Experimental Models of Reentry, Antiarrhythmic, and Proarrhythmic Actions of Drugs Complexities Galore!

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In this issue of Circulation, a report by Brugada et al. describes an experimental model of functional reentry in which circus movement could be induced in a thin layer of "normal epicardium" obtained by an endocardial cryotechnique in Langendorff perfused rabbit hearts. The model was used to study the proarrhythmic effects of flecainide. The study concludes that flecainide significantly enhanced the inducibility of reentrant ventricular tachycardia and modified its mode of induction. It was suggested that the marked depression of conduction induced by flecainide coupled with only modest increase of refractoriness resulted in a higher incidence of local functional block and the potential of developing sustained circus movement around shorter arcs of block. The study comes from a laboratory that has played a leading role in the development of the concept of functional reentry. However, much of the impact of the study depends upon how closely the model resembles possible clinical situations. Further, the study raises several important questions regarding the validity of experimental models of reentry in general and of models that investigate the mechanisms of antiarrhythmic and proarrhythmic effects of pharmacologic agents in particular.

Understanding Experimental Models of Reentry

Circus movement reentry can be classified into anatomical and functional types. In the former type, the reentrant pathway is fixed and anatomically determined. The earlier models of circus movement consisted of rings of cardiac and other tissue obtained from a variety of animals including mammals. In the intact heart, excitable bundles isolated from surrounding myocardium can form anatomical rings for potential circus movement. Examples include circus movement involving normal AV conducting bundles and AV accessory pathways, bundle branches or Purkinje network, and surviving myocardial bundles in a postinfarction scar. It is important to remember, however, that having an anatomically determined pathway that can potentially support reentry does not automatically create circus movement. A critical functional perturbation of part of the pathway must take place before circus movement is initiated. Central to the initiation of circus movement in an anatomical ring is the development of unidirectional block. Here, a stimulus will block in one direction because of nonhomogeneous electrophysiologic properties, but will continue to conduct in the other direction. A circus movement will be established if the returning wave front finds that the site of unidirectional block has recovered excitability permitting conduction to proceed uninterrupted. Thus, it is clear that in an anatomically predetermined circuit a significant functional component exists that could be modulated by pharmacologic agents.

The other type of reentry is purely functional in nature and develops in the interconnected syncytium of myocardial bundles in the atria or ventricles. Central to the development of a functional circus movement is the creation of a functional barrier of conduction block. The nature of this barrier has been investigated in some detail during the initiation of circus movement. Functional conduction block initiating a circus movement could be caused by 1) abrupt changes in cardiac geometry, 2) decremental conduction leading to propagation failure, 3) regional differences in refractory periods, or 4) differences in conduction properties relative to fiber orientation. The last two mechanisms have received wider attention. Allessie et al. were the first to show that differences in refractory periods of atrial fibers
at adjacent sites can result in functional block if premature stimulation is applied to the site of shorter refractoriness. Later, Gough et al.\textsuperscript{12} showed that circus movement developed around arcs of functional conduction block in the surviving epicardial layer overlying canine ventricular infarction due to spatial inhomogeneity of refractoriness. The latter could be due to differences in active membrane properties of adjacent fibers that affect their depolarization or repolarization characteristics or due to discrete differences in intercellular connections. Recent studies from the same laboratory using high resolution mapping of activation and refractory patterns have shown that functional block is necessary for both the initiation and sustenance of reentrant excitation and that the functional block necessary for initiation of reentry was due to abrupt changes in refractoriness occurring over distances equal to or less than 1 mm.\textsuperscript{13} The abrupt changes in refractoriness did not seem to be related to specific geometrical characteristics or anisotropic conduction properties of ischemic myocardium. On the other hand, and primarily through the work of Spach and colleagues,\textsuperscript{14} anisotropic discontinuous propagation was shown to produce all of the conduction disturbances necessary for circus movement reentry without the presence of spatial differences in refractoriness. The safety factor for propagation of early premature impulses was shown to be dependent on fiber orientation with unidirectional block occurring during propagation along the long axis of the fibers and slowed conduction persisting across the fibers, thus setting the stage for reentrant excitation. Recently, Spach et al.\textsuperscript{15} suggested that spatial inhomogeneity of refractoriness and anisotropic conduction properties may both contribute to one model of reentrant excitation in the canine atria. The combination of spatial inhomogeneity of refractoriness and anisotropic conduction properties may be applicable to other models of reentry. The model of reentry investigated by Brugada et al.\textsuperscript{1} would have been considered the quintessential example of the so-called “anisotropic reentry.”\textsuperscript{15} However, critical examination of the arcs of functional conduction block during both the initiation and sustenance of circus movement in this model show that these did not necessarily follow the anisotropic characteristics of the myocardial sheet. This would suggest that spatial inhomogeneity of refractoriness may have also contributed to the formation of the arcs of functional block.

The nature of the central arc of functional block during sustained reentry has been more difficult to investigate. In a study by Dillon et al.\textsuperscript{16} it was suggested that most of the central barrier around which circus movement orients in the surviving epicardial layer of postinfarction canine hearts was in fact a line of pseudoconduction block due to very slow conduction across the longitudinal fiber axis. However, high resolution recordings of the central arc of block in this model\textsuperscript{13} as well as in other atrial models of functional reentry\textsuperscript{17,18} clearly showed the presence of a discrete finite zone of functional conduction block explained by the bidirectional invasion of this zone by the opposing activation wave fronts on either side of the central barrier. Electrotonic conduction in this zone could create a constant functional block around which circus movement is oriented. The factors that determine the location and orientation of the central functional barrier during sustained reentry are not well defined and may be related to refractoriness or anisotropic differences.

The length of the central functional barrier is also of interest. A circuit with a very small central barrier, that is, a central core of functional refractory tissue, will be typical of the leading circle model of reentry\textsuperscript{19} and will resemble the vortex-like waves or “rotors” that have been demonstrated in a number of excitable media\textsuperscript{20} and recently in normal isolated ventricular muscle.\textsuperscript{21} However, in most of the functional circuits that have been mapped in vitro or in vivo, including the original leading circle model\textsuperscript{19} and the model of reentry by Brugada et al., the central obstacle was shown to consist of an arc of block of some finite length rather than a confluent central vortex.

The topology of functional circus movement is of both theoretical and practical importance. The typical functional circus movement in a syncytium will have a figure eight configuration consisting of a clockwise and counterclockwise wave fronts around two functional arcs of block that coalesce into a central common front that commonly represents the slow zone of the circuit.\textsuperscript{22} This zone is the most vulnerable part of the circuit and the site where pharmacologic agents or ablative procedures could selectively modulate the circus movement. On the other hand, a single reentrant functional loop could also develop in a syncytium. However, it usually develops contiguous to an anatomical barrier. The most typical example of the development of a single functional reentrant loop has recently been shown by Schoels et al., in a study of circus movement atrial flutter in the canine sterile pericarditis model. In this model, the majority of atrial flutter is due to a single loop circus movement. During the initiation of a single reentrant loop, an arc of functional conduction block extends to the AV ring, forcing activation to proceed only as a single wave front around the free end of the arc before breaking through the arc at a site close to the AV ring. Activation continues as a single circulating wave front around an arc of block in proximity of the AV ring or around a combined functional/anatomical obstacle with the arc usually contiguous with the inferior vena cava. Spontaneous\textsuperscript{18} or pharmacologically induced\textsuperscript{23} termination of single loop reentrant circuit occurs when conduction fails in a slow zone and the arc of block rejoins the AV ring. It is interesting to note that the development of a single loop circus movement in the model of Brugada et al may have followed similar rules. In Figure 6 of their article, the premature stimulus that initiated a single loop reentry resulted in a functional arc of block that extended to the edge of
the surviving epicardial sheet, that is, up to an anatomical obstacle, forcing activation to proceed only as a single wave front.

**Antiarrhythmic Mechanisms**

Though the effects of antiarrhythmic drugs on specific ion channels and action potential characteristics have been well characterized (with the greatest percentage of studies directed to the effects on normal cellular activity), a precise mechanism of antiarrhythmic action in any model of reentrant rhythms has not emerged to date. While cellular and subcellular studies provide a selective insight into drug effects, the interaction of ionic currents and the means by which electrical activity is propagated between cells require a more integrated approach for understanding the multifaceted mechanisms of arrhythmias and their possible treatment. A working hypothesis is that class I blocking effect on the fast Na⁺ channel is a critical determinant of their antiarrhythmic action with respect to reentrant arrhythmias. Conduction in the reentrant circuit ceases because there is insufficient excitatory current flowing through depressed fast channels that are blocked further by the action of the antiarrhythmic agent. Schoels et al have recently shown that the slow zone of single loop reentrant circuit in the atria, that is, the zone at which Na current may be least intense, is most susceptible to the blocking action of procainamide.

Changes in conduction in the reentrant circuit induced by pharmacologic agents involve a complex interplay of functional properties, including excitability and refractoriness, as well as of anisotropic properties. Antiarrhythmic agents have generally been classified by their ability to alter active membrane ionic properties. Less is known about their direct and indirect actions on cellular coupling and anisotropy. For example, Kadish et al have shown that procainamide normalizes anisotropy by decreasing the ratio of longitudinal to transverse conduction velocity. Our lack of understanding of how these agents affect the heart may be due in part to the present lack of quantitative analyses by which multiple drug effects can be analyzed and compared in vivo. Some investigators have developed experimental models in which the mechanisms of drug action can be evaluated. Allessie and coworkers, using the leading circle concept of reentry, have proposed that the "wavelength hypothesis" may be used as a model to study the effects of antiarrhythmic agents on reentrant activation.

Early studies on arrhythmias caused by circus movement recognized that reentry was possible only if the length of the path exceeded the wavelength of the impulse. Lewis subsequently postulated that an antiarrhythmic drug would terminate circus movement only if it prolonged refractoriness more than it slowed conduction, so that the wavelength of refractoriness exceeded the path length. The wavelength of the cardiac impulse was mathematically formulated by Wiener and Rosenblueth as the distance the depolarization wave traveled during the duration of the refractory period (wavelength equals conduction velocity times refractory period). Since many antiarrhythmic agents affect both refractory period and conduction velocity it was suggested that measurement of the wavelength of the impulse may help to understand their mechanism of action. This approach has been criticized because of the lack of homogeneity in most preparations in which reentry is observed. In other words, the conduction velocities and refractory periods are not uniformly distributed within the reentrant path. Schoels et al have recently investigated the antiarrhythmic mechanism of procainamide on the single loop reentrant circuit in the canine sterile pericarditis model of atrial flutter. In this functional model of reentry, the electrophysiologic properties of the reentrant pathway are markedly nonuniform and the mean spatial value of the wavelength of refractoriness is obviously of little value. The effects of procainamide on refractoriness throughout the reentrant pathway were relatively modest, and the drug always terminated the arrhythmia without abolishing the excitable gap. In fact, procainamide slowed conduction in the slow zone of the reentrant circuit more than it prolonged refractoriness. Termination of circus movement atrial flutter was typically preceded by a large increase in cycle length, which predominately resulted from further slowing of conduction in the slow zone. This increase in conduction time was accompanied by a marked increase in the threshold of excitability and by broadening and slurring of the electrograms in the area of slow conduction. These findings provide evidence that supports the hypothesis that procainamide interrupted circus movement reentry by depressing conduction in the slow zone to a point at which propagation of the impulse became impossible. In contrast to the study by Schoels et al in which the effects of procainamide on refractoriness at crucial sites of the reentrant circuit were investigated, Brugada et al have only shown that flecainide modestly increased refractoriness at selected sites not related to the reentrant circuit, which limits the validity of conclusions drawn from these measurements.

**Proarrhythmic Mechanisms**

The term proarrhythmia is used commonly in reference to provocation of new arrhythmia or aggravation of preexisting ones. However, it is important to remember that the side effects of a drug may be related to depression of ventricular function that would increase the likelihood that an arrhythmia will become hemodynamically unstable. Although most investigators have attributed the increase in sudden death observed in CAST to the proarrhythmic actions of flecainide and encainide, it is also possible that the increase in sudden death mortality was related to the negative inotropic action of these drugs.
One mechanism of proarrhythmia due to drug-induced prolonged repolarization, early afterdepolarizations, and triggered activity, seems to be well established. The proarrhythmia will manifest clinically as prolonged QTU and polymorphic ventricular tachyarrhythmia usually called torsade de pointes. On the other hand, proarrhythmic mechanisms based on reentrant rhythms are less well understood. The study by Brugada et al suggests that a type IC drug that depresses conduction more than it lengthens refractoriness will enhance the chance for circus movement because a shorter functional arc of conduction block will be required to sustain reentry. However, the mechanism by which a type IC drug can create new functional arcs of block is not clear. More importantly, drugs that depress conduction in part of the reentrant pathway would induce a slower reentrant tachycardia. In fact, Brugada et al have shown that flecainide could significantly slow the rate of control reentrant tachycardia that would make the arrhythmia hemodynamically more stable (provided there is no drug-induced cardiodepression). Thus it is difficult to explain the proarrhythmic effect of flecainide solely based on the induction of relatively slower reentrant tachycardia. One possible mechanism for the proarrhythmia will be the induction of one or more smaller reentrant circuits with relatively faster circulation times, thereby enhancing the potential for degeneration into ventricular fibrillation. Such a mechanism has yet to be shown in an experimental model of reentry.

Conclusions

The electrophysiologic substrates of reentrant arrhythmias and their modulation by pharmacologic agents involve a complex interplay of functional properties. The ultimate impact of experimental models of reentrant arrhythmias depends upon how closely these resemble possible clinical situations.

References


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