Antiarrhythmic drug (AAD) use in the clinical setting remains an often frustrating empirical exercise, despite significant advances in understanding the effect of AADs on myocardial ion channels and action potential. Not only is efficacy lower than desired, but prediction of antiarrhythmic versus arrhythmogenic effects of AADs in a particular case is nearly impossible. Vaughan Williams classification helped to describe and group AADs and to differentiate between AADs mainly acting on the low diastolic polarization cells (sinoatrial and atrioventricular nodes) for their effect on β-adrenergic receptors and Ca^{2+} channels and those capable of slowing conduction velocity and/or prolonging the action potential duration of the working myocardium and Purkinje cells. Unfortunately, usefulness of the Vaughan Williams classification for clinicians was limited because it provided incomplete links among AAD actions, arrhythmia mechanisms, and therapeutic results.

Modern arrhythmology is dominated by the concept of reentry as the bases of most clinical tachyarrhythmias. Reentry has been conceived generally as continuous activation rotating around a central obstacle, be it fixed or functional, and the equilibrium necessary between refractory period, conduction velocity, and circuit circumference to maintain reentry has been nicely synthesized in the wavelength (WL) concept. WL is the circuit length covered by the activation front in the time lapse of refractory period duration (Figure 1) and, obviously, it must be shorter than total circuit length in order to leave an excitable gap; otherwise, activation would be extinguished by meeting a barrier of refractory tissue. In animal experiments, the WL of the initiating premature impulse was related to the type of inducible atrial arrhythmias, atrial fibrillation (AF) being induced with the shortest WL, and flutter with slightly longer WL. The concept of a critical WL for reentrant arrhythmias led to the suggestion that AADs effects should be described in terms of their influence on the WL. However, most class I AADs slow conduction velocity at the same time as they prolong refractory periods, and the final effect on WL is difficult to predict (Figure 1). Amiodarone, a class III AAD that prolongs action potential duration, also slows conduction velocity on the basis of its ability to block Na^+ channels.

Until very recently, atrial flutter and AF have been considered as parts of the same entity from the clinical point of view, so that “Atrial flutter and/or fibrillation” has become an established term including a variety of atrial arrhythmias. The Sicilian Gambit did try to rationalize a different AAD indication for flutter and fibrillation on the basis of estimated excitable gap length. It was assumed that the excitable gap in flutter would be too large to be closed by refractory period prolongation alone, and excitability depression by class I AADs was proposed as the best treatment. On the other hand, AF was viewed as having a very short excitable gap, and it was predicted that selective refractory period prolongation by class III AADs would be effective therapy. Perhaps this later concept was influenced by the well-known efficacy of amiodarone in AF, because at the time the Sicilian Gambit was proposed, there was little experience with any other class III AAD.

Contrary to these predictions, the introduction of Na^+ channel blockers flecainide and propafenone, classified as Class IC AADs,1 was a significant breakthrough in management of AF because of their ability to interrupt in 65% to 85% of cases of recent onset AF, after both intravenous or oral administration.5,6 On the other hand, administration of Class IC AADs in atrial flutter results usually in slowing of conduction within the circuit and cycle length prolongation, but rarely interruption of the circuit.7 In fact, flutter rate slowing may lead to 1:1 atrioventricular conduction, an important complication that could be considered a contraindication for intravenous administration of Class IC AADs in patients with atrial flutter. In sharp contrast, and also against predictions, newly developed class III AADs, such as ibutilide and dofetilide, have shown a greater efficacy in atrial flutter, which is interrupted in 60% to 80% of patients after intravenous administration, whereas AF can be interrupted in only 30% to 40% of the cases.8,9 Flutter interruption is not preceded by cycle length prolongation, a behavior compatible with excitable gap obliteration on the bases of refractory period prolongation, without change in conduction velocity. The recent report by Singh et al9 is particularly remarkable because it shows that dofetilide not only produced a significantly higher conversion rate to sinus rhythm in atrial flutter than AF but also a higher chance of long term sinus rhythm maintenance in flutter than AF.

This relative specificity of AAD effects has no precedent. It is apparent that the pathogenetic concepts of AF and flutter

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in which the Sicilian Gambit based its recommendations 10 years ago may have been inaccurate and these new observations must be exciting to their authors as they point to a possible breakthrough in understanding of the relationship between arrhythmia mechanisms and AAD action. In the last 10 years, typical flutter has been better defined as a right atrial macroreentrant tachycardia using a circuit bound anteriorly by the tricuspid ring and posteriorly by a mixed obstacle made by the superior and inferior vena cava orifices and a line of functional block related to the terminal crest.10 The flutter circuit has an anatomical isthmus between the inferior vena cava and the low tricuspid ring that is probably also the most sensitive target for AAD action.11 On the other hand, a possible mechanism of reentry in AF is by rotors, a spiral wave turning without a central obstacle but on the basis of excitability gradients that make activation advance slower in the center than in the periphery of the rotor12 (Figure 2).

The relative specificity of class IC AADs for AF and class III AADs for flutter could possibly be explained by taking into account these newer concepts of arrhythmia mechanisms. Depression of excitability could be a significant antiarrhythmic action of class IC AADs in AF, making rotors lose the ability to turn sharply.13,14 A larger turning radius means a prolongation of the rotation period and/or less space to sustain the minimum critical number of rotors (or wavelets) necessary to maintain AF, even in the presence of an excitable gap.15 In flutter, class IC AADs would generally result in marked conduction-velocity slowing preventing WL shortening (Figure 1B). On the other hand, class III AADs would prolong refractory period without affecting conduction velocity, thus increasing WL (Figure 1C). This effect would result in obliteration of the excitable gap in atrial flutter, because the tightly bound circuit cannot increase its radius. However, in AF, reentrant circuits are not bound in the periphery by fixed barriers and, as already suggested by Lewis16 in 1925, an increase in WL could be compensated by a modest increase in circuit radius, especially if action potential prolongation is decreased at short cycle lengths. Whatever the exact explanation might be, understanding of specificity of AAD effects in AF and flutter could open the way to a better understanding of arrhythmia mechanisms, as well as to a rationalization of ADD use, including the basis for potential association of class IC and class III AAD in different clinical situations.

And yet, surprisingly, the literature often still refers to Atrial Flutter/Fibrillation as a single entity, even in articles

Figure 1. A, Schematic representation of the relationship between reentry circuit size and refractory period (Ref Period), conduction velocity (Cond Vel), and wavelength (WL). Circular reentrant activation develops into a helical shape on a left-to-right time dimension. The action potential shape is taken as a representation of refractory period duration. The darkened portion of the reentry circuit represents WL and the remainder the excitable gap. B, Na+ channel blockade by a class IC AAD prolongs refractoriness but also slows conduction velocity, and the excitable gap is not closed. C, A class III AAD prolongs refractory period without slowing conduction velocity, thus making WL longer than total circuit length. The excitable gap is closed and activation stops.

Figure 2. A, Schematic representation of a rotor turning without a central obstacle. The center of rotation is slowed by low excitability. B, When excitability is further depressed, the radius of rotation increases so that the rotor needs more space to proceed.
demonstrating relative specificity of class III AAD for flutter.\textsuperscript{8,9} "Atrial Flutter/Fibrillation" threatens to remain an established clinical concept to the point that recently published Guidelines for Cardiopulmonary Resuscitation of the American Heart Association, in the section "Tachycardia Algorithms",\textsuperscript{17} make no attempt to separate the management of these 2 arrhythmias. To whom this is useful is a good question. The greatest advances in the field of Clinical Cardiac Electrophysiology have come, not unexpectedly, from deep understanding of arrhythmia mechanisms. Separation of the old PAT (paroxysmal atrial tachycardia) into accessory pathway, nodal reentrant, or focal tachycardia, led the way to effective ablation and often the cure of these arrhythmias. On the other hand, understanding of ventricular arrhythmias is still hampered by the habit of lumping sustained ventricular tachycardia and ventricular fibrillation into a single entity, despite evidence of different mechanisms and prognosis.\textsuperscript{18–20} We still have time to avoid making the same mistakes of the past with atrial flutter and fibrillation by considering them as separate entities, both mechanistically and therapeutically.

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