia-induced life-threatening arrhythmias. Without a clear understanding of the mechanisms, mortality and morbidity statistics don't help identifying the proper actions that should be taken for counteracting the phenomenon, eventually give directions for future drug development and avoid such problems in the future.

We present simulations of class I antiarrhythmics action under both normal and ischemic conditions trying to reveal the differences in drug effect when consider a pathological tissue. Binding and unbinding properties were taken into account to link drugs kinetics with their final effect on arrhythmia management. Our aim is to find out why that Na^+ channel blockers have a greater proarrhythmic than antiarrhythmic potential during normal and especially during coronary disease conditions, trying to explain the results of the CAST trials. We also explored drugs with faster kinetics in order to parallel their action with that of the "classical" drugs attempting to give an answer to the so much asked question: "Are the class I drugs in general any good?" We wanted to probe if the proarrhythmic potential of these drugs lies in the mechanism of action itself and if it has a plausible explanation.

II. METHODS

Antiarrhythmic drugs display a "use-dependent" behavior in that they bind only to specific channel configurations, a fact that demonstrates the transient availability of channels' binding site. When the channel is not in one of these configurations, the drug molecule simply escapes from the channel. Starmer [10] proposed a simple model of guarded access (instead of continuous access as with most ligand-receptor interactions) - the "guarded receptor hypothesis" that has been exhaustively validated in Na^+, Ca^{2+} and K^+ channels with a wide range of antiarrhythmic compounds. We used this approach to study the mechanism of Na^+ channel blockade on ventricular tissue.

Under normal conditions, channels flip between open and closed state according to the actual state of the membrane potential (voltage gating properties) and so the process can be described as:

$$Closed \underset{1-m}{\overset{\alpha_m}{\Leftrightarrow}} Open \quad \overset{\beta_m}{\ldots} \quad (1)$$

where m is the fraction of channels in open state, α_m and β_m are the switching rates and represent the voltage-gating variables of one particular channel. The activating process (channel opening) is thus described by the following first order equation:

$$\frac{dm}{dt} = \alpha_m (1-m) - \beta_m m \quad (2)$$

The same applies to the third cardiac channel status – inactivated state:

$$Activated \underset{1-h}{\overset{\alpha_h}{\Leftrightarrow}} Inactivated \quad \overset{\beta_h}{h} \quad (3)$$

described by:

$$\frac{dh}{dt} = \alpha_h (1-h) - \beta_h h \quad (4)$$

where h is the fraction of channels affected by inactivation (during refractory period).

When a drug binds to a channel it forms a drug-channel protein complex:

$$U + D \underset{l}{\overset{k}{\Leftrightarrow}} B \quad (5)$$

where U is the total number of unblocked channel, D is drug's concentration and B is the total number of blocked channels. This is a dynamic process described by the binding k and unbinding l rate constants of the drug involved [11][12]:

$$\frac{dB}{dt} = k \cdot U \cdot D - l \cdot B \quad (6)$$

Observing that $U + B = C$ is the total number of channels, the fraction of blocked channels, $b = B/C$, is expressed by the following equation:

$$\frac{db}{dt} = k \cdot D \cdot (1-b) - l \cdot b \quad (7)$$

The association between drug and channel protein is possible only when the channel finds itself in a certain conformation for a certain period of time. Most of the Na^+ blockers bind to channel protein during the third channel state – inactivation. Binding during active state is specific only to few drugs for this transition state has a very short duration and thus the binding site is available only for a fraction of time. In both cases channel blocker form a drug-channel complex unable to conduct, so pharmacological channel blockade mimic voltage dependent channel inactivation. Starting from the equation (7) the gated blockade model of inactivated sodium channels can be written as:

$$\frac{db}{dt} = k \cdot D \cdot (1-b) \cdot (1-h) \cdot (1-j) - l \cdot b \quad (8)$$

where h and j are the gating variables characterizing respectively fast and slow inactivation. Thus, during blockade only a fraction of channels will be able to respond to excitation and conduct current, so the net sodium current will be:

$$I_{Na} = g_{Na} \cdot m^3 \cdot h \cdot j \cdot (1-b) \cdot (V_m - V_{Na}) \quad (9)$$

where g_{Na} is the sodium channel specific conductance, m, h and j are channel's gating variables, b is the fraction of blocked channels, V_m is the membrane potential and V_{Na} is the sodium equilibrium potential.

A modified version of the Luo-Rudy phase I (LR I) cellular formulation with the guarded receptor model [10] was used as starting point in our analysis. Ischemic conditions were induced according to our model presented in [3]. The different phases of acute ischemia were simulated based on the time depend alteration of chemical parameters experimentally measured on canine hearts [13]. Hyperkalemia and hypoxia were induced by gradually increasing the extracellular potassium concentration according to the experimental data. Acidosis was simulated by its contribution to decreasing sodium and calcium channels specific conductance. Alterations of the gap-junction resistance were not considered for two reasons: first, during acute phase of ischemia cell uncoupling does not manifest yet [13] and second, we wanted to isolate drug-induced from pathologically induced conduction block in order to better evaluate antiarrhythmics action. Simulations were carried out in a modeled cardiac fiber with a radius of 7 microns, built of 200 ventricular cells interconnected by a 200 Ω·cm effective axial resistance r_j lumped at cell-to-cell junction and a specific membrane capacitance C_m of 1 μF/cm^2 [3], which in our analysis led to a normal propagation velocity of 50 cm/s:

$$C \cdot \frac{\partial V_m}{\partial t} = -I_{ionic} + I_{stim} + \frac{1}{R_j} \cdot \frac{\partial^2 V_m}{\partial x^2} \quad (10)$$

with

$$C = 2 \cdot \pi \cdot radius \cdot C_m$$

$$R_j = \frac{r_j}{\pi \cdot radius^2}$$

where C_m is cell's membrane capacitance, Rj is cable specific axial resistance, $radius$ is fiber's radius, I_{ionic} is the total ionic current flowing across the membrane and I_{stim} is the stimulation current. A –85 mV resting membrane potential was considered and the above cable equation was solved numerically using Crank-Nicholson implicit algorithm, taking a spatial integration step of 0.312 mm and a time integration step of 15.625 μs [14]. Although not so sensitive to time step changes, the differential equations describing cellular ionic currents involved in the model were also solved using implicit methods. This has contributed positively to obtaining a fast and stable algorithm.

Behind a depolarization wave traveling along a cardiac fiber the cells recover gradually their excitability (Fig. 1).

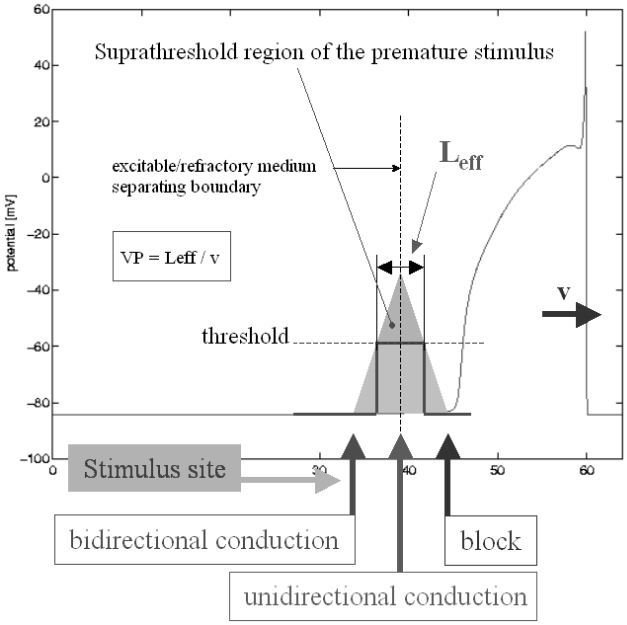


Fig. 1. Vulnerable period can be measured at the excitable-refractory separating boundary, behind a propagating depolarization wave. The vertical arrows show the location of the test stimulus. Abscissa represents the spatial axis along the simulated cardiac fiber (cell numbers).

At the cellular level the boundary separating excitable-unexcitable state is defined by the refractory period. In a multidimensional arrangement this boundary is moving together with the depolarization wave with a propagation velocity v. A test stimulus applied behind the repolarization wave will encounter this moving boundary between excitable/unexcitable medium, which will cross the stimulus field. The presence of a stimulus field (width) is imposed by the second threshold of activation at the tissue level called liminal length [15]. A successful propagation develops only when the stimulus amplitude is higher than the activation threshold and its suprathreshold field (L_{eff} in Fig. 1) exceeds the liminal length. If the stimulus amplitude excides the activation threshold several situations can be noted. The propagation patterns that might form are dependent only on the suprathreshold region of the stimulus field as only stimuli exciding the threshold can initiate a successful propagation. As long as the excitability boundary falls at the left of the suprathreshold region we will have no response as the stimulus is applied inside the unexcitable region (Fig. 8C). If the separating boundary finds itself totally at the right of the suprathreshold region of the stimulus the result will be bidirectional conduction (Fig. 8A) as the stimulus was in this case applied on a totally recovered region of the cardiac fiber. At last, if the stimulus is applied with such timing that the excitable/unexcitable separating boundary crosses its suprathreshold region, propagation will fail in the normal propagation direction because the tissue is refractory, but it will form a successfully propagating wave in the antegrade direction (Fig. 8B) where the tissue is at rest (recovered). This non-

symmetric propagation characterized by propagation block in one direction is the key factor in generating spiral waves in the cardiac tissue [16][17]. The time interval necessary for the separating boundary to cross the stimulus field (during which the result of stimulation will be unidirectional conduction) is called vulnerable period (VP). Obviously VP period is directly dependent on propagation velocity.

We employed a two stimulus protocol - first (s1) initiating the conditioning wave and second (s2) applied at the same location, but with variable delay behind s1 to explore the boundaries vulnerable period in the modeled cardiac fiber. A short (0.5 ms) conditioning stimulus of 480 $\mu A/cm^2$ current density was "injected" at one end of the cardiac fiber, while the second one was applied each time at the same location, somewhere inside the cable with different delays trailing the repolarization tail of the excitation wave. Chosen stimulus amplitude was determined to be the minimum current required to assure successful propagation under all simulated conditions (normal, ischemic, normal with drug and ischemic with drug). This was a necessity as VP is dependent on stimulus amplitude (Fig. 1) so, to have a proper base of comparison the same stimulus amplitude had to be kept for all conditions in order to avoid stimulus induced modulation of vulnerable window. The test stimulus was applied far enough from the cable boundaries to avoid reflection artifacts [18]. The above described stimulation protocol was modified to explore VP boundaries after sodium channel blockade [19]. Due to the use-dependent nature of most antiarrhythmics, a pulse train of 5 conditioning stimuli was delivered before the test stimulus (s2) in order to achieve steady state [20]. Different binding/unbinding rate constants were tested at different simulated heart rates in order to identify a possible relationship between the two parameters. Three cardiac cycle lengths were employed: 500 ms, 600 ms and 800 ms (normal heart rhythm). Measurements were taken at the cellular and cardiac fiber level in order to identify the link between the antiarrhythmic and proarrhythmic properties of the drug [21].

We considered in our simulations the following situations: normal heart with normal heart rate, drug injection at normal heart rate and drug injection at faster heart rate. The same set of simulations was then carried out on ischemic heart both in the absence and in the presence of the drug. At the cellular level we analyzed cell response, membrane potential first derivative, sodium current peak and the fraction of bound channels with periodic heart stimulation. After the steady state was reached we note the time and initiated the measurements of VP in the cardiac fiber.

After a cardiac cycle is initiated an extra stimulus can elicit a response only after at least the refractory period (RP) has passed. Out of the remaining time until the next normal cardiac excitation, an extra stimulus can induce dangerous unidirectional conduction only during the vulnerability window. Thus, we can define the likelihood of unidirectional conduction block (p_{ub}) as a ratio between the VP duration and the excitable interval ($cc - RP$):

$$p_{ub} = \frac{VP}{cc - RP} \quad (11)$$

where cc represents the cardiac cycle length. As unidirectional conduction block is one of the necessary conditions for initiating a spiral wave, we used relation (11) to evaluate the proarrhythmic potential of different drugs. However, the likelihood defined above should not be seen as reentry probability, as a spiral wave develops into reentry only if other additional requirements are met [17]. RP was determined at the single cell level with a test stimulus, with variable delay (increased in 1 ms steps) from the conditioning stimulation, trailing recovery foot of the action potential. We considered the cell having recovered its excitability when the response to the test stimulus displayed an upstroke crossing the 0 mV line.

III. Results

With periodic stimulation, drug binding follows an exponential time course between each heartbeat (piecewise exponential binding/unbinding) (Fig. 2) [10]. We probed the effect of drugs with different binding-unbinding properties on normal and ischemic myocardium in two different situations: at normal pacing (800 ms cardiac cycle) and at a slightly increased heart rate (500 ms cycle). We found that in normal heart a medium fast (hundreds of ms unbinding time constant) class I antiarrhythmic drug (Fig. 2a) will have mild effect on channel availability at physiological heart rate because during two successive stimulations it has enough time to unbind. However the suppressing efficiency (according to “traditional” classification) of these drugs seems to be poor as we can see by analyzing the sodium current evolution. In contrast, simulations revealed a strong use-dependence at higher heart rate (Fig. 2b). After the steady-state is reached, every one out of two heart beats is suppressed as the interval between two additional heart beats does not give enough time for the drug to completely unbind from the channel protein (Fig. 2b). The level of blockade is maintained for more than a cardiac cycle due to relatively slow unbinding, so the next stimulus finds the channels in inactivated state. Viewed strictly at the cellular level this is a strong antiarrhythmic effect that could convert a tachycardia into slow pacing. At higher heart rate even the very fast (tens of ms) unbinding sodium blocker (Fig. 3) displayed an increased use-dependent behavior, although fast unbinding (see the blockade level evolution) means poor suppression of the stimuli. Additionally to the use-dependent behavior of the drug, higher heart rate increases the availability of drug binding sites, promoting the formation of drug complexed channels [10] (Equation 8).

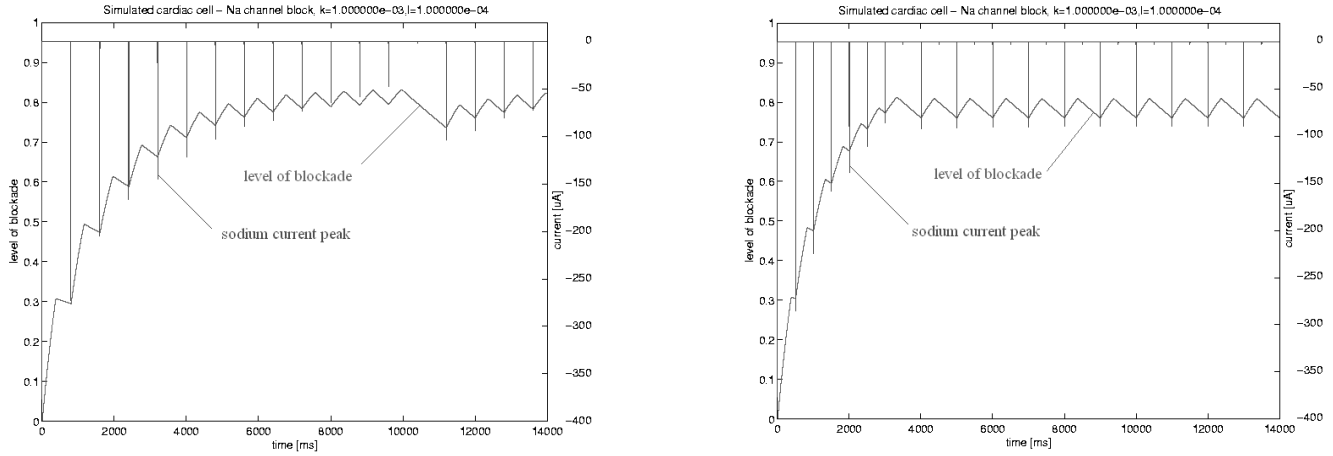
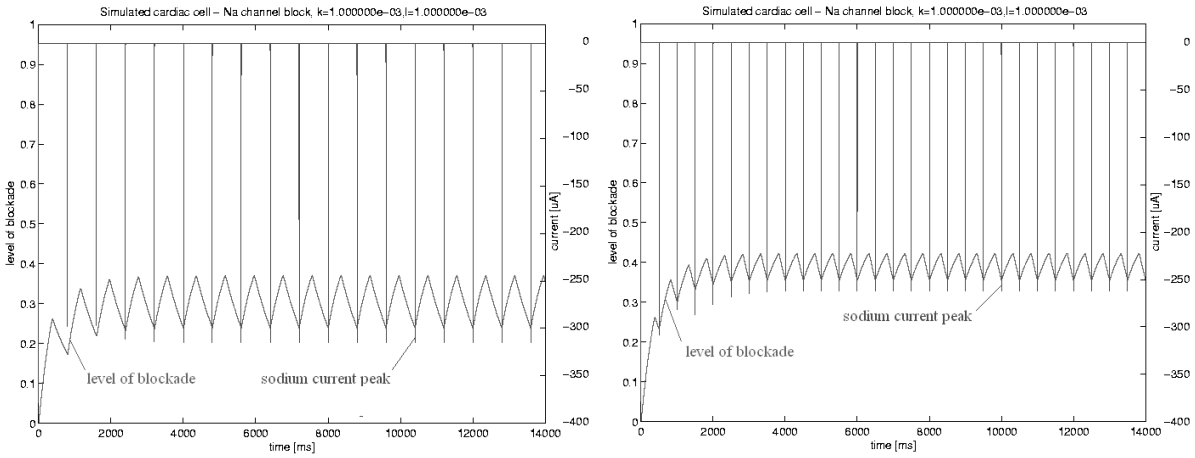


Fig. 2. The action of a reference Na^+ blocker at the cellular level (sodium current peak and fraction of blocked channels)

These results already anticipate what would happen after administering a slow unbinding blocker (Fig. 4). Our simulations revealed for the slow unbinding agent an almost complete block of the sodium channels after reaching the steady state (5 successive stimulations in our analysis). The blockade level (Fig. 4) shows that after binding the drug needs several cardiac cycles to free up the channels from inactivity, allowing recovery of excitability. As a result, during the slow unbinding process the cell is not able to respond to stimuli for several cardiac cycles (strong suppression effect). The effect on channels availability is so prominent that the cell looses almost completely its excitability, exactly the cellular action that led to class I drug classification as premature ventricular contractions (PVC) suppressors. Note that in all cases the drug dosing properties used in simulations were identical in order to have a common base of comparison. As the major trend after the CAST failure was to design drugs with faster kinetics [22], we were interested to analyze a drug that has fast binding-unbinding properties. Fig. 5 shows the results from our simulations of a drug with 50% faster binding time constant. Accelerated kinetics makes the drug-channel complex formation faster (binding requires significantly less time than unbinding – see the level of blockade in Fig. 5). Despite easy dissociation in between two additional stimulations, drug rebind very easy at the next cardiac cycle reducing channels availability in a similar manner with a slow unbinding drug, but by a slightly different mechanism. In case of slow unbinding drug there is little rebinding during a cardiac cycle because the slow time constant does not allow "freeing up" too many channels. The drug with faster kinetic escapes easily from the binding site, but its affinity for the channel protein makes it quickly reestablish the bound at the next cardiac cycle, keeping a mean blockade level similar with that imposed by a slow unbinding drug (Fig. 4 & 5). That's why we observed in this case a higher suppressing effect than the reference drug we used (Fig. 2 & 5).

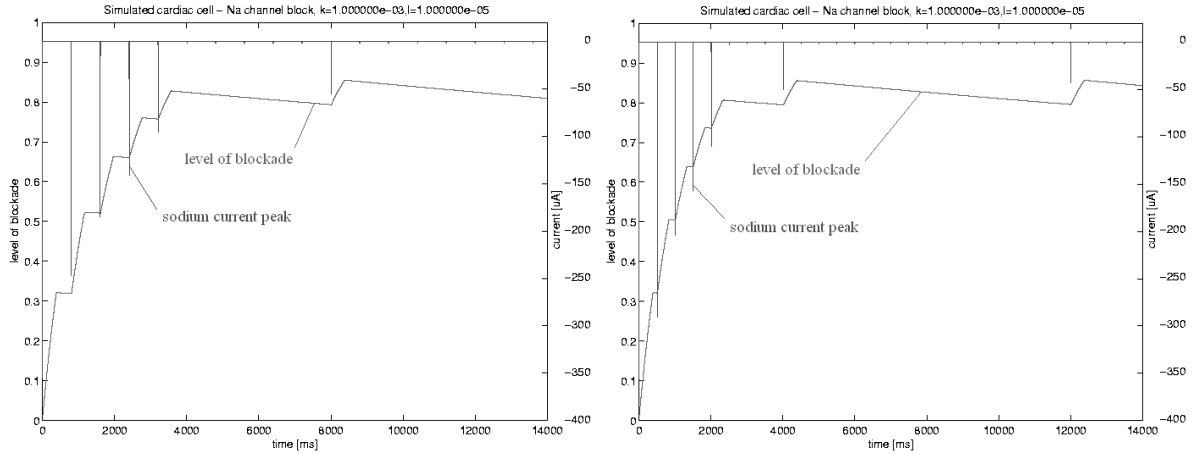
In all these cases we intentionally ignored the pathological conditions and we analyzed only the cellular effect as the initial classification scheme suggested. We expected a more prominent proarrhythmic effect in case of ischemic myocardium where the excitability is already largely reduced pathologically (Fig. 6 & 7). In order to probe this hypothesis we measured the VP in several different simulated situations: normal heart and after delivering a slow and a fast unbinding sodium blocker at normal and faster heart rhythm. Then we simulated different degrees of ischemia and rerun the test with the same settings. Using the stimulation protocol described in the methods section we determined the VP as the time interval during which a variable delay stimulus elicit a unidirectional conduction. In the absence of drug in simulated normal cardiac fiber we measured a 2 ms interval of vulnerability at a conduction velocity of 50 cm/s. At normal heart rate we found a slightly increased VP (5 ms) after administrating the reference, medium fast unbinding drug (Fig. 9). Faster heart rate (500ms cardiac cycle) extended VP to 9 ms, almost doubling the interval of vulnerability in comparison with normal heart rhythm. Simulations in case of slow unbinding drug delivery revealed a considerable extension of vulnerability. At normal heart rate we measured a VP of 12 ms, while at 500 ms heart cycle we found a value of 17 ms, almost 9 times higher than normal (Fig. 9). As the cellular analysis predicted, the fast binding drug, displaying similar blocking properties with the slow unbinding drug led in our measurements to a 13 ms VP at normal heart rhythm and 19 ms at 500 ms cardiac cycle.

Our model gives a 368 ms refractory period under normal conditions. At 800 ms cardiac cycle this means a 432 ms ($cc - RP$ in equation 11) interval during which the ventricle might respond to potential PVCs. Out of this interval only the VP leads to unidirectional conduction. So, in case of normal heart and in the absence of drug this means a probability of 0.0046 that a PVC randomly occurring during the excitable interval might induce reentry by unidirectional conduction block (or 1 out of about 200). This picture changes dramatically at high stimulation rate in the presence of the drug. For the last analyzed case of a fast



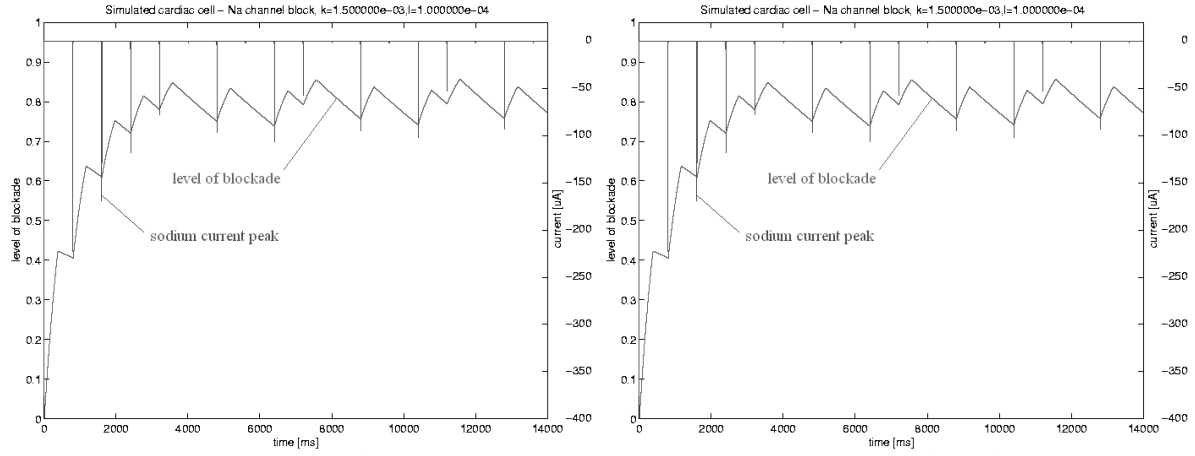
800 ms cardiac cycle 500 ms cardiac cycle

Fig. 3. The action of a fast unbinding sodium blocker at the cellular level (sodium current peak and fraction of blocked channels)



800 ms cardiac cycle 500 ms cardiac cycle

Fig. 4. The action of a slow unbinding sodium blocker at the cellular level (sodium current peak and fraction of blocked channels)



800 ms cardiac cycle 500 ms cardiac cycle

Fig. 5. The action of a fast binding sodium blocker at the cellular level (sodium current peak and fraction of blocked channels)

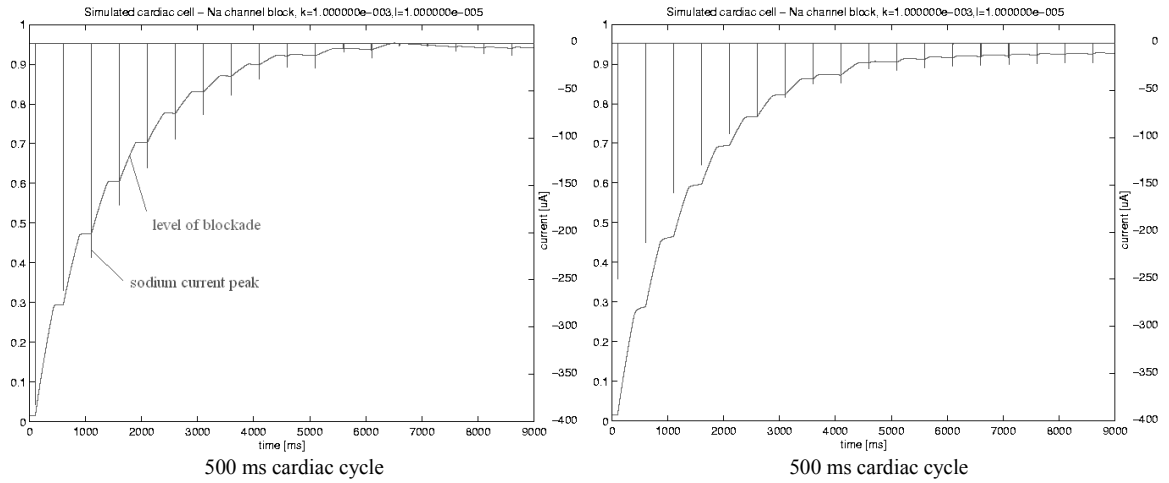


Fig. 6. Cellular action of a slow unbinding sodium blocker in suppressing ischemia induced tachycardia 5 min after the coronary attack (left) and 10 min after the coronary attack (right)

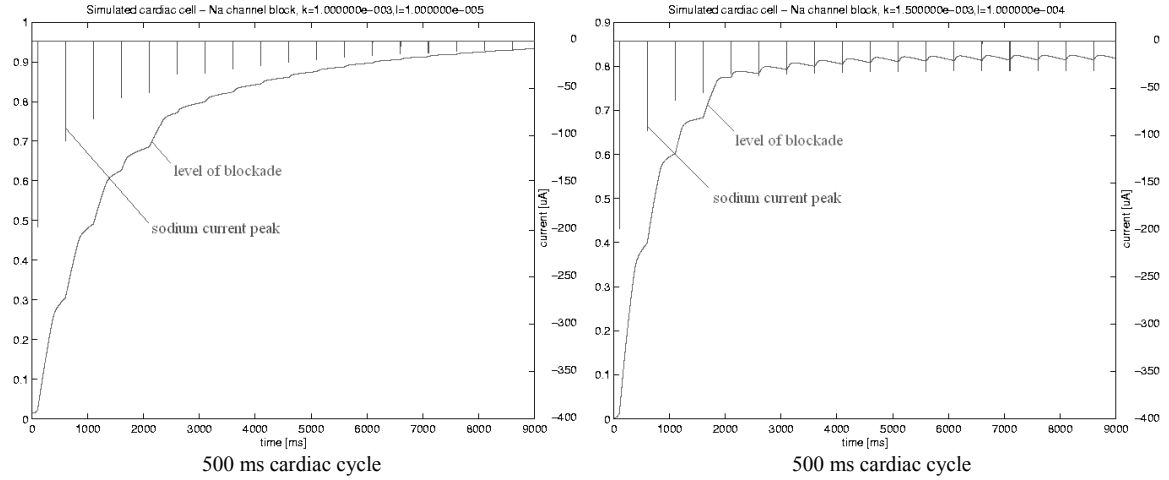


Fig. 7. Cellular action of a slow unbinding sodium blocker (left) and a fast binding drug (right) in suppressing ischemia-induced tachycardia (15 min after the coronary attack)

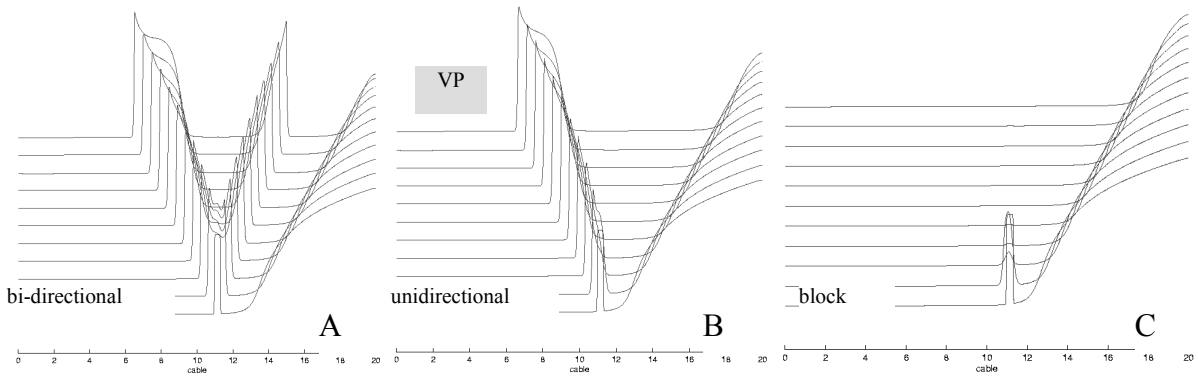


Fig. 8. The three types of propagation induced by a test stimulus trailing the repolarization behind a propagating wave (simulations performed under normal conditions, with no drugs; plotted every 15 ms)

binding drug at 500 ms cardiac cycle when VP is 19 ms long, the likelihood of inducing unidirectional conduction is 0.143. This means one out of about 7 PVCs could lead to conduction block.

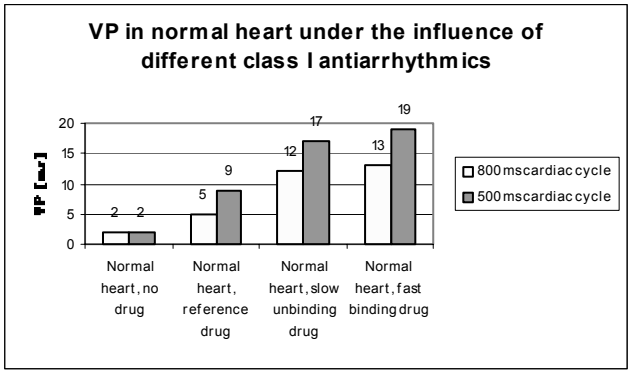


Fig. 9 Vulnerable period in normal heart, modulated by sodium blocking antiarrhythmics

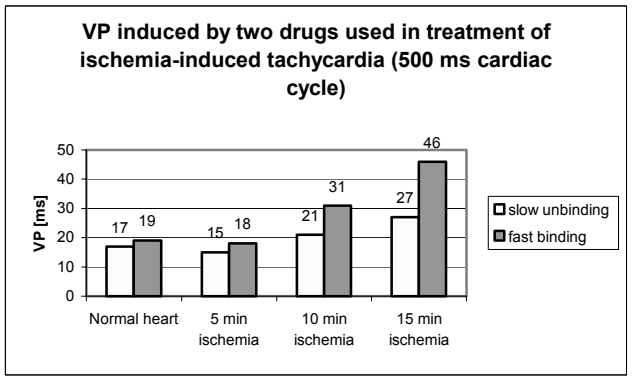


Fig. 10 Vulnerable period modulation in ischemic heart by two categories of sodium blockers

In all these estimations we assumed pure Na^+ blocking properties and non-pathologic myocardium. Any sodium channel blocker that additionally affects repolarization by increasing the refractory period (both class I and class III effect) without disturbing the heart rhythm, increases unidirectional conduction block probability by a double mechanism: VP extension and RP prolongation. During ischemia, cell excitability is gradually diminished and the tissue becomes unstable due to membrane depolarization [23][24]. At rest the cell membrane has an electrical potential closer to the activation threshold [25][26] and so the cell is more susceptible to auto-oscillation. This provides the tissue with an unstable substrate, which might be the source of randomly occurring PVCs. We analyzed the effects of sodium blockers on myocardium gradually affected by acute ischemia. In Fig. 10 are presented the effects of two drugs on vulnerable period, on a simulated ischemia-induced tachycardia (500 ms cardiac cycle) at different moments after the coronary occlusion. We based our simulations on the two drugs "tested" above on normal myocardium (a slow unbinding drug and a fast binding drug). After 5 minutes of continuous coronary occlusion an interesting phenomenon can be observed. The period of vulnerability is slightly decreased (from 17 ms to 15 ms in case of slow unbinding drug and from 19 ms to 18 ms in case of fast binding drug) due to transient hyperexcitability we described in our previous study [3]. This increase of excitability diminishes the apparent blocking potential of the drug. Vulnerability is largely increased as ischemia advances due to double (pathologic and pharmacological) mechanism of sodium current reduction. Ten minutes after the coronary occlusion the vulnerable period extends to 21 ms in the case of slow unbinding drug and to 31 ms in case of the fast binding one. At more advanced level of ischemia the VP values go to 27 ms and to 46 ms, respectively. These values alone suggest a large likelihood of reentry. But how large? In order to give a correct estimation we should take into account the refractory period at different levels of ischemia. Despite reduced action potential duration, cell refractoriness is extended in ischemic heart [3] [27]. In our model, after 10 min ischemia RP = 375 ms and after 15 min ischemia RP = 392 ms. A simple calculation gives a likelihood of reentry by unidirectional conduction block of 0.25 at advanced level of ischemia in case of slow unbinding drug and 0.42 in case of fast binding drug (Fig. 11). So, in case of an ischemia-induced tachycardia treated with sodium blocking antiarrhythmics 1 out of 4 randomly occurring PVCs may induce reentry in case of slow unbinding drug and almost 1 out of 2 in case of fast binding drug.

IV. Discussion and Conclusions

Taken together the two CAST studies pointed out that sodium blockers class antiarrhythmics increase rather than decrease mortality. However the two studies gave no hint about the underlying mechanism of these deaths although it became obvious that the adverse effect of class I antiarrhythmics is linked to the degree of slowing conduction [28], which is the basis for the expected PVC suppression. Also, the antiarrhythmics that made the subject of these studies were drugs displaying long dissociation time constants (10 - 20 seconds) like flecainide and moricizine from which one can easily expect proarrhythmic effects. The faster unbinding (hundreds of ms to seconds dissociation time constants) drugs effect is still a largely untouched subject. That's why even today these drugs are quite common in the clinical environment although the last 10 years have conducted to major safety concerns about their therapeutic use.

In this study we examined the link between the use-dependent properties of Na^+ channel antagonists and the proarrhythmic tendency at myocardium level. We showed that slow unbinding class I drugs, prolong the cardiac vulnerable period displaying strong proarrhythmic properties virtually at any heart rate. As a result, drugs like flecainidine (UTC = 21 s), disopyramide (UTC = 15.7 s) or moricizine (UTC = 17 s) [29] are almost total blockers of the Na^+ channel with most likely fatal influence on VP.

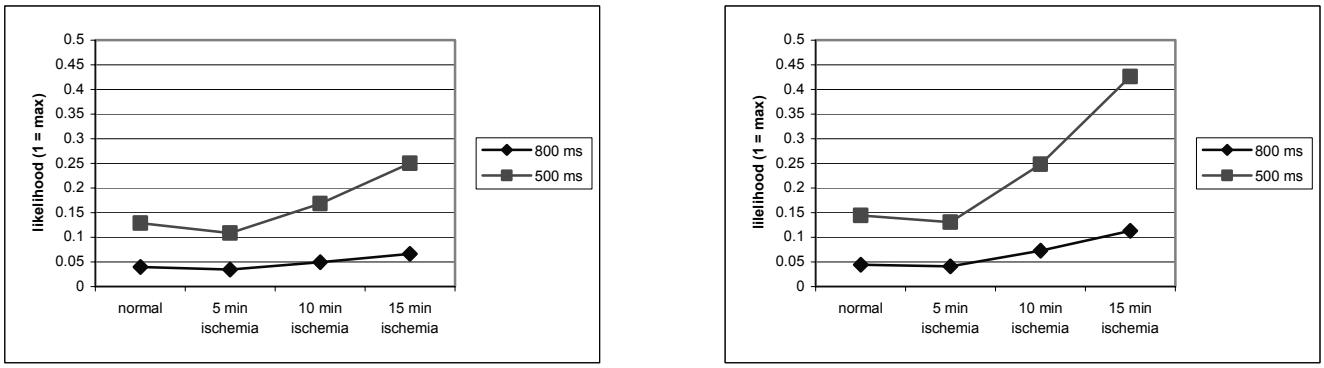


Fig. 11 Likelihood of reentry at different levels of ischemia, after administration of a slow unbinding drug (left) and a fast binding drug (right). The legend at right shows the cardiac cycle length used in simulations. The graphs show the contribution of both refractory period (affected by ischemia) and vulnerable period (modulated both pathologically and pharmacologically) in changing the likelihood of reentry

Cocaine for instance has a faster recovery time (8.5 s) and experimental results proved an increase in VP to 22 ± 12 ms [19], so we can expect a larger extension in case of the above drugs. In addition abused substances (like heroine and cocaine) block multiple types of channel and thus leading to uncontrollable effects. This "feature", however is not specific only to abused substances, most class I antiarrhythmic agents not being pure use-dependent Na^+ channel antagonists [29]. This is not always a negative property. A moderately slow unbinding drug, amiodarone (UTC = 1.6 s) which blocks also calcium channels can significantly reduce EADs probability by reducing an inward current during the plateau, although the unbinding time constant makes it a good candidate for VP extension. In the same category enters quinidine (UTC = 4 s), the prototype class IA agent, which has a moderate Na^+ channel blocking properties, but blocks significantly potassium channels. In tachyarrhythmia, where this drug is mostly used, both tendencies have a strong proarrhythmic potential.

As we demonstrated in our analysis, the proarrhythmic properties of Na^+ channel blockers are amplified in case of ischemia-induced arrhythmia where the cardiac vulnerability is already increased by the pathological lose of excitability and slowed down myocardial conduction. Vulnerable period may become twice or triple longer when the antiarrhythmic is used for suppressing an acute ischemia-induced form of arrhythmia, dependent on the agent used. As we showed in a previous study [3], uneven spreading of chemical alteration during acute ischemia offers already the substrate for spiral wave formation even in the absence of an early afterdepolarization (EAD). A sodium channel blocker can amplify the effect or change its morphology. We can speak about double vulnerability: an increased vulnerable period over a vulnerable substrate.

It is reasonable to assume that increasing the vulnerable period is the necessary, but not sufficient condition of spiral wave formation. Every EAD occurring during this period can lead to reentry. However it has been suggested [28] that an altered repolarization by K^+ current depression might result in transient dominance of the total inward currents with oscillatory tendency, so in case of ischemia-induced arrhythmic episode treated by sodium channel blockade we have both the initiator – a potential oscillatory tissue and a double increased vulnerable period – due to pathologically reduced excitation and channel blockade, during which any extra excitation leads to partially blocked conduction. This localized reentry increases the severity of the initial arrhythmia attempting to suppress. This is the mechanism by which a ventricular tachycardia arising in normal tissue at the ischemic region border might degenerate into ventricular fibrillation after drug administration.

By analyzing (11) we can easily observe that the likelihood of inducing unidirectional conduction block is dependent on a cellular property (RP) and a tissue level parameter (VP). The first idea that comes to one's mind is that initial drug classification and the two CAST studies, which focused only on cellular activity, could have predicted at least one of the mechanisms. However, not taking into account the presence of VP (an intrinsic property of the myocardium as an excitable system) these studies simply assumed that extension of refractoriness means shorter remaining interval during which the heart might respond to potential PVC, which seems logical, but unfortunately wrong when taking into account the whole mechanism of propagation.

The adverse reaction of the drug in treating ischemia-induced arrhythmia worsens further by improper administration timing. If the channel blocker is administrated prior to coronary attack, the reduced blood flow prevents the drug being washed out of the ischemic tissue having as a result sustained blockade due to high drug concentration [22]. The likelihood of ventricular fibrillation is increased several times in this case.

In conclusion, we think that Na^+ channel blockers have a high risk of inducing self-sustaining arrhythmias based on the increased likelihood of reentry secondary to parallel prolongation of the VP and the RP. Slow unbinding agents are dangerous at any heart rate and with extremely high probability fatal if administrated for suppressing ischemia-induced arrhythmias. Fast unbinding drugs should be used also with precautions as at higher heart rate their proarrhythmic tendency increases significantly. As we have demonstrated drug's blocking affinity is a property equally important and fast binding time constant makes a drug as dangerous as a slow unbinding one when it comes to

vulnerable period modulation. All these conduct to the conclusion that sodium blockers as a class increase the vulnerable period to the extent that reentry and ventricular fibrillation seem imminent, especially when applied on an already impaired myocardium.

A similar study concerning class III antiarrhythmics is currently under development. After CAST results were published, medical community switched its attention to potassium channels blockers as an alternative to class I antiarrhythmics. We cannot indicate yet to which extent K^+ channel blockade affects the vulnerable period duration. However, the increase of RP and delayed cell repolarization seem to be potential proarrhythmic mechanisms. At least during ischemia, when VP is enlarged by reduced cell excitability a double increased refractoriness (pathologic and by K^+ channel blockade) provide enough reasons to believe that class III antiarrhythmics can be as proarrhythmic as sodium channel blockers.

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