Electropharmacological effects of antiarrhythmic drugs on atrial fibrillation termination. Part II: New insights into the electrophysiological mechanisms of atrial fibrillation termination

Leonardo Calò, Luigi Sciarra*, Filippo Lamberti, Maria Luisa Loricchio, Antonio Castro, Leopoldo Bianconi, Claudio Pandozi, Fiorenzo Gaita**, Massimo Santini

*Department of Cardiac Diseases, San Filippo Neri Hospital, Rome, *Department of Cardiology, Conegliano Hospital, Conegliano (TV), **Department of Cardiology, Mauriziano Hospital, Turin, Italy*

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Antiarrhythmic drugs have been largely used to convert atrial fibrillation to sinus rhythm. Classes Ia, Ic and III antiarrhythmic agents are all known to be effective. Nevertheless, the electrophysiological properties of such agents even of the same class are very different. The mechanisms of the pharmacological termination of atrial fibrillation is an interesting issue that has not been so extensively studied yet. In this review we try to summarize the principal concepts about the electrophysiological substrate of atrial fibrillation and to give a unified and modern overview of the issue of the mechanisms of the pharmacological termination of the arrhythmia.

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Address:

Dr. Leonardo Calò

Via della Pedica, 348
00046 Grottaferrata (RM)
E-mail: leonardo.calo@tin.it

Introduction

The restoration and maintenance of sinus rhythm are the main objectives of the therapy of atrial fibrillation (AF). The increasing understanding of the electrophysiological mechanisms of the arrhythmia as well as the important progress in the study of the function and pharmacology of the ion channels provided a new basis for a better comprehension of the mechanisms of the termination of AF. Most of the available data come from experimental studies in animal models. Unfortunately, data in human series are still limited and incomplete.

The electrophysiological substrate of atrial fibrillation

To better understand the mechanisms of antiarrhythmic drugs in terminating AF, a brief view of the present knowledge about the electrophysiological mechanisms of this arrhythmia is necessary. On the basis of Coumel's triangle, this issue may be schematically divided into three topics: the trigger, the role of the autonomic nervous system, and the electrophysiological substrate. For the aims of the present article, we will focus our attention only on the electrophysiological substrate.

The reentrant nature of AF was demonstrated for the first time in 1959 by Moe and Abildskov[1]. These authors proposed that the perpetuation of AF depends on the continuous and random propagation of various individual wavelets through the atria. The grossly irregular wavefront becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may then be considered as an independent offspring. Such a wavelet may accelerate or decelerate when it encounters tissue in a more or less advanced state of recovery. It may extinguish itself when it encounters refractory tissue; it may divide again or sum up with an adjacent wavelet; it may be expected to fluctuate in size and change in direction. Therefore, AF would be a state in which randomly wandering wavelets coexist. Other studies lent further support to this innovative multiple reentrant wavelet theory[2-6].

An important concept to explain the electrophysiology of AF is the wavelength,

defined as the product of the refractory period and the conduction velocity: the slower the conduction velocity and the shorter the refractory period, the more likely the occurrence of reentry; besides, the very short wavelengths facilitate more complex forms of reentry, such as fibrillation versus flutter[3]. If the wavelength is relatively long, only a few waves can circulate through the atria, and AF tends to terminate. Fibrosis and inflammation (decreasing conduction velocity), parasympathetic activity and thyrotoxicosis (shortening the refractory period), ischemia (decreasing both), and stretch (shown to shorten refractoriness)[7] can favor short tissue wavelengths. Several other pharmacological, endocrine, electrolytic and autonomic factors may influence both the conduction velocity and the refractoriness of the atria. Moreover, for the maintenance of AF a critical mass of myocardium is required, since larger tissue masses allow for a greater space available for the wavelets to circulate[8]. This concept provides evidence for the importance of the atrial size in the maintenance of AF. Thus, the pathologic substrate of AF may be considered as a balance between the atrial mass and the wavelength.

However, we have to consider that the wavelength is a theoretical concept that just describes the minimal distance necessary for the wavelet to circulate. If we assume that the wavelength is the real pathway of the wavelet, we should affirm that no excitable atrial myocardium could be present in the fibrillating atria. This condition describes the leading circle reentry. Nevertheless, it has been observed that both in animals[9] and in humans[10] a temporal excitable gap between the fibrillation waves exists (Fig. 1). As a consequence we have to consider that at least the real pathway of the wavelet does not always coincide with the wavelength. On the contrary, the pathlength, the product between the AF cycle length and the refractory period, can better describe the real pathway of the wavelet in the fibrillating atria. Moreover, the difference between the pathlength and the wavelength can be considered an estimate of the excitable gap.

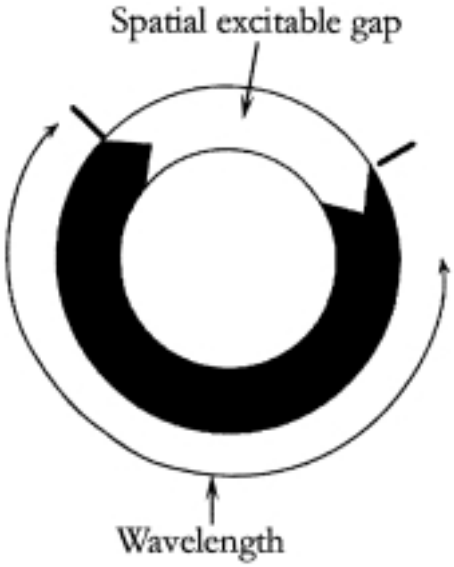

Figure 1. *Relationship between the wavelength and the excitable gap. The whole circuit is the real pathway of a given wavelet during atrial fibrillation: the pathlength. The difference between the pathlength and the wavelength is the spatial excitable gap of the circuit.*

Another important concept to be considered is the dispersion of the refractory periods. The heterogeneity of refractoriness may provide the setting for unidirectional block, required for the reentry when an extrasystole arising in a zone with short refractory periods fails to excite an area with long refractory periods[11]. The importance of the heterogeneity of the refractory periods is underlined by several observations of the increased dispersion of refractoriness in patients with AF[12-18].

Recently, the old controversy of whether AF results from the activity of independent reentrant wavelets circulating in the atria or from the activity of a "mother wave" (a rotor) cycling in a self-sustaining manner[19-22] re-emerged. Recent studies supported the hypothesis that AF may be sustained by a shorter reentrant circuit that acts as a dominant frequency source, while the rapid successive wavefronts emanating from these sources propagate through the atria and interact with anatomical and/or functional obstacles, leading to fragmentation and wavelet propagation[23-26]. This theory may also explain the particular importance of some areas such as the posterior wall of the left atrium or the pulmonary vein ostia, in the maintenance of AF.

Mechanisms of action of antiarrhythmic drugs in terminating atrial fibrillation

It is generally acknowledged that the crucial antifibrillatory effect of the antiarrhythmic drugs should be considered in terms of their effects on the wavelength. Only those drugs that lengthen the wavelength have been considered as being effective in the treatment of AF. This favorable electrophysiological effect is provided by the lengthening of the refractory periods of the atria[27,28]. On the basis of this consideration it is not surprising that some class I antiarrhythmic drugs known to shorten the atrial action potential duration, such as lidocaine, tocainide, diphenylhydantoin and mexiletine, have no antifibrillatory effects on AF and atrial flutter. Cardiac glycosides have a significant vagomimetic action and tend to shorten the atrial action potential duration and refractoriness, and hence they tend to be profibrillatory. They tend to convert atrial flutter (sustained by a single atrial macroreentry) to AF and to prolong the duration of AF thus favoring chronic AF. The conversion to sinus rhythm of recent-onset AF by digoxin has been hypothesized as being due to an improvement in hemodynamics linked to the slowing down of the ventricular rate via a depressant effect on the atrioventricular nodal conduction[29].

Drugs commonly used to convert AF to sinus rhythm include class Ia, Ic and class III antiarrhythmic agents. These drugs have different electrophysiological properties, and important differences have been found even between drugs of the same class. Nevertheless, quinidine, procainamide, propafenone, flecainide, sotalol, amiodarone and more recently ibutilide and dofetilide are all considered to be effective in restoring sinus rhythm in patients with AF. The different electrophysiological mechanisms of action of these drugs in AF have still not been completely defined even though some experimental studies tried to clarify this complex issue. Rensma et al.[30] observed that the drug effects on the atrial rhythm response to premature stimulation are related to the modifications of the wavelength for reentry. A subsequent study, conducted in a conscious dog model of AF, observed that an experimental class Ic drug ORG 7797 terminated AF by a diminution of the physiologic rate-dependent shortening of refractoriness resulting in a prolongation of the wavelength[31].

In 1992 Wang et al.[32] evaluated the mechanisms of flecainide in terminating AF in an experimental model of sustained AF in the dog, produced by a brief burst of atrial pacing in the presence of vagal stimulation. Flecainide effectively terminated AF in all the animals of the study. The drug increased the effective refractory periods of the atria and reduced the conduction velocity in a tachycardia-dependent manner. The doses of flecainide which effectively terminated AF induced larger changes in the refractoriness versus conduction velocity with a consequent favorable effect on the wavelength. Moreover, flecainide was able to reduce the atrial regional inhomogeneity of refractoriness, an action opposite to that of vagal stimulation. Atrial epicardial mapping showed that the drug progressively increased the size of the reentry circuits, decreased the number of the circuits and slowed the frequency of atrial activation during AF until the arrhythmia was terminated. These observations regarding the antifibrillatory effects of flecainide, were in accordance with the known property of flecainide of inducing a rate-dependent prolongation of the atrial action potential duration[33,34].

The same group of Wang et al.[35] evaluated the effects of procainamide, propafenone and sotalol on sustained cholinergic AF and on the atrial electrophysiological properties in anesthetized, open chest dogs. They found that clinically used doses of procainamide and propafenone were highly effective in terminating AF (100 and 75% respectively), while sotalol at a dosage of 2 mg/kg (slightly larger than the standard clinical dose of 1.5 mg/kg) was able to terminate AF only in 25% of the dogs examined; a cumulative dose of 8 mg/kg of sotalol (largely exceeding that used in daily clinical practice) was able to terminate AF and prevent its re-induction. In this model, all the drugs, at the dosage effective in terminating AF, significantly increased the wavelength at faster atrial rates, in the presence of vagal stimulation. The effect on the refractoriness was use-dependent for propafenone and reverse use-dependent for sotalol. The inefficacy of clinical doses of sotalol in terminating AF was explained by the authors just on the basis of this reverse use dependence of its effects on the atrial refractory period that resulted in reduced effects on the wavelength at faster rates. On the other hand, the use dependence of propafenone on the refractoriness contributed to increase the wavelength at rapid rates and thus to terminate AF. The effect of procainamide on the effective refractory periods did not change as a function of the cycle length. Moreover, the authors observed that both propafenone and procainamide can decrease the conduction velocity, and hence they need to cause a larger increase in refractoriness if the wavelength is to be increased sufficiently to terminate AF. Figure 2 shows the different effects of these antiarrhythmic drugs on the effective refractory period, conduction velocity and wavelength as a function of the cycle length.

Allessie et al.[36] studied the effects of hydroquinidine and flecainide in a goat model of sustained AF in which the repetitive induction of AF by burst pacing decreased the atrial effective refractory period and progressively prolonged the paroxysms of AF until they became sustained. The drugs were intravenously infused until sinus rhythm restoration. Hydroquinidine and flecainide respectively restored sinus rhythm in 86 and 67% of cases. Immediately before cardioversion, the two drugs increased the average atrial cycle length by 72 and 50% respectively. The same group[37] compared the antifibrillatory effects of class Ia, Ic, and III drugs in their goat model of chronic AF. Surprisingly, although all the drugs of the study were found to be

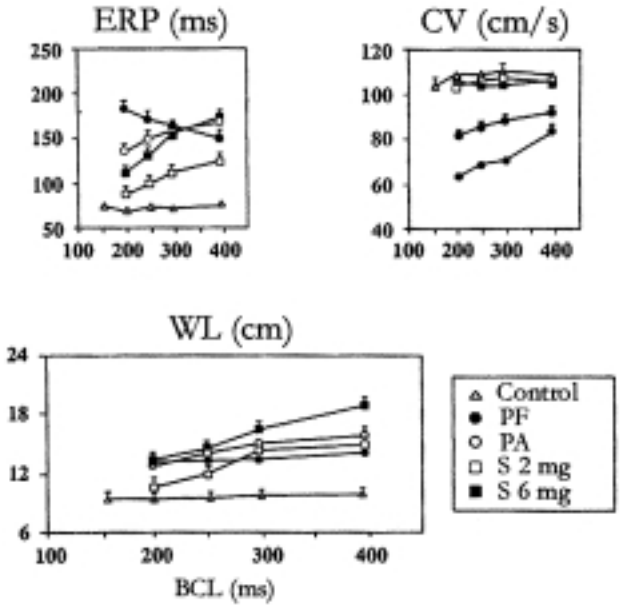

Figure 2. *Effects of propafenone (PF), procainamide (PA), sotalol (S) 2 and 6 mg on the atrial effective refractory period (ERP), conduction velocity (CV) and wavelength (WL) as a function of the cycle length (BCL). From Wang et al.[35], modified.*

highly effective in restoring sinus rhythm, the atrial wavelength measured immediately after cardioversion was not prolonged. This observation was consistent with the very high vulnerability of the atria after cardioversion. These results highlight the discrepancy between the marked efficacy of such drugs in terminating AF and their inefficacy in preventing recurrences.

These preliminary observations were further confirmed by a recent study[38] in the well-known goat model of chronic AF, in which a new technique was employed to measure the atrial refractory period during AF. The effects of the intravenous infusion of cibenzoline (Ic), hydroquinidine (Ia), flecainide (Ic), and d-sotalol (III), on the AF cycle length, refractory period, conduction velocity, wavelength, pathlength and excitable gap were evaluated during sustained AF. Surprisingly, the restoration of sinus rhythm was not correlated with the prolongation of the wavelength. In fact, d-sotalol and hydroquinidine did not significantly affect the wavelength, whereas both flecainide and cibenzoline even shortened it. The only parameter that correlated with the termination of AF was the excitable gap (Fig. 3).

The authors proposed a number of possible mechanisms by which the excitable gap was prolonged by the class I drugs. It is known that during AF both anatomic and functional reentry occurs[3,39]. In the case of an anatomic circuit, the temporal excitable gap is the difference between the conduction time and the refractory period. As such, drugs that slow down conduction consequently increase the excitable gap of the circuit. Functional reentry is characterized by a line of functional block; around this line, the impulse circulates, often describing a sharp U-turn at the pivot points[40]. At these particular points, because of the high degree of wavefront curvature, a current-to-load mismatch leads to conduction delay. The widening of the excitable gap could be due, according to the authors' hypothesis[38], to an aggravation of the wavefront curvature effect at the pivot points. This observation is supported by the findings of Ortiz et al.[41] who found that the termination of flutter by moricizine was not due to the prolongation of the wavelength, but to an effect of the preferential depression of conduction at the pivot point of the circuit. The effect of the depression of conduction around a pivot point induced by flecainide and potassium was further confirmed by Danse et al.[42] in a study conducted on 16 rabbit hearts in which U-turning wavefronts were experimentally reproduced. In this study, flecainide and potassium increased the conduction times of the U-turning wavefronts 1.6 times more than the longitudinal or transverse planar wavefronts. Moreover, at a critical lowering of the excitatory current, functional conduction block occurred at the pivot point and the wavefront was forced to make a longer U-turn. Random reentry is also known to be present during AF[43]. Random reentry is characterized by wavelets that reenter an area previously activated by other wavelets. In this kind of reentry the excitable gap is determined by the time that myocytes have to wait until they are activated another time. It is clear that drugs that act by decreasing the number of the wavelets may increase the excitable gap. In fact, the time that a given myocyte has to wait until it is reactivated will be longer. Moreover, the increasing size of functional reentrant circuits could incorporate an anatomic obstacle that could be included in such circuits; the increase in the excitable gap will be a consequence of the shift from a functional to an anatomic reentrant circuit.

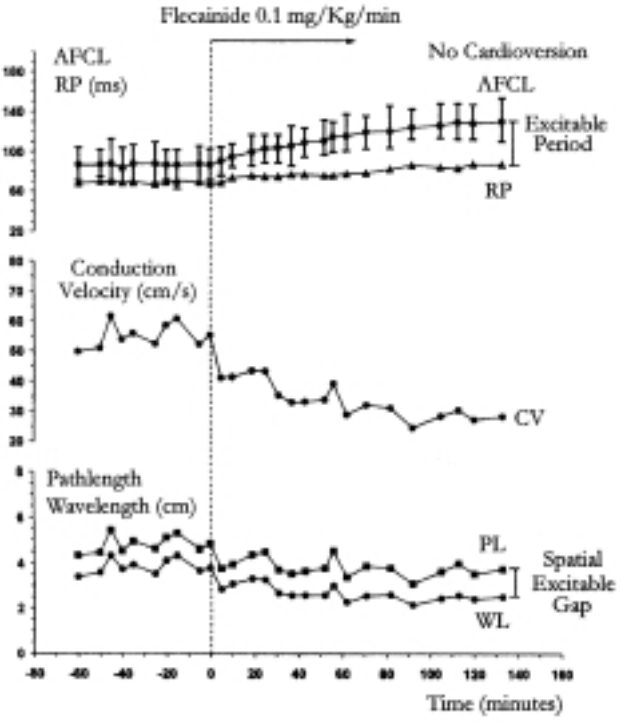

Figure 3. *Example of the effects of flecainide on the atrial fibrillation cycle length (AFCL), refractory period (RP), conduction velocity (CV), pathlength (PL) and wavelength (WL). The median AFCL and P_5 and P_{95}* (bars) *are plotted together with the RP. From Wijffels et al.[38], modified.*

In summary, according to the Allessie's view, class I antiarrhythmic drugs would act by depressing conduction, particularly of wavelets with a marked curvature. This effect causes a critical delay at the pivot points that leads to an increase in the average AF cycle length and a widening of the excitable gap. The increased excitable gap will lower the chances that fibrillation waves encounter areas of partially refractory tissue with a consequent less frequent fragmentation and slowing down of the wavelets. "… the balance between fusion and fragmentation of wavelets will change in favor of fusion"[38] and thus the probability of AF termination will be increased with the reduction in the number of the AF waves.

We recently studied the mechanisms of termination of AF by flecainide in humans[44,45]. The terminations of episodes of sustained AF by flecainide in 10

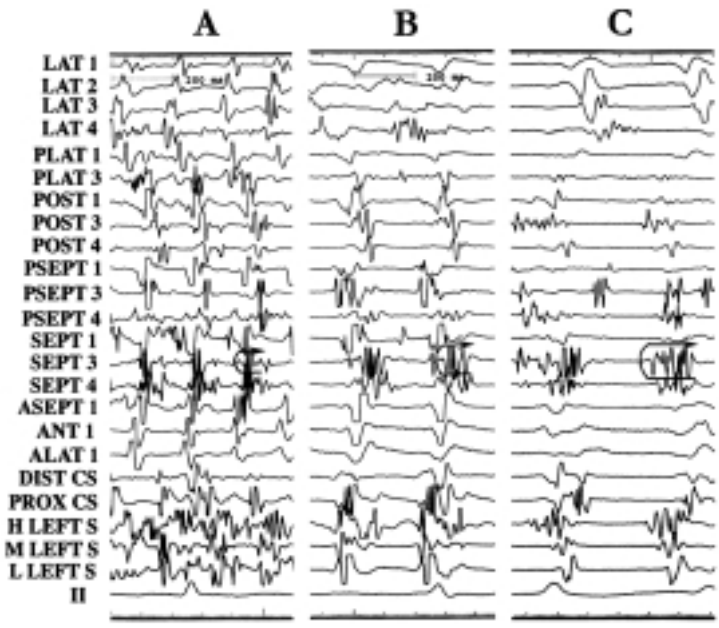

Figure 4. *Intracardiac electrograms recorded before and after flecainide administration in a patient with atrial fibrillation. After flecainide administration, irrespectively of the fiber direction, a sharply turning wavefront markedly slows down at the pivot point leading to a possible functional block. ALAT = anterolateral right atrial wall; ANT = anterior right atrial wall; ASEPT = anterior interatrial septum; DIST CS = distal coronary sinus; H LEFT S = high left septum; L LEFT S = low left septum; LAT = lateral right atrial wall; M LEFT S = middle left septum; PLAT = posterolateral right atrial wall; POST = posterior right atrial wall; PROX CS = proximal coronary sinus; PSEPT = posterior interatrial septum; SEPT = interatrial septum; II = D2 surface ECG recording.*

patients undergoing electrophysiological evaluation were assessed. The episodes of AF had to be sustained for at least 30 min. The right and left atria were mapped by means of a basket catheter and two multipolar catheters. Flecainide effectively restored sinus rhythm in all the subjects within 10 min. After flecainide administration, a significant increase in the mean FF cycle and in the width of the electrograms was observed. The major increase in the mean FF cycles, leading to a greater spatial homogeneity of the electrograms (as confirmed by the reduction of the coefficient of dispersion) was observed in correspondence of the right interatrial septum, right posterior wall, left atrial septum and coronary sinus. In these areas the baseline fragmented electrograms became even more fragmented after flecainide. Activation mapping after flecainide administration showed a reduction in the number of the circulating wavelets, and immediately before AF termination a macroreentrant circuit similar to atrial flutter was observed. Our data seem to confirm in humans what the group of Allessie[38] observed in the goat model of sustained AF. The effect of flecainide of sodium channel blocking, led to a preferential conduction delay in the areas with fragmented electrograms at baseline (pivot points) (Fig. 4). Consequently the mean FF cycles are prolonged and the activation wavefronts become more homogeneous thus favoring a reduction in the number of circulating waves and increasing the chances of AF termination.

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