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Alteration of defibrillation threshold by antiarrhythmic drugs: a theoretical framework

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Drugs may alter the ventricular defibrillation threshold, either to make resuscitation easier or more difficult. Assuming that cardiac defibrillation is essentially large scale stimulation of non-refractory areas in the fibrillating muscle mass [1], the action of cardiac drugs can be understood theoretically in terms of their influence on the transmembrane sodium and potassium currents, I_{Na} and I_K . The magnitudes of these ionic currents are functions of the transmembrane potential, E_m , as shown in Figure 1(a).

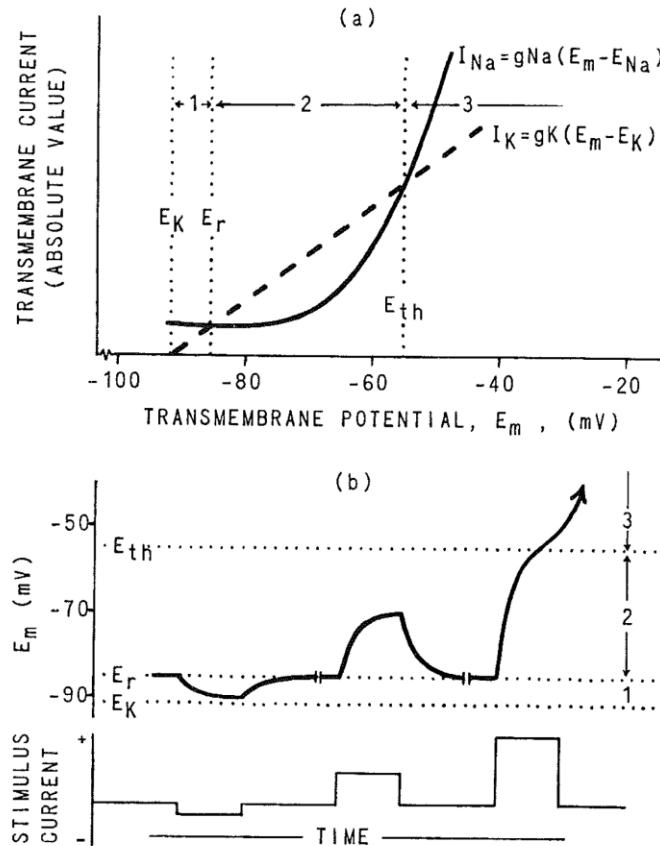


FIG. 1. Balance of inward sodium and outward potassium currents in ventricular cells during diastole. (a) Absolute values of sodium and potassium currents as a function of transmembrane potential. (b) Effects of alterations in membrane potential by electrical stimuli.

Here g_{Na} and g_K denote sodium and potassium conductances of the membrane, and E_{Na} and E_K denote Nernst equilibrium potentials. The solid curve denoting sodium current is concave upwards because of the voltage dependence of fast sodium channels.

Depolarization itself induces a sudden increase in g_{Na} ; while at this stage of the cardiac cycle, g_K is essentially constant. The sodium and potassium current curves, therefore, cross at two points where inward sodium current and outward potassium current are equal. One point represents a stable equilibrium--the resting membrane potential, E_r . The other is an unstable equilibrium--the cellular firing threshold, E_{th} . These two points divide the transmembrane potential domain into three zones, labeled 1, 2, and 3 in Figure 1(a).

The intensity of the electrical stimulus required to excite the ventricular muscle cell is related to the width of zone 2. As illustrated in Figure 1(b), if E_m is transiently driven into either zone 1 or zone 2, it will return to the stable equilibrium value, E_r , driven by the net ionic current. However, if E_m is driven past the cellular firing threshold into zone 3, an action potential will be initiated and the cell will become refractory. The intensity of the stimulus required to excite the cell in this way depends upon the extent of zone 2.

In theory, drugs that increase g_K or decrease g_{Na} will widen zone 2 ($E_{th} - E_r$) and so increase the strength of the stimulus required for excitation. In turn, these drugs will increase the defibrillation threshold. Drugs that decrease g_K or increase g_{Na} will narrow zone 2 and reduce the defibrillation threshold.

The authors have studied a variety of antiarrhythmic drugs to determine their effect on ventricular defibrillation threshold in dogs. Drugs that decrease sodium conductance, such as quinidine, or that increase potassium conductance, such as lidocaine, raise the defibrillation threshold [2]. The new antifibrillatory drug, cloflium (LY 150387), which decreases potassium conductance and prolongs the action potential duration, in fact lowers defibrillation threshold, as predicted from theory. Digitalis glycosides, which act by inhibiting the membrane bound sodium-potassium "pump" and reduce the net outward sodium current, also lower the defibrillation threshold.

One final ionic mechanism should be mentioned. Shift of the potassium equilibrium potential, E_K depends upon the $(\log K_o/K_i)$, where K_o and K_i represent extracellular and intracellular potassium concentrations. Moderate elevation of extracellular potassium concentration makes E_K less negative, shifting the dashed line for potassium current in Figure 1(a) to the right without changing its slope. This effect decreases the extent of zone 2 and increases excitability. Infusion of potassium chloride in dogs is known to lower defibrillation threshold, and at a critical level of K_o spontaneous defibrillation occurs [5]. Extremely high levels of K_o , which cause a shift of the potassium current line completely to the right of the sodium current curve, make the cell inexcitable, because a normal resting potential cannot be restored. This last state may exist during the use of "cardioplegic" solutions to immobilize the heart at surgery.

A summary of results from animal studies of ventricular defibrillation is given in Table 1.

Table 1

Treatment	Maximal % change in threshold cur- rent	Maximal % change in threshold energy
Lidocaine (3 mg/kg)	+26	+48
Quinidine (50 mg/kg)	+70	+172
Clofilium (0.34 mg/kg)	-21	-54
Ouabain (0.05 mg/kg)	-14	-28
Hyperkalemia (7.5 mEq/L)	-19	-37

Evidently, the actions of cardiac drugs on the defibrillation threshold can be understood in terms of basic electrophysiology. In practice, classical antiarrhythmic drugs do not reduce the defibrillation threshold and should not be given for this purpose. Potassium doses lower threshold but also produces an unwanted negative inotropic effect. Digitalis lowers threshold, but only at toxic doses. Newer agents, such as clofilium, which act by other than a local anesthetic mechanism, may have the dual advantage of reducing defibrillation threshold while preventing recurrent episodes of fibrillation. Such drugs may offer a special theoretical advantage for the hospitalized patient with recurrent ventricular fibrillation and may even be of value when administered during advanced life support.

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