BASIC PRINCIPLES OF ELECTROPHYSIOLOGY

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Modification of the Electrophysiologic Matrix by Antiarrhythmic Drugs

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Evidence from many experiments and observations suggests that the likelihood of ventricular fibrillation is increased in some proportion to the magnitude of local differences in the electrophysiologic state of the ventricular myocardium. Many local anesthetic antiarrhythmic drugs have differing affinities for resting, open and inactivated fast channels. In ischemic or otherwise damaged hearts, local differences in resting potential, action potential upstroke and action potential duration will result in varying degrees of block of fast channels by local anesthetic antiarrhythmic drugs. Such drugs can be expected to add to the preexisting local inhomogeneities of electrophysiologic state and thereby increase the likelihood of fibrillation.

(J Am Coll Cardiol 1985;5:28B-30B)

Fibrillation occurs when the wave front of the impulse propagating in the ventricles fractionates to form a sufficient number of reentrant circuits (1,2). For the fibrillation to persist, the mass of the ventricles must be great enough to sustain multiple reentrant circuits (3), depending on the imbalance between the duration of refractoriness and the speed of conduction. In ventricles of sufficient size, no other special conditions are necessary for initiation of fibrillation because the arrhythmia can be started by single, properly timed premature impulses or by a progressively accelerating tachycardia (4,5). In human subjects, evidence for the vulnerability of normal ventricles is provided by hearts in which there is an accessory atrioventricular pathway with a short anterograde effective refractory period. Among the most important conditions that increase the likelihood of ventricular arrhythmias and probably predispose to fibrillation are: 1) localized differences in the duration of refractoriness or the period of reduced responsiveness (6), 2) localized differences in the effectiveness of impulse propagation, and 3) localized abnormalities of structure and interfiber communications (7). In the presence of localized differences in the rate of recovery of full responsiveness, a premature impulse is more likely to block in some areas while still propagating in others and in this way establish multiple reentrant circuits.

Effect of Antiarrhythmic Drugs

To reduce the likelihood of fibrillation it thus would seem reasonable to attempt both to prevent premature or other inciting impulses and to decrease the magnitude and extent of local differences in electrophysiologic properties such as refractoriness and safety factor for impulse propagation. It is important to realize that many of the antiarrhythmic drugs administered to prevent or partially suppress ectopic impulses and repetitive ventricular responses can, under appropriate conditions, significantly increase both local differences in the duration of the period of refractoriness or reduced responsiveness and local differences in the speed and certainty of impulse propagation. The antiarrhythmic drugs most likely to do this can be classified as local anesthetics since they block fast inward channels in a dose-dependent manner. The basis for the undesirable effects results directly from their mechanism of action. All of these drugs show a property described as "use-dependence" (8,9). This means that the intensity of effect at a constant concentration is a function of the repetition rate of the action potentials. Thus at a low heart rate and a given drug plasma level, there might be little block of fast inward channels and little drug effect on impulse conduction or refractoriness. At a more rapid heart rate, however, block of fast
channels would increase and effects of the drug on both conduction and recovery of responsiveness would be intensified.

The dependence of the intensity of effect on the interval between action potentials is generally assumed to result from a change in affinity of the drug receptor in the fast channel when the channel passes from the resting, to the open and to the inactivated states (8,10). The affinity of a drug for the channels in the inactivated state typically is much higher than for the resting channel (11). Thus with each action potential, as the channels enter the inactivated state they bind drug. Moreover, the drug-complexed inactivated channel requires a transmembrane potential more negative than the normal resting potential for all of the inactivated channels to return to the rest state.

**Tocainide.** An example of the development of use-dependent block of fast channels in canine Purkinje fibers by tocainide is shown in Figure 1. At a low rate of stimulation, $V_{\max}$, the maximal slope of phase 0, is reduced only slightly from control, but with the onset of more rapid stimulation $V_{\max}$ decreases exponentially to a much lower value. For this example, changes in $V_{\max}$ are assumed to occur in parallel with changes in blockade of fast sodium channels. If the rate of stimulation is then reduced, the increment in block disappears with a time constant typical of the drug employed. The rate of development of block during rapid stimulation is a function of the drug and drug concentration; the rate at which the drug dissociates from blocked channels is a property of the drug.

If the rates of association and dissociation are quite fast, as for lidocaine, use-dependent block will be prominent only at short cycle lengths. Conversely, if association is rapid and dissociation relatively slow, then, at a fixed rate of stimulation, use-dependent block will be prominent only at short cycle lengths. At any rate of stimulation, under conditions of rapid dissociation, use-dependent block will be prominent only at short cycle lengths.

![Figure 1](image1.png)  
**Figure 1.** The effect of tocainide concentration on the rate of development and recovery from use-dependent block. **A,** After maximal rest recovery with either $4 \times 10^{-5} \text{M}$ (△) or $1 \times 10^{-4} \text{M}$ (○) of tocainide, the decline in the maximal slope of phase 0 ($V_{\max}$) during stimulation has been plotted on a logarithmic scale as the difference between $V_{\max}$ obtained at the beginning of the stimulus train and the final reduced value of $V_{\max}$. $\tau$ (tau) the time constant for association of drug with channel decreased from 6.1 to 3.4 beats after the increase in drug concentration. Basic cycle length = 400 ms. **Inset,** Representative action potential configuration changes caused by tocainide. **Upper trace = control,** **lower trace = $1 \times 10^{-4} \text{M}$** of tocainide. Calibrations show 50 ms and 20 mV for voltage traces and 0.5 ms and 200 V/s for dV/dt (rate of change of voltage with time). **B,** The time course of $V_{\max}$ recovery plotted as the percent of maximal rest recovery. Increasing the drug concentration did not influence the rate of recovery of $V_{\max}$ (same fiber as in A). $[K^+]_0 = 5 \text{mM}$. **Inset,** Chart recording from a similar experiment illustrating protocol. **Upper trace** represents $V_{\max}$ signal from peak hold circuit; **lower trace** displays transmembrane potential. Calibrations: 100 V/s and 50 mV vertical, 5 seconds horizontal. (Reproduced from Gintant GA, et al. [14] by permission of the American Heart Association, Inc.)

![Figure 2](image2.png)  
**Figure 2.** The local anesthetic effects of benzocaine. **A,** Control was first determined by varying $[K^+]_0$ in steps from 2.7 to 12 mM, noting the maximal slope of phase 0 ($V_{\max}$) and corresponding membrane activation voltage (MAV) values (○). This sequence was then repeated after equilibration with benzocaine. Shortening the basic cycle length (BCL) from greater than 1 second (○, ○) to 250 ms (△) resulted in slight reductions of $V_{\max}$ of similar magnitude during superfusion with either benzocaine (open symbols) or drug-free Tyrode’s solution (closed symbols). (Reproduced from Gintant GA, et al. [14] by permission of the American Heart Association, Inc.)
slow, as is the case for many antiarrhythmic drugs (11), only a few action potentials in rapid succession will be enough to cause a marked increase in the degree of block.

**Benzocaine.** Figure 2 shows the effect of this local anesthetic antiarrhythmic drug on the relation between membrane potential and \( V_{\text{max}} \). The control curve shows the usual relation, with the maximal value of \( V_{\text{max}} \) obtained at membrane potentials equal to or slightly negative to the normal resting potential, and a reduction in \( V_{\text{max}} \) to 50% at a membrane potential around \(-70\) mV. In the presence of the drug, the curve is shifted to the right, that is, to more negative potentials. Under this condition, \( V_{\text{max}} \) is not restored to its maximal value at the normal resting potential, and the 50% reduction occurs at a potential more negative than \(-70\) mV. The effect of this apparent shift of the curve on refactoriness and conduction can be significant.

**Localized inhomogeneities of conduction and refractoriness.** The ability of this type of drug action to cause localized inhomogeneities of conduction and refractoriness in the ventricles is clear. At a normal heart rate, if resting potential in some area has been reduced by ischemia, drug effect in this area will be more intense than elsewhere because a greater than usual fraction of fast channels will persist in the inactivated state. As a result, the safety factor for impulse propagation will be reduced, even above the reduction resulting directly from the reduced resting potential. Since current in fast channels contributes to action potential duration (12,13), the augmented block of fast channels may cause a local reduction in action potential duration. More important, however, will be a local increase in the period of refractoriness and reduced responsiveness. This happens because at a less negative resting potential, the dissociation of drug from inactivated channels will be slowed. If, under the same conditions, there was an increase in heart rate, the changes just described would be intensified to a degree that caused marked slowing of impulse propagation in the ischemic area with the development of local areas of block. A similar increase in inhomogeneity of refractoriness might occur as a consequence of a significant decrease in heart rate. In this case, one can assume that before the period of cardiac slowing, block of sodium channels by local anesthetic had decreased action potential duration throughout the ventricles. With the onset of the long cardiac cycles, action potential duration in normally polarized areas will increase significantly as use-dependent block of fast channels diminishes. In partially depolarized areas, dissociation of drug from fast channels will be less complete and the action potential and refractory period will remain short.

**Matrix for repetitive ventricular responses and fibrillation.** Local differences in the functional properties of the ventricles seem to increase the likelihood of repetitive responses and fibrillation or rapid stimulation. The mode of action of many local anesthetic antiarrhythmic drugs suggests that they have the potential to greatly increase the degree of functional inhomogeneity and thus create a matrix suitable for sudden death.

**References**


