Ionic Currents and Ventricular Fibrillation Dynamics

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Ventricular fibrillation is the principal immediate cause of sudden cardiac death. Yet, in contrast to other arrhythmias, ventricular fibrillation is considered to be inaccessible to pharmacologic therapy because of its characteristic and apparently never-ending disarray of electrical waves that seem to propagate chaotically throughout the ventricles. Its prevention has historically been focused on the suppression of ventricular ectopy, with the idea of eliminating potential triggers of fibrillation, which from a clinical standpoint has proven to be detrimental. During the last decade, the application of the theory of wave propagation in non-linear excitable media to the study of cardiac fibrillation has led to a dramatic increase in our understanding of its mechanisms. It is now clear that fibrillation is generated and maintained by rotors that gyrate at exceedingly high frequencies. From such rotors emanate spiral waves of excitation that propagate throughout the myocardium in very complex ways. Among the most important factors that determine rotor dynamics are the electrophysiological properties of the ventricular cells, established by their underlying transmembrane ionic currents. Thus, in recent years, studies have focused on the roles played by specific ionic mechanisms and their modulation by antiarrhythmic drugs in ventricular fibrillation dynamics. This review article summarizes the main findings of such studies, which pave the way for a better understanding of fibrillation, and for the development of new pharmacological approaches that aim to prevent rotor formation and maintenance rather than to suppress the triggering ectopic event.

Key words: *Fibrillation. Ions. Antiarrhythmics agents.*

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Corrientes iónicas y dinámica de la fibrilación ventricular

La fibrilación ventricular es la causa principal de muerte súbita cardíaca. A diferencia de otras arritmias, en general se ha considerado farmacológicamente inabordable, dado que parece una sucesión de innumerables frentes eléctricos descoordinados que circulan de manera caótica desde su inicio. Durante varias décadas, su prevención se centró básicamente en la supresión de las extrasístoles ventriculares que pudieran precipitarla. Este enfoque terapéutico se tradujo en pésimos resultados clínicos. En la última década, gracias a los conceptos de la teoría de propagación de ondas en medios no lineales, la visión global de la fibrilación ventricular ha cambiado de manera radical. Se ha demostrado que la fibrilación está mediada por reentradas funcionales con forma helicoidal que rotan siguiendo una dinámica determinada por su pivote organizativo o rotor. Estos rotores se comportarían como el centro que genera los múltiples frentes de activación eléctricos. Los rotores, a su vez, están condicionados por las propiedades electrofisiológicas del miocardio, determinadas por la dinámica de las diferentes corrientes iónicas. Así, recientemente se han publicado numerosos trabajos experimentales y de simulación sobre el papel que desempeña cada corriente en la dinámica de los rotores y se han analizado los efectos de su bloqueo mediante antiarrítmicos. Esta revisión detalla los hallazgos de los principales trabajos publicados, así como los análisis teóricos que describen sus autores. De estos trabajos se desprenden nuevos enfoques terapéuticos farmacológicos que buscarían evitar no ya el latido desencadenante, sino el propio mantenimiento de la fibrilación.

Palabras clave: *Fibrilación. Iones. Antiarrítmicos.*

INTRODUCTION

Historically, the prevention of sudden cardiac death

ABBREVIATIONS

AF: atrial fibrillation.
VF: ventricular fibrillation.
AP: action potential.
TTX: tetrodotoxin.
VT: ventricular tachycardia.

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from ventricular fibrillation (VF) has focused on the suppression of ventricular ectopies.[1,2] This is achieved through the administration of antiarrhythmic drugs which reduce the conduction velocity or extend the duration of cell action potentials (AP). However, clinical studies have revealed an apparent paradox: the effective pharmacological suppression of ectopies is associated with no clear improvement in survival[3-5]— in fact it often seems to have the opposite effect.[6-9] On the other hand, drugs that have not clearly demonstrated their efficacy in the suppression of ventricular ectopies (such as antagonists of beta-adrenergic receptors) can be useful in preventing sudden death.[10,11] To date, neither predictions based on theory or experiments, nor those concerning ectopy prevention, have been sufficient for establishing valid pharmacological solutions to sudden cardiac death by VF. Recently, interest has turned towards the tissue mechanisms that propagate ventricular tachyarrhythmias (especially VF), rather than what starts them. This review examines several concepts concerning the creation and fragmentation of rotors as a model of VF maintenance,[2] and discusses the latest findings regarding the role of ionic currents in the appearance, organization and maintenance of the rotors and spiral waves that are thought to sustain VF. The numerous experimental results recently published are not easy to interpret, and integrating them into a single model is particularly difficult. Furthermore, the diversity and complexity of the results obtained for each ion channel (sometimes completely opposite at the cellular and tissue or organ levels) highlight the difficulty in predicting the clinical effects of antiarrhythmic drugs.

Some general concepts related to the rotors that maintain VF are reviewed first, followed by descriptions of the changes induced in them by the modification of the main ionic currents. Efficient antiarrhythmic therapy requires the modification of the ionic mechanisms that determine rotor dynamics since these mechanisms ultimately lead to rotor formation, maintenance and termination.

GENERAL POINTS ON REENTRIES IN VENTRICULAR FIBRILLATION

It has been clearly shown that rotors are the driving force behind electrical activity in ventricular tachycardia and VF.[13-15] According to Winfree,[16] a rotor is "a stably rotating pattern of reaction and diffusion that surrounds a pivot point." These pivots, or phase singularities (PS), form after the breakage of a wavefront which, during its propagation, runs into refractory tissue or an anatomical obstacle. At this breakage point, or wavebreak, the propagation front curves and slows down until it converges with its own refractory tail, creating an activation rotor (Figure 1A). Rotors can occur in any excitable medium (chemical or biological) in which wavefronts with non-linear dynamics can form.[17] A curvilinear wavefront radiates out from the rotor towards the excitable medium in the shape of an Archimedean spiral (Figure 1B). Changes in the cardiac tissue voltage recorded by high resolution optical systems[13,14] (Figure 1C) show that the pivot, in its rotation, generates a trajectory around an organizing center or core (Figures 1A and B). The excitability and refractoriness of the medium determine the rotor's dynamics.[18] The excitability of the medium controls the velocity of the wavefront in its propagation around the core, and therefore the frequency of rotation. It thereby determines the radius of the core since it controls the critical value of curvature of the spiral tip and impedes the propagation of the wavefront towards the interior of the core (Figure 1A). The duration of the total refractory period at the wavefront tip is defined as the sum of the duration of the AP of the recently depolarized cells (absolutely refractory period) plus the low excitability interval that follows it (relatively refractory period). Both establish the status of the tissue ahead of the reentry wavefront in the vicinity of the core. In this way, refractoriness also modulates tissue excitability at the spiral tip, and therefore determines the frequency and size of the rotor core.[18,19] Intracavity pressure during VF might also modulate reentry frequency.[20]

Core Dynamics

The core is the organizing center that determines the development and the dynamics of a rotor. Simulations[22] have shown that the core is composed of excitable muscle that remains inactive because the wavefront never manages to invade it[18] (Figure 1A). This inability of the wavefront to enter the core is caused in part by the great local curvature at its tip, and is necessary for maintenance of stationary reentry. In fact, the extreme curvature at the tip creates an imbalance between the depolarizing current supplied by the wavefront at that location and the current

Figure 1. A: wavefront (red) and tail (green) in the vicinity of the rotor core (black dash circle). The wavefront propagation velocity (black arrows) becomes reduced towards the tip. At the tip, or phase singularity (yellow circle), conduction is blocked because the great curvature causes an excessive imbalance between the depolarization charge of the wavefront and the surrounding non-excited tissue. The phase singularity pivots around the core which is maintained in an excitable but unexcited state. The numbers 1 and 2 correspond to points on the wavefront and tail respectively that are close to the core. B: reentrant excitation wave obtained by numerical simulation (Luo-Rudy cellular ionic model). The wavefront is shown in red, the tail in green, and the resting tissue in blue. The wavefront follows a spiral trajectory whose curvature increases towards the center. The dotted circle indicates the limit of the core (N). AP1 represents a very short-lasting action potential close to the core.
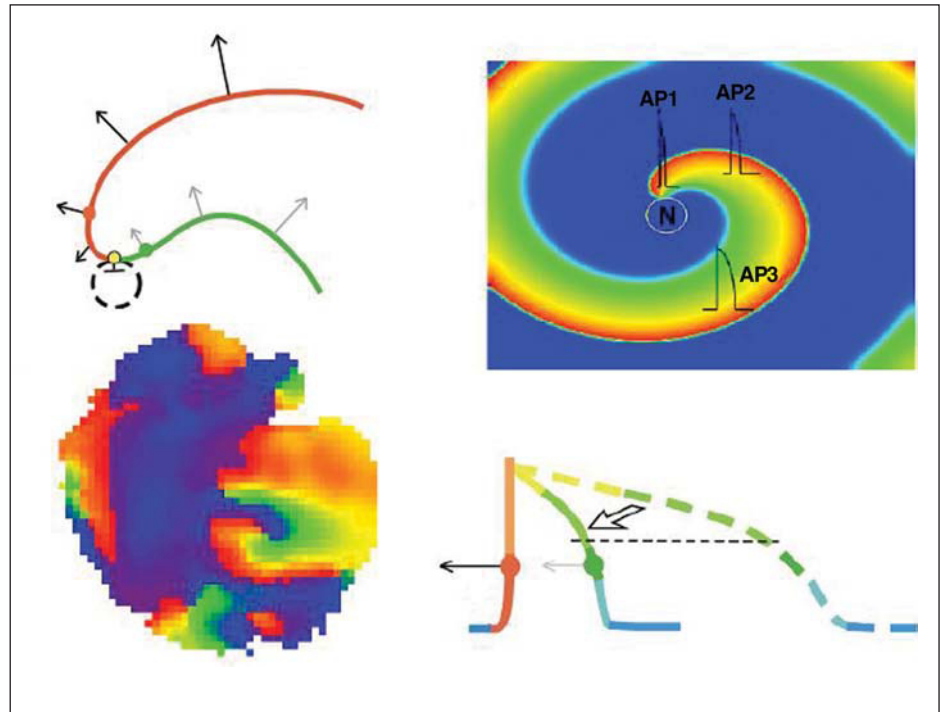
The duration increases progressively as the distance from the core increases, as shown by AP2 and AP3. C: plate showing a localized rotor in the left ventricle of an isolated guinea pig heart (from Samie et al[61]). D: action potential (solid line) in the immediate vicinity of the core. Its premature repolarization is due the strong electrotonic effect of the non-depolarized core (inclined arrow). After reaching the threshold voltage for IK1 activation, this current repolarizes the membrane to resting potential. In this diagram, the wavefront and the tail are propagated towards the left under the influence of independent ionic mechanisms (black arrow, gray arrow). The action potential represented by the dotted line corresponds to conditions of propagation, which do not lead to reentry. The color scale represents the same sequence of action potential phases as in panels B and C.

needed to depolarize the large amount of tissue ahead of the wavefront ("sink-to-source mismatch"). The curvature of the wavefront depends on the excitability of the medium. In turn, this is mediated by the relationship between the depolarizing sodium current (I_{Na}) and the repolarizing rectifying potassium current (I_{K1}). The former supplies very large quantities of sodium to depolarize the membrane and determines the propagation velocity. The latter stabilizes the membrane potential by removing intracellular potassium during phases 3 and 4 of the AP. Thus, I_{K1} causes a continuous repolarizing effect that opposes the sodium current-mediated depolarization arriving from contiguous cells. The greater the I_{Na} and smaller the I_{K1}, the greater the excitability of the medium.

Close to the core, AP are extremely brief, but they become longer as the distance from the core increases. Far away from the core, the wavefront is much more linear and its velocity is maximal (Figures 1B and D). Beaumont et al[21] showed numerically that this effect is owed to electrotonic interactions between the core and the adjacent tissue.

Fragmentation of the Wavefront

During VF, the continuous displacement and peripheral fragmentation of reentrant activity occurs, and this is responsible for the electrocardiographic turbulence observed. Several mechanisms are known to encourage the fragmentation of the reentrant wavefront. Traditionally, the intrinsically heterogeneous anatomical structure and electrophysiological properties of the myocardium[23] have been regarded as the main mechanism involved. Recently, however, it has been suggested that dynamic heterogeneities associated with the high frequency excitation emanating from rotors play a significant role in the complexity of VF.[24] Defenders of this theory suggest that high rotor frequencies and sequential activation of the surrounding tissue in each rotation cause dynamic changes in AP duration that encourage wavefront fragmentation and the generation of the daughter wavelets characteristic of VF.[25,26]

We believe that at least some forms of VF are the result of a very small number of three-dimensional rotors that remain relatively stable and which rotate at high frequencies. The electrocardiographic complexity observed during VF can then be explained by the
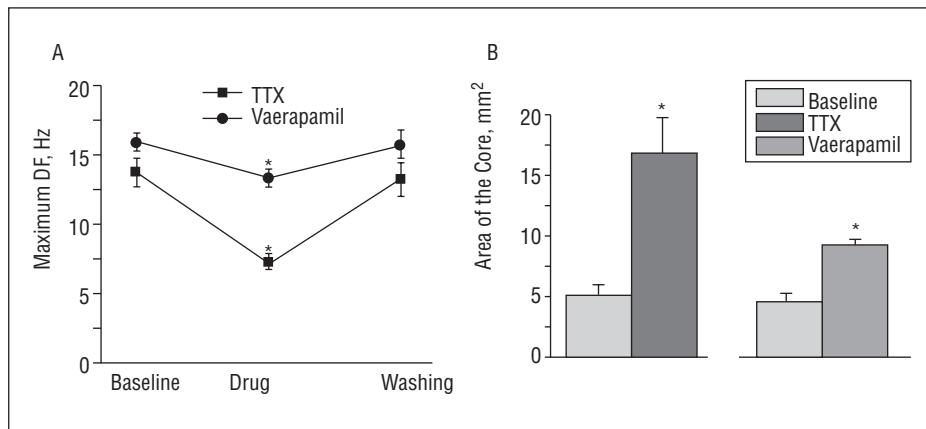
Figure 2. Effect of blocking sodium current (with tetrodotoxin) and calcium current (with verapamil) on the dynamics of ventricular fibrillation. A: changes in the maximum dominant frequency. B: increase in core area. *Significant change (*P*<.05) with respect to baseline values.

fragmentary propagation (fibrillatory conduction) of waves emanating from the rotors moving towards the surrounding tissues at different stages of recovery. Alternatively, the displacement (drift) of a rotor[27] throughout the myocardium would produce beat-to-beat changes in electrocardiographic deflections. Under these conditions, the complexity of the ECG pattern would depend on the rotation frequency and velocity of drift—but not on the breakage of the main rotor.[28]

IONIC CURRENTS AND VENTRICULAR FIBRILLATION

Sodium Current

This current starts the AP via the massive and rapid entry of sodium. It is activated following the initial depolarization caused electrotonically by contiguous depolarized cells.[29] The availability of sodium is a major determinant of the excitability of the medium and the conduction velocity of the wavefront. Blockade of the I_{Na} would therefore reduce excitability and proportionally reduce the propagation velocity of the wavefront.

Most studies on the role of this current in VF have involved analyzing the effects of its antagonists. Our group[30] analyzed the effect of depressing excitability on rotor dynamics in isolated rabbit hearts. During VF, the administration of tetrodotoxin (TTX)—a potent, selective and reversible antagonist of sodium channels[31]—tripled the area of the core (Figure 2B). Accordingly, TTX reduced the VF frequency (Figure 2A), organized the electrical activity and reduced the number of wavelets. Lowering the excitability reduces the degree of curvature at which propagation is blocked near the spiral tip, and thus increases the perimeter of the core.[32,33] As the core increases in size, the rotation frequency of the spiral that maintains the VF becomes lower. This facilitates 1:1 conduction, and reduces the degree of peripheral fragmentation.

Similar results were obtained with procainamide in a dog model.[34] However, the authors of the latter study justified the reduction in wave fragmentation by a flattening of the AP-duration restitution curve induced by the perfusion of the drug.

During the global ischemia that accompanies an episode of VF, partial blockage of I_{Na} occurs due to partial depolarization of the ischemic cells.[35] It would be expected that, under such conditions, the slower calcium channels would be the main agents responsible for maintaining electrical activity during VF,[36] since the I_{Na} channels are inactivated.[35] However, a study involving intracellular microelectrodes has shown, *in vivo*, that even in depolarized tissue in which sodium channels are supposed to be inactivated, TTX continues to reduce the rate of rise of the AP upstroke during VF, and that it does so more strongly than diltiazem.[37] In the same study it was reported that both isolated blockade of either the I_{Na} or the slow calcium current was insufficient to terminate VF, and it was concluded that both channels can sustain reentry and maintain VF.

In an acute regional ischemia model in the isolated rabbit heart, TTX administration impeded the induction of VF.[8] This protection was attributed to TTX increasing the degree of ventricular post-repolarization refractoriness by delaying the reactivation of the sodium channels, thus blocking propagation of new, closely-coupled impulses.[35] This antifibrillatory effect might explain the efficacy of lidocaine in recurrent VF in the first few hours after a myocardial infarction.

Simulation experiments suggest, however, that the pharmacological reduction of sodium channel availability increases vulnerability to reentry through an increase in post-repolarization refractoriness.[39] This increase creates a proarrhythmic substrate[39,40] that the authors believed could explain the detrimental clinical effects observed with class I antiarrhythmic drugs in the prevention of sudden death. Increased vulnerability was particularly significant with class Ic

drugs; the pharmacodynamic characteristics of these agents increase the vulnerability to unidirectional impulse blockage in patients suffering premature ventricular beats. Such an impairment of propagation would facilitate the appearance of arrhythmias caused by reentry.

Calcium Current

The duration of the AP is partly subordinate to the depolarizing effect of calcium entry during phases 1 and 2 of the AP. The slow calcium current ($I_{Ca,S}$) allows the entry of positive charge at a slower rate than the sodium current, but it lasts longer because of its slow inactivation.[41] Blockade of these channels produces significant shortening of the duration of the AP.[42] In theory, this reduction in myocardial refractoriness should lead to greater vulnerability to VF and an increase in the rotation frequency of the reentry circuits that maintain it.

Watanabe et al[43] managed to systematically turn VF into ventricular tachycardia (VT) using verapamil. If the shortening of AP duration is considered on its own, this change of VF into VT associated with a clearly reduced arrhythmia frequency is paradoxical. Our group found that verapamil induces a clear reduction of wave fragmentation in the isolated heart. It also reduces the appearance of PS,[44] and leads to a significant reduction in the rotation frequency of those PS lasting more than one rotation (Figure 2A). This slowing of the arrhythmia is not due to the decrease in conduction velocity but to the increased radius of the core of the spiral wave that maintains it. Verapamil significantly increased the area of the core to as much as double the baseline values (Figure 2B).

As illustrated in Figure 3, computer simulations have confirmed that reducing the slow inward calcium current (I_{si} in Figure 3) increases the radius of the spiral wave core, which increases the period of rotation and therefore reduces the rotation frequency.[44] The better organization and normalization of the VF obtained after verapamil administration can be explained by the reduction in the frequency of the main rotor and the shortening of AP duration. Both phenomena facilitate regional 1:1 conduction and markedly reduce wave fragmentation. Thus, the increase in the perimeter of the core and the reduction in AP duration obtained with verapamil both stabilize reentry by reducing the migration of the rotor. This, along with the disappearance of fragmentation, generates an electrocardiogram compatible with VT.

Similar results have been obtained with nifedipine.[45] Methoxyverapamil (D600) reduces $I_{Ca,S}$ at low doses. At high doses, however, it blocks both the calcium and sodium channels. The effect of different concentrations of D600 on the dynamics of VF has recently been studied.[46] At low doses it systematically
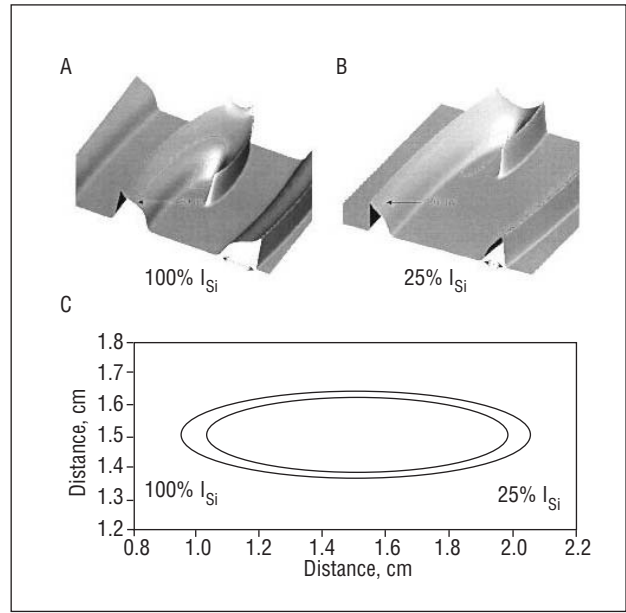

Figure 3. Luo-Rudy anisotropic model simulating sustained reentrant activity. The figure shows the effect of reducing the slow inward calcium current (I_{si}) on the size of the core and the rotation period. A: three dimensional representation of a reentrant wave under control conditions (I_{si}=100%). The rotation period is 133 ms; the size of the core, for an isopotential of −30 mV, is 17.5 mm². B: after reducing Isi by 75% compared to the control situation, the core increases to 23.5 mm² (isopotential=−30 mV) and the period of rotation becomes 148 ms. C: comparison of core size at I_{si}=100% and at I_{si}=25% (from Samie et al)[44].

converts VF into VT. As with other calcium antagonists, this is associated with a reduction in the main reentry frequency. At high doses, VT degenerates into a new although clearly slower VF since excitability is also modified.[46]

Some authors have suggested that AP restitution explains these effects.[26,46] It has been observed that blockage of the calcium current leads to a flattening of the restitution curve.[26,46] The modification of this curve would cause the wavefronts to be transmitted to the rest of the myocardium with no fragmentation. This would explain the increase in the spatiotemporal organization of arrhythmia during its transformation into VT. However, this theory does not clearly explain the significant reduction in the reentry frequency.

Calcium antagonism is the main effect of acute intravenous amiodarone.[47] Therefore, it is not surprising that in a model in which isolated pig hearts in VF were infused with this agent, the frequency of arrhythmia was reduced, the degree of organization increased, and the reentry cores enlarged.[48]

Unlike the findings observed by our group, Chorro et al[49] report that verapamil produces a significant increase in the dominant frequency and a reduction in the estimated reentry core area. However, several methodological differences exist between these studies, which make comparison difficult. The work of

Chorro et al involved a smaller number of electrical recording channels and significantly lower drug concentrations—sometimes ten times smaller. Furthermore, their observations focused on dominant frequencies measured 30 s after the induction of VF in hearts previously treated with verapamil. In our verapamil experiments, optical mapping was performed 5 min after the induction of VF to allow sufficient time for equilibration of the activity.

Potassium Channels

Potassium outward currents are not activated homogeneously but depend on the membrane potential, as well as their heterogeneous activation and recovery kinetics. The transient outward potassium current (I_{To}), (which is rapidly activated and deactivated), initiates repolarization immediately upon completion of the AP upstroke). Later, the more slowly activated delayed rectifying current mediates the outflow of potassium and thus the repolarization during the AP plateau. Finally, as the membrane repolarizes, the strong outward component of I_{K1} predominates, rapidly restoring the membrane potential to resting values. In resting conditions, I_{K1} is the only potassium channel open.

Delayed Rectifying Current

The delayed rectifying current (I_K) is determined in the ventricle by 2 components: the rapid potassium outward current (I_{Kr}) and the slow potassium outward current (I_{Ks}), thus called because of their particular activation kinetics. The majority of class III anti-arrhythmic drugs mainly block I_{Kr}. The relatively long time required for I_{Kr} and I_{Ks} to be activated means they are unlikely to explain the very short AP durations in the immediate vicinity of the core of the reentry.[22]

Numerous studies report that I_{Kr} and I_{Ks} antagonists modify vulnerability to tachyarrhythmias and alter their dynamics. In animal models, dofetilide and azimilide reduce the probability of VF appearing spontaneously in the setting of prolonged ischemia.[50,51] Tedisamil, an I_K and I_{To} blocker, increased the spatiotemporal organization and slowed down VF in a dog model.[52] Similar results have been obtained with current antagonist I_{Kr}, E4031[53] azimilide[54] and sotalol.[49] These studies suggest that increased AP duration modifies VF dynamics towards greater organization and deceleration. However, the shortening of AP duration following blockade of the calcium current also reduces the frequency and leads to the spatio-temporal organization of VF. Regarding this contradiction, one study that examined the effect of bretylium on VF dynamics stands out.[25] This drug regulates VF until it either transforms it into VT or terminates it. When cromakalim (an ATP-dependent potassium current [I_{K-ATP}] agonist) was administered, the lengthening of AP duration induced by bretylium was prevented, but the results were similar in that the drug converted VF to VT. The authors explained this effect of bretylium by a reduction in the slope of the restitution curve which, according to them, would favor homogeneous conduction without fragmentation. This, however, contradicts the findings of another study published by the same authors, in which AP duration seemed to play an important role in VF dynamics.[55] Though these results and conclusions are interesting, they should be understood as preliminary since the bretylium experiments need to be repeated and the results confirmed by other laboratories.

The ATP-Dependent Potassium Current

The ATP-dependent potassium current is carried by potassium channels that become activated when cells are faced with ATP depletion (for example in ischemia or metabolic stress). Activation of the current shortens AP duration. Activators of I_{K-ATP} have been used to analyze the effect of increasing the potassium outflow on VF dynamics. Pharmacological activation with pinacidil[56] and nicorandil[57] increase vulnerability to fibrillation. In an isolated canine ventricular tissue model,[55] cromakalim, an I_{K-ATP} activator, shortened AP duration and increased sensitivity to reentry and stabilization. Without cromakalim, spiral waves disappeared rapidly as they drifted and collided with the edges of the tissue. By reducing AP duration, this drug reduced the probability of interactions between the wavefront and its tail, thereby reducing rotor displacement and encouraging stabilization. The reentry frequency therefore increases as the area of the rotor core diminishes. The authors of the study, however, do not clearly explain the cause-effect relationship between the shortening of AP duration and the reduction in the core perimeter.

It is paradoxical that the shortening of AP duration should cause a reduction in the size of the core. This occurs even when excitability remains unchanged since the diameter of the core depends basically on the excitability of the medium and the wavefront's radius of curvature.[58] Figure 4 shows a possible mechanism. The curved tip of the wavefront moving at the perimeter of the core is a point (a PS) characterized by the convergence of all the AP phases. At progressively longer distances from the core these phases gradually separate, resulting in a continuous change in the wavelength. At the very tip, the wavelength is at a minimum and the wavefront is extremely curved, and the rotor follows a circular or elliptical trajectory, the diameter of which depends on the presence of
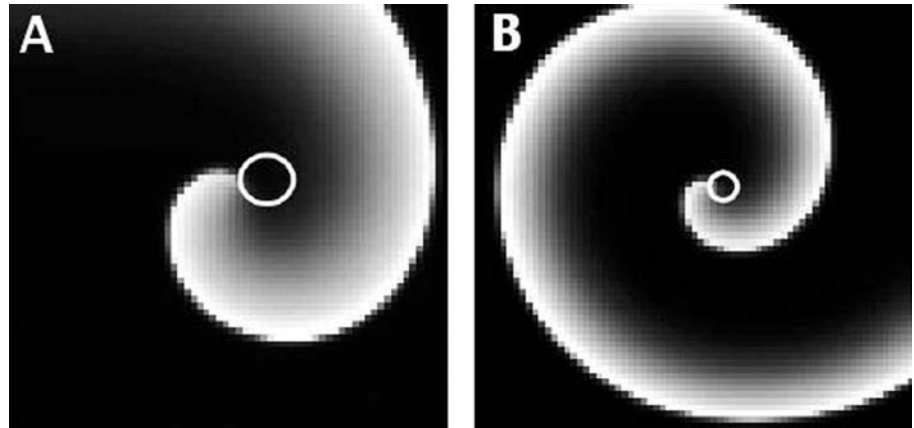
Figure 4. Computer simulations of reentry propagation: (A) longer wavelength, (B) shorter wavelength. The perimeter of the core is marked by the white circle.
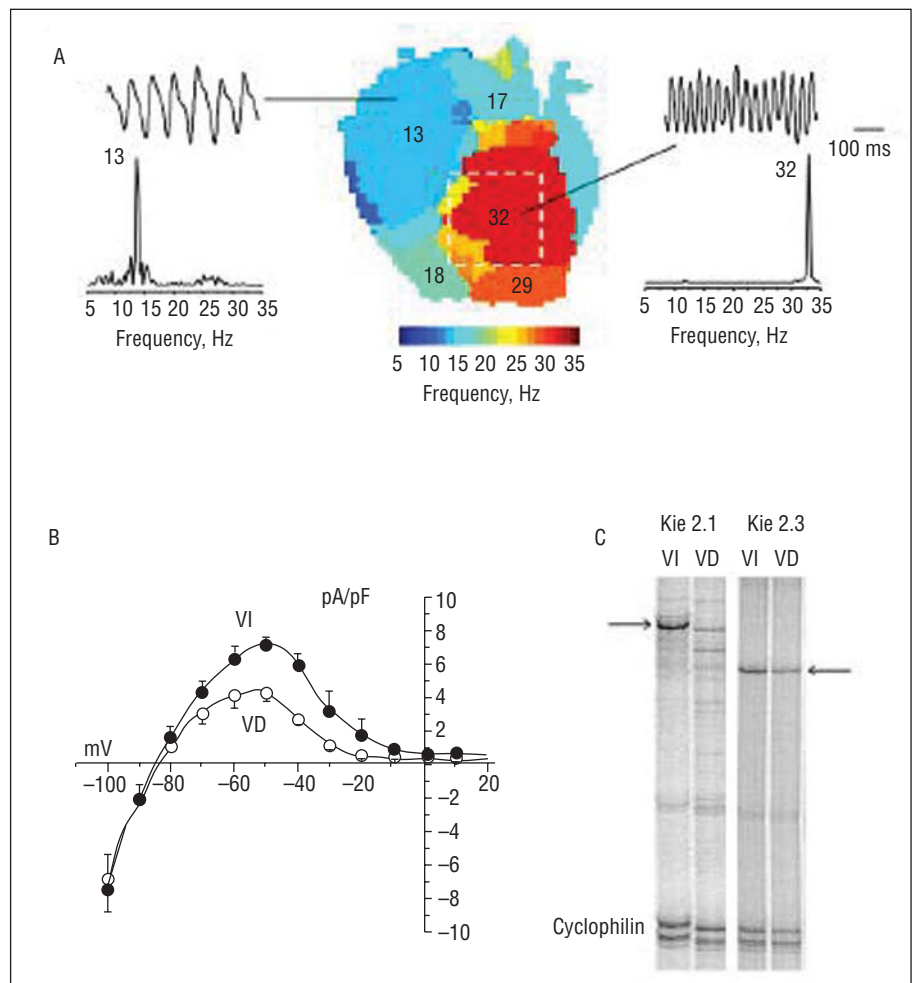

Figure 5. Correlation between dominant frequencies during ventricular fibrillation and the ventricular distribution of I_{K1} in guinea pig hearts. A: map of dominant frequencies, anterior face of the heart. The numbers indicate the local dominant frequency (see color scale). Two fluorescent signals are also shown which were obtained from a single camera pixel recording from the left ventricle and another one from the right ventricle, with their respective Fourier transformations and dominant frequencies. B: mean rectification profiles for I_{K1} for the left and right ventricles; the right ventricle clearly shows greater rectification. C: bands showing mRNA values for the proteins Kir2.1 and Kir2.3 in the left and right ventricles of a single heart obtained with the RNAse protection assay. The message of both proteins is stronger in the left ventricle (from

sufficiently excitable tissue. If the wavelength increases rapidly from the center to the periphery, the refractory tail would force the rotor to follow a more open trajectory (Figure 4A), and thus the core diameter would be large. However, when drugs are used to reduce AP duration, more excitable tissue becomes available in the vicinity of the wavefront, and both the rotor trajectory and the core's perimeter become shorter (Figure 4B).

The Inward Rectifying Current

The inward-rectifying potassium channels (Kir2.x) are responsible for the inward-rectifying current (I_{K1}),
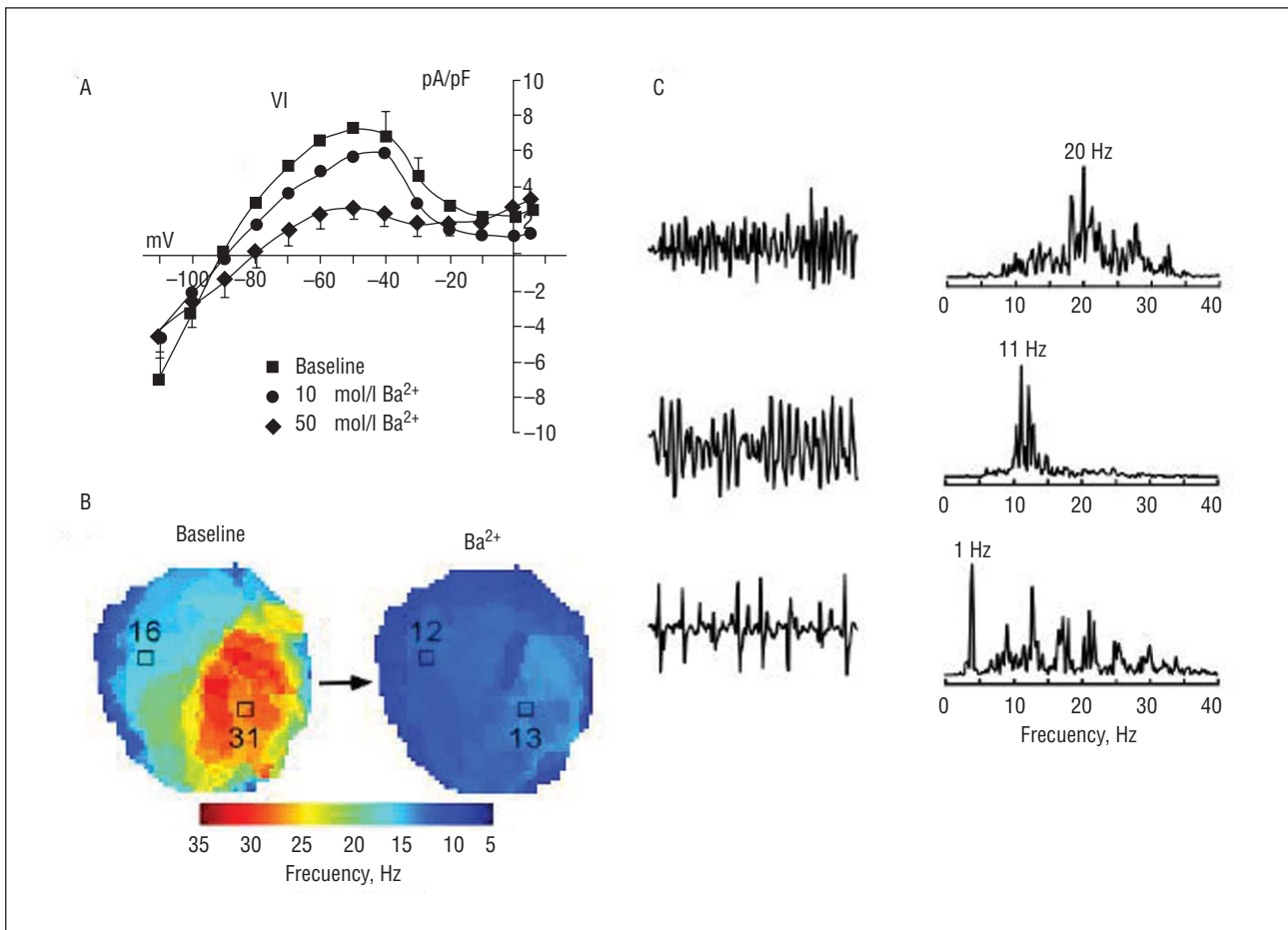
Figure 6. Blockade of I_{K1} and ventricular fibrillation. A: rectification of I_{K1} in left ventricular myocytes from a guinea pig heart under baseline conditions and during perfusion with barium chloride at 2 different concentrations. B: mean maps for the dominant frequencies (DFs); barium administration reduces DF in both ventricles. However, the effect is much stronger in the left ventricle. C: electrocardiogram and Fourier transformations during VF (upper panels) and after barium administration. Note conversion to sinus rhythm with polymorphic ventricular complexes of focal origin (from Warren et al[62]).

and are involved in the depolarization, repolarization and resting phases of the cardiac AP. They show great permeability to potassium ions at voltages of between –30 and –80 mV, which allows them to define and maintain the resting potential.[59] These channels show strong rectification between –50 and 0mV which means they remain closed during the AP plateau; they only open when the membrane potential returns to levels between –30 and –80 mV, which in a normal AP occurs during the last phases of repolarization.[59] Rectification is achieved through a voltage-dependent blockade by intracellular magnesium and/or one of the polyamines (putrescine, spermine and spermidine)[59] which are known to interact with at least 2 amino acid residues located in the intracellular channel complex gate.[60]

The importance of I_{K1} in determining rotor dynamics led our group to analyze its role in VF. Optical mapping of VF in isolated guinea pig hearts showed a significant correlation between the greater rotation frequency of rotors in the left ventricle (Figure 5A) and the magnitude of the rectification caused by the local I_{K1} (Figure 5B).[61] This heterogeneity in I_{K1} rectification is owed to the greater quantities of the proteins Kir2.1 and Kir2.3 in the left ventricle[62] (Figure 5C), which confer a weaker rectifying profile upon the tissue of this chamber.[63] In simulations, we showed that less rectification in the left ventricle generates shorter AP, allowing higher frequency rotors to stabilize.[61] On the other hand, stronger rectification in the right ventricle has the double consequence of making the tissue more excitable and the duration of the AP longer. Such greater excitability allows reduction of the rotor core diameter, and this, in conjunction with the longer AP duration, creates a favorable substrate for the wavefront to interact with its tail. This destabilizes the rotor, and in a guinea pig model prevents the right ventricle from maintaining stable high frequency spiral waves.[61] The electrical activity of this ventricle therefore depends on the

fibrillatory conduction emanating from the rotors in the left ventricle.[61]

Recently,[62] we used different concentrations of barium to selectively block I_{K1}[64] in guinea pig hearts undergoing VF in order to confirm the hypothesis that I_{K1} rectification is involved in the stabilization of high frequency rotors (Figure 6A). Blocking I_{K1} reduced excitation frequencies in the left ventricle (Fig. 6B) and increased VF organization (Figure 6C). On the other hand, the frequency of excitation of the right ventricle was reduced to a much lesser extent. High degrees of I_{K1} blockade systematically converted VF into another type of polymorphic arrhythmia of much lower frequency in which sinus rhythm coexisted with closely coupled premature ventricular complexes (Figure 6C). In a dog model, other authors have shown barium to increase VF organization.[65]

In simulations designed to analyze the effect of I_K and I_{K1} blockers independently, we observed different rotor dynamics associated with each channel.[22] Partial blockage of I_K increased the duration of the AP in the periphery, but not close to the core. This caused multiple peripheral conduction blockages and the creation of new rotors until a disorganizing fibrillatory activity was generated. Partial blockade (25%) of I_{K1} modified the reentry activity at the spiral tip, which destabilized the core and induced a continuous displacement without generating new spiral waves. Despite the fact that AP duration was increased at the spiral tip, the effect was not sufficient to terminate reentrant activity.

ANTIARRHYTHMIC DRUGS AND FIBRILLATION: CLINICAL STUDIES

Finally, the following briefly describes the most important clinical experience concerning the use of antiarrhythmic drugs with patients in fibrillation. Unfortunately, few papers have been published on this matter, and those available have involved either small numbers of patients or situations where electrical defibrillation has failed. As such, VF is associated with high level ischemia, acidosis and metabolic stress, and the true effects of antiarrhythmic drugs in these conditions are hard to predict.

The ARREST[66] study showed that, compared to placebo, amiodarone slightly improved the percentage of patients with persistent VF who could initially be resuscitated. However, 66% of those treated with amiodarone (which blocks the majority of channels) also received some other antiarrhythmic agent. Extrapolating the results to ionic currents is therefore practically impossible.

In another study with a similar population, amiodarone was compared to lidocaine. The former was associated with greater initial survival. These results might allow one to extrapolate that the non-

selective blockage of ionic currents, especially the calcium and potassium currents, is more effective as an auxiliary defibrillation therapy than the sole blockade of sodium channels. However, the limitations of the previous study also apply to this one. Moreover, amiodarone has electrophysiological effects that can be fatal.[67]

In extreme ischemia and acidosis there is an important reduction in excitability due to the inactivation of the sodium currents. Any reentry would therefore have a very slow propagation velocity and a wide excitable gap.[68] Pharmacological measures aimed at eliminating these reentries by prolonging the refractoriness of the tail so that this collides with the activation wavefront, would *a priori* be of little use. Therefore, it is unlikely that pharmacological modification of cell repolarization could provide any clinical benefit in VF that might last several minutes.

The following briefly describes clinical experience obtained with antiarrhythmic drugs in recent onset atrial fibrillation (AF). While AF resembles VF in some ways, there are clear differences between these arrhythmias, and between AP of the atria and ventricles. Nevertheless, the absence of ischemia in recent onset AF may provide more clear results than the studies mentioned so far. The latest ACC/AHA/ESC guides[69] state that the class I antiarrhythmic drugs (flecainide, propafenone and quinidine) are of greatest benefit in the chemical cardioversion of recent onset AF. Procainamide, amiodarone, dofetilide and ibutilide are less useful. Neither sotalol, the remaining beta blockers, nor calcium antagonists have shown any ability to cardiovert. Pilsicainide, an Ia group drug, is also of clear benefit in cardioversion of recent onset AF.[70] These data suggest that modifying sodium-mediated excitability is clinically of greater benefit for terminating fibrillation than approaches such as flattening the restitution curve with verapamil or exclusively lengthening refractoriness with selective I_K antagonists. The reduction in excitability following partial sodium blockade reduces the conduction velocity and increases the radius of the rotor core. These two effects reduce the rotation frequency of spiral waves and increase the need for physical space if they are to remain stable, thus increasing the chances of termination through collision with anatomical boundaries. There have been no clinical studies on selective modifiers of I_{K1}, which in theory should provide benefits by modifying excitability and the refractoriness of rotor cores.

CONCLUSIONS

It is more than 30 years since it was first suggested that rotors were the driving force behind the electrical activity of fibrillation.[16] The ample demonstration of

this in experimental studies[13-15,28] has led to a new focus in arrhythmia research based on the integration of our knowledge on the dynamics of non-linear wave propagation and recent information on the molecular biology and biophysics of ion channels and their regulation. Though debate continues over whether VF is a random propagation of multiple, independent waves,[23] and whether it is caused by the unceasing activity of a few vortices rotating at high frequencies and generating fibrillatory conduction,[28] it is clear that the development of an efficient antiarrhythmia therapy will require a detailed understanding of which ionic mechanisms determine rotor dynamics; such dynamics underlie the electrical activity of the most lethal arrhythmias.

Though there remains a great divide between discerning the basic mechanisms behind arrhythmias and the practical application of this knowledge in hospitals, there is hope on the horizon regarding the development of new and effective measures for preventing and treating the most complex and dangerous forms. For example, it is clear that the magnitude of I_{K1} and its heterogeneous distribution play an important role in VF dynamics and could be important in prevention. To make headway, detailed knowledge is required of the molecular and biophysical mechanisms that determine the rectification profile of this current—we may then be able to precisely modify them. A new generation of drugs or therapies can be envisaged (e.g., based on the genetic manipulation of Kir2.x channels) that might reduce the rectification of I_{K1} during fibrillation, either through direct modification of these channel or through agents that block them. Studies are underway to learn more about the details of this relationship and should indicate whether the manipulation of I_{K1} alone or in combination with other currents is the way forward in preventing sudden death by VF.

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