Drug Induced Changes in Ventricular Defibrillation Threshold

Charles F. Babbs
Purdue University

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DRUG INDUCED CHANGES IN VENTRICULAR DEFIBRILLATION THRESHOLD

A Thesis

Submitted to the Faculty

of

Purdue University

by

Charles Frederick Babbs

In Partial Fulfillment of the
Requirements for the Degree

of

Doctor of Philosophy

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ABSTRACT


A theory is developed that the minimal current required for electrical ventricular defibrillation (the defibrillation threshold) is proportional to the gap between the resting transmembrane potential and the threshold transmembrane potential of myocardial cells. This voltage gap is, in turn, related to the sodium conductance (gNa) and the potassium conductance (gK) of the membrane and to the transmembrane equilibrium potentials for sodium (E_{Na}) and potassium (E_{K}). To test the theory pharmacologic studies were performed. First, the stability and precision of control data and, second, the effect upon defibrillation threshold of quinidine (which alters gNa), lidocaine (which alters gK), and potassium chloride (which alters E_{K}) were evaluated in pentobarbital-anesthetized dogs. Threshold was determined by repeated trials of fibrillation and defibrillation with successive damped sinusoidal shocks of diminishing current intensity, each 10 percent less than the preceding shock. The lowest shock intensity that defibrillated was defined as threshold.
Threshold current and energy in five dogs averaged 2 percent and 13 percent less, respectively, under surgical levels of pentobarbital anesthesia than thresholds in the same animals in the awake, unanesthetized state. In dogs given sufficient pentobarbital to produce apnea and supported by mechanical ventilation, threshold current and energy averaged 3 percent and 17 percent less than comparable awake values. These differences were not statistically significant. Pentobarbital was consequently selected as the anesthetic for defibrillation studies.

Over 200 measurements of ventricular defibrillation threshold were made to determine the stability and precision of threshold data. In three groups of five dogs each, threshold was measured at intervals of 60, 15, and 5 minutes over periods of 8, 5, and 1 hour, respectively. Similar results were obtained for all groups. There was no significant change in mean threshold current with time. Due to a decrease in transchest impedance, threshold delivered energy decreased by 10 percent during the first hour of testing. Standard deviations for threshold peak current and delivered energy in a given animal were 11 and 22 percent of their respective mean values. Arterial blood pH, pCO₂, and pO₂ averaged 7.38, 34 mmHg, and 72 mmHg, respectively. The rates of change of pH, pCO₂, and pO₂ were not significantly different from zero. Ventricular defibrillation threshold is therefore a stable
physiologic parameter which may be measured with reasonable precision for pharmacologic studies.

Drug effects on threshold delivered energy and peak current, expressed as percentages of pre-drug threshold, are given in the table. Table entries indicate maximal changes in mean defibrillation threshold.

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Observed drug effects are consistent with theoretical predictions that drugs which decrease gNa or increase gK increase defibrillation threshold and drugs which make $E_K$ less negative decrease defibrillation threshold.
CHAPTER 1

BACKGROUND AND THEORY

Statement of the Problem

The studies described in this thesis were conducted to determine the manner in which selected drugs influence the electric shock intensity required for ventricular defibrillation. Electrical defibrillation, the application of a strong electric shock to the heart, is the only safe and effective therapy for ventricular fibrillation, an otherwise lethal cardiac rhythm. In theory, the passage of an electric shock on the order of 100 ma/cm$^2$ through the ventricles for 2-30 msec will simultaneously stimulate most ventricular muscle cells, causing potentially excitable cells to be refractory for a brief interval thereafter. This intervention stops the self-propagation of the multiple random waves of excitation which constitute fibrillation. The minimum shock intensity required to produce defibrillation is defined as the "defibrillation threshold." In Chapter 1 of this thesis a theory is developed which states that defibrillation threshold is determined by the difference between the resting transmembrane electrical potential and the
firing or threshold potential of individual myocardial cells. Drugs which act at the cellular level to narrow the gap between the resting potential and firing potential of working myocardial cells would be expected to decrease the electrical defibrillation threshold. Obversely, drugs which widen this gap would be expected to increase defibrillation threshold. Further theoretical analysis based upon fundamental principles of membrane physiology indicates that drugs which alter the sodium or potassium conductance of cell membranes, or the ratio of intracellular to extracellular sodium or potassium concentration should alter the difference between the resting potential and firing potential of cardiac cells and in turn alter the defibrillation threshold.

The present research, therefore, includes three aspects: first, development of a theory which predicts in a semiquantitative fashion the electrical shock intensity for defibrillation and the possible mechanisms by which drug treatments could alter the threshold; second, the development of a suitable animal model for experimental investigation of drug effects on ventricular defibrillation threshold; and third, the comparison of experimentally produced drug effects with theoretical predictions. Chapters 1, 2, and 3 deal respectively with these aspects of the problem.
Mechanisms of Fibrillation

Ventricular fibrillation, the most dangerous cardiac arrhythmia, is a common immediate cause of death in patients with heart, lung, or kidney disease. During this arrhythmia, there is random, uncoordinated contraction of multiple areas of muscle in the cardiac ventricles. When viewed directly, the heart appears as a shimmering mass of tissue. Upon close inspection multiple, unsynchronized waves of contraction and relaxation can be seen traversing the ventricular surface in random directions. As a result of this arrhythmia no blood is pumped and circulation to the brain, the heart itself, and other vital organs comes to a standstill. Ventricular fibrillation causes certain death if resuscitative measures and definitive therapy are not begun within three to five minutes (Stephenson, 1974). Circulation adequate to sustain life may be maintained for up to several hours by massage of the fibrillating ventricles, using open or closed chest techniques in conjunction with artificial ventilation. However, spontaneous defibrillation of the ventricles virtually never occurs in humans.

The Circus Motion Theory

The simplest theory describing a mechanism for ventricular fibrillation is the circus motion theory of Garrey (1914). Development of a "circus motion" may be demonstrated in rings of myocardium such as those illustrated
in Figure 1-1. Such rings were created by Mines (1913) by cutting the atria of the ray fish and by Garrey (1914) by cutting the turtle ventricle. Such a ring of mammalian ventricle is normally excited by Purkinje fibers which first stimulate subendocardial muscle fibers. The impulse then spreads from subendocardial muscle to the epicardial surface (Figure 1-1(a)). Further spread of the impulse is impossible because ventricular muscle is refractory for about 300 msec. Hence such a normally conducted impulse cannot become self-propagating.

A typical premature ventricular contraction (PVC) is likewise not self-propagating. An impulse arising from a single focus in the ventricular wall and spreading in all directions will coalesce on the side of the heart opposite its origin and annihilate itself due to the refractoriness of the converging masses of recently excited tissue (Figure 1-1(b)).

In injured hearts containing patchy areas of refractoriness during early diastole, however, PVCs are more dangerous. In Figure 1-1(c) an impulse arising from an irritable focus at the edge of an injured area is blocked in one direction due to prolonged refractory period in the injured tissue. The impulse therefore travels only clockwise around the ventricular wall. Traveling at 50 cm/sec such an impulse would close the loop around a 5 cm diameter ventricle (16 cm in circumference) in 320 msec,
Figure 1-1. Development of circus motions in rings of ventricular myocardium. (a) Normal excitation via subendocardial Purkinje fibers. (b) Excitation during a typical PVC, originating at an irritable focus. (c) Excitation by a PVC originating at the edge of a transiently refractory area, leading to a self-perpetuating circus motion. (d) Development of a circus motion in a dilated heart.
adequate time for the muscle first stimulated by the PVC to recover sufficiently to be excited by the "reentrant" impulse. Under these conditions, a self-propagated "circus motion" would develop, that is, the impulse would be conducted around and around the myocardium.

The time available for recovery of the initially excited myocardium and the probability of development of circus motions are enhanced in failing hearts which are both injured and dilated. In such hearts, the path length of potential circus motions is increased (Figure 1-1(d)). For example, in a dilated 8 cm diameter ventricle (25 cm in circumference), a blocked unidirectional impulse would require 500 msec to travel completely around the wall, allowing ample time for recovery of initially refractory fibers.

The Impulse Wavelength

From Figure 1-1 it is evident that the impulse conduction velocity multiplied by the refractory period gives the length of the strip of refractory myocardium. The product of conduction velocity and effective refractory period may be defined as the "wavelength" of the impulse of depolarization. A normal value for the impulse wavelength in mammals is about 10-30 cm (Hoffman and Cranefield, 1960). As illustrated in Figure 1-1(d), if the impulse wavelength is less than the ventricular
circumference then the development of circus movements becomes possible, especially in the presence of patchy areas of refractoriness caused by ischemia, cooling, or rapid, repetitive stimulation. On the other hand, small hearts of circumference less than 10-30 cm (diameter less than 3-10 cm) may be unable to sustain fibrillation according to the circus motion theory. Rabbits possess hearts with dimensions equal to or below the theoretical limit for circus motion, and indeed smaller rabbit hearts will not sustain fibrillation at normal body temperatures whereas larger rabbit hearts may fibrillate (Geddes, 1977).

The Relation of Circus Motions to Fibrillation

If a circus motion of the type diagrammed in Figure 1-1 occurred circumferentially about the long axis of a left ventricle composed of uniformly excitable tissue, the rhythm known as ventricular flutter would be present. Ventricular flutter usually exists only for a short time and usually degenerates into fibrillation. Because of the asymmetrical geometry of the heart, the depolarization wavefront of a circus motion soon breaks up into multiple wavefronts upon encountering the junction between right ventricular free wall and interventricular septum, the mitral and tricuspid valve rings, or islands of refractory tissue. The closed-loop pathways permitting ventricular re-excitation become multiple, convoluted, and ever-changing as true ventricular fibrillation develops.
The Ectopic Focus Theory

The ectopic focus theory concerning the electrical events leading to fibrillation was proposed by Scherf and Terranova (1944). They postulated that rapid, repetitive excitations arise spontaneously from hyperirritable foci of myocardium to which the cardiac tissue is unable to respond in a synchronous fashion. Friedberg (1966) has suggested several mechanisms by which such ectopic foci could arise. First, several of the areas of latent pacemaker tissue might become active simultaneously, for example, in response to beta adrenergic hormones. Second, electrical potentials might be created between different areas of cells, resulting in stimulation of the fibers. Such potentials might develop if some cells were damaged, and maintained resting membrane potentials less than the potentials found in normal adjacent fibers. Finally, cells which do not normally act as pacemakers might become pacemakers under pathological circumstances. Heart size is also an important factor in the multiple pacemaker theory, in that the likelihood of multiple pacemaker sites increases when larger masses of tissue are available. Both the circus motion theory and the ectopic focus theory may be invoked to improve one's understanding of the phenomenon of ventricular fibrillation. The ectopic focus theory emphasizes pathophysiologic factors which can initiate ventricular fibrillation. The circus motion theory
emphasizes pathophysiologic factors which lead to the perpetuation of ventricular fibrillation. A synthesis of both theories is therefore possible in which the presence of ectopic foci in sufficiently large hearts may lead to the phenomenon of sustained ventricular fibrillation.

**Mechanisms of Defibrillation**

Application of a strong, electric shock to the heart is the only dependable and definitive therapy for ventricular fibrillation. When properly applied, this shock causes all heart muscle fibers to cease contracting and stops the fibrillation. Usually, within a few seconds after the shock, a normal pacemaker will begin triggering synchronous ventricular contractions and cardiac pumping is resumed.

The phenomenon of electrical ventricular defibrillation was first reported by Prevost and Battelli (1899 a-d). However, interest in the phenomenon was not revived until after Hooker (1930) had developed the chemical method of defibrillation. This method, which was used when appropriate in clinical medicine until the late 1950s, involved injecting KCl solution directly into the left ventricle. Massage of the heart, especially with occlusion of the thoracic aorta, forced the potassium solution into the coronary circulation. This achieved defibrillation but also left the heart completely hypodynamic. Therefore,
CaCl₂ solution was next injected into the left ventricle and massaged into the coronary bed to expel the KCl and counteract its depressant effect. Subsequently Hooker, Kouwenhoven, and Langworthy (1933) came upon the Prevost and Battelli papers and confirmed that although low intensity alternating current shocks produced ventricular fibrillation, higher intensity shocks could arrest fibrillation. After over a decade, the technique of 60 Hz alternating current defibrillation was introduced into clinical medicine by Beck (1947), using electrodes applied directly to the heart, and Zoll (1956), using transchest electrodes. Thereafter several investigators including Gurvich (1947), Kouwenhoven (1954), and Lown (1962) discovered that, compared to alternating current shocks, a brief direct current shock provided by discharge of a capacitor or a capacitor in series with an inductor could also defibrillate the atria with less danger of producing ventricular fibrillation at low shock intensity. These studies led to the development of modern defibrillators, most of which contain a capacitor and an inductor. The capacitor is charged by a direct current power supply to a preset voltage. At the time of defibrillation, the capacitor is switched in series with the inductor and the subject. A heavily damped sinusoidal pulse of current lasting 2-10 msec is thereby delivered. If the current passes through a critical mass of myocardium
and is of sufficient intensity, defibrillation is routinely achieved.

The Electrophysiologic Requirement for Defibrillation

The effect of current delivered by defibrillators upon the cellular electrophysiology of the heart has not yet been studied directly. This section presents a theory which indicates that although extremely high currents and voltages appear across the heart and thorax during defibrillation, the stimulus at the cellular level is physiologic, and inherently nontoxic if properly applied. Moreover, the hypothesis supports the notion that the actions of drugs upon transmembrane ionic conductances and equilibrium potentials should influence the effectiveness of electrical ventricular defibrillation.

The fundamental tenet of the hypothesis is that the essential requirement for defibrillation is excitation of a critical mass of the nonrefractory cells in the myocardium (Zipes, 1975). It must be recognized that at any instant in time during fibrillation myocardial cells may be found in any phase of polarization (Figure 1-2).

Phases 0, 1, 2, 3, and 4 of the cardiac action potential, identified in the literature of cardiac electrophysiology (Vassale, 1977; Arnsdorf, 1976, Hoffman and Cranefield, 1960), are defined as follows. Phase 4 is the resting membrane potential, typically -80 to -90 mV (inside
Figure 1-2. Temporal dispersion of action potentials in fibrillating myocardium. Action potentials of 4 hypothetical cells, A, B, C, and D are indicated as functions of time. During fibrillation cells may be found in any stages of polarization at any instant in time. During fibrillation Phase 4 is usually abbreviated (Cells B and C), and often excitation may occur in the latter part of Phase 3 (Cell A); the height of typical action potentials in fibrillation is about 75 mV (Sano, 1958).
of the cell negative). During Phase 4 small inward sodium and outward potassium ionic currents are in balance for working myocardial cells. In pacemaker cells, gradual diastolic depolarization may occur due to an imbalance in these ionic currents. Phase 4 is succeeded by Phase 0, or depolarization, the rapid upstroke of the cardiac action potential. Phase 0 is associated with a rapid increase in sodium conductance and inward sodium current caused by suprathreshold stimulation of the cell, as the transmembrane potential is caused to exceed a critical "firing threshold" voltage (typically \(-50\) to \(-60\) mV). Phase 1 is the brief overshoot or reversal of the transmembrane potential at the time of maximal sodium conductance. Phase 2, the plateau of the cardiac action potential, has recently been shown to be sustained by inward calcium current. In Phase 3 potassium conductance becomes dominant and the resultant outward potassium current leads to repolarization of the cell and a return to Phase 4. During Phases 0, 1, and 2 the cell cannot be stimulated, since it is already depolarized. This period is defined as the absolute refractory period. During the midportion of Phase 3, the descending limb of the action potential, the cell may be stimulated by suprathreshold stimuli and is said to be relatively refractory. During the terminal portion of Phase 3, the cell may be hyperirritable.
If fibrillation is conceived as the presence of numerous randomly oriented wavefronts of depolarization, spreading throughout the myocardium as represented in Figure 1-3, then electrical defibrillation requires simultaneous excitation of the cells just ahead of each wavefront. These cells would be found either in Phase 4 of polarization or in the latter part of Phase 3. A critical assumption of this hypothesis is that for the purpose of defibrillation the cells requiring the strongest stimulus for excitation are those completely repolarized cells in Phase 4. A noteworthy implication of this assumption is that it is not necessary to excite those cells in the midportion of Phase 3, which are relatively refractory, in order to defibrillate. Nor is it necessary to effect cells in Phases 0, 1, or 2. The hypothesis assumes that it is necessary only to depolarize one side of the cell membrane of each cardiac muscle cell to the extent of the difference between the resting (Phase 4) membrane potential and the cellular firing threshold. This stimulus would be sufficient to excite all fully recovered cells as well as all cells just emerging from their relative refractory period.

The Action of Defibrillating Current
At the Cellular Level

Consider a rectangular block of ventricular myocardium containing muscle cells, extracellular fluid, blood vessels,
Figure 1-3. Schematic representation of multiple, random wavelets of depolarization traversing the ventricles during fibrillation. Heads of arrows indicate the wavefront of each wavelet and its direction of propagation. Tails of arrows indicate length of refractory tissue strips trailing each wavefront. When a wavefront encounters a refractory strip it will split into daughter wavelets or become extinguished. In sustained fibrillation successive generations of wavelets are always able to spread into areas of excitable myocardium. In theory, an effective stimulus from a defibrillator simultaneously excites and renders refractory the tissue just ahead of each wavefront, abolishing their propagation.
and connective tissue. Assume that the long axes of the muscle cells are oriented perpendicular to the flow of defibrillating current as would be true for most of the circumferential ventricular fibers in open chest defibrillation (Figure 1-4(a)). Consider a very thin section of this block of tissue 15µ thick and 1cm² in surface area, as illustrated in Figure 1-4(b). The 15µ thickness is chosen because this is the diameter of a typical ventricular muscle fiber. This thin slice of tissue can be divided conceptually into resistive and capacitive components, as shown in Figure 1-4(c). The resistive component consists of the electrolyte filled extracellular space which comprises about 30 percent of the volume of mammalian ventricular muscle (Frank and Langer, 1974). The capacitive component consists of muscle and connective tissue cells, about 70 percent of ventricular volume, which are surrounded by high resistivity cell membranes. The cell membranes of cardiac muscle have been modeled as parallel resistive-capacitive networks (Woodbury, 1962), but membrane resistance is so large with respect to the extracellular fluid resistance (2,000 ohms for 1cm² versus 0.3 ohms for 1cm²) that membrane resistance can be ignored for the present discussion and the membranes considered as purely capacitive, as shown in Figure 1-4(d).

If a direct current pulse is applied to the network depicted in Figure 1-4(d), current will flow initially onto the series capacitors, causing them to charge. This
Figure 1-4. Scheme for analysis of the action of defibrillating current upon myocardial cells. (a) Bundle of myocardial fibers oriented perpendicular to electric current field. (b and c) Hypothetical tissue element 1 cm² in cross-sectional area and one cell diameter in thickness, containing cells and extracellular fluid. (d) Equivalent circuit for hypothetical tissue element.
charging of membrane capacitance will tend to depolarize the cathodal side and hyperpolarize the anodal side of the cell. The time for membrane capacitors to charge maximally is about five "RC" time constants; thereafter all of the current flows through the extracellular fluid resistance, at which time the final voltage across both series capacitors is equal to the voltage drop across the resistor, $R_{ECF}$.

Values of $R$ and $C$ from the literature may be substituted into the equivalent circuit of Figure 1-4(d) in order to estimate the gross electrical effects of the passage of a $100 \text{ ma/cm}^2$ threshold pulse of defibrillating current through the hypothetical $15\mu \times 1 \text{ cm}^2$ slice of myocardium. The estimate of $100 \text{ ma/cm}^2$ threshold current density is derived from data on open-chest defibrillation with electrodes of specified size, obtained recently in our laboratories (Grubbs and Wilcox, 1975). This figure is also consistent with estimates derived from published open-chest threshold data (Geddes, 1970; 1974). Membrane capacitance of Purkinje fibers has been measured by Weidmann, (1952) and confirmed by others (Arnsdorf and Bigger, 1975), who obtained a value of approximately $10\mu \text{F}$ for $1 \text{ cm}^2$ of membrane. These authors also determined the overall resistivity of intracellular fluid to be approximately 100 ohm-cm. The resistivity of extracellular fluid is assumed to be approximately that of plasma, or about 60 ohm-cm. Given
these values, the resistances and capacitances of Figure 1-4(d) may be calculated and are indicated in Figure 1-5. The resistance of the extracellular fluid, indicated in Figure 4-1(c), is the product of the resistivity of the medium and the "length" of the fluid slab in the direction parallel to current flow, divided by the cross-sectional area of the fluid slab: $60 \text{ ohm-cm} \times 0.0015 \text{ cm} / 0.3 \text{ cm}^2$ or 0.3 ohm. The final voltage to which both series membrane capacitors are charged by a $100 \text{ ma/cm}^2$ defibrillating shock is $100 \text{ ma} \times 0.3 \text{ ohm}$ or $30 \text{ mV}$.

Charging the membrane capacitors results in hyperpolarization of the anodal side and depolarization of the cathodal side of the typical 15μ diameter cell, shown in Figure 1-5(b). If $30 \text{ mV}$ potential difference is divided equally across the series membrane capacitors, the anodal side of the 15 micron cell is depolarized by $15 \text{ mV}$ and the cathodal side hyperpolarized $15 \text{ mV}$. Such a change is of the order of that necessary to bring the transmembrane potential on the cathodal side of the cell from a resting potential to the firing threshold.

Note that if the myocardial fibers in the hypothetical block of tissue were oriented parallel rather than perpendicular to the direction of current flow, the "length" of the slab of extrafluid extracellular fluid would be greater. A greater final voltage difference would develop across this distance causing correspondingly greater changes.
Figure 1-5. Equivalent circuit for a hypothetical slice of myocardium 1 cm$^2$ in cross-sectional area and one cell diameter in thickness. (a) Approximate values of the circuit elements. (b) Steady state voltage differences caused by the passage of an electric current of defibrillating intensity.
in the transmembrane potential at the cathodal and anodal ends of the cell. Hence any shock able to stimulate fibers oriented perpendicular to the current flow would also be able to stimulate fibers oriented parallel to the current flow.

Also note that the time for membrane capacitance to charge to very near the maximal voltage is a matter of several "RC" time constants for the myocardial cells. Using the values 10 ohm-cm$^2$ for membrane capacitance, 100 ohm-cm for intracellular fluid resistivity, and 0.0015 cm for cell length and 1 cm$^2$ for aggregate cell surface area, the time constant for charging of membrane capacitance is $5 \times 10^{-6}$ sec. The time constant for voltage-dependent activation of sodium conductance, however, is much longer, on the order of 0.5 msec (Ehrenstein, 1976; Hodgkin and Huxley, 1952).

The passage of current through cardiac tissue via macro-electrodes rapidly changes the transmembrane potential of cells within a few microseconds. However, the cathodal side of the cell must remain above the firing potential for several milliseconds before sodium activation will become sufficient to cause rapid sodium inrush, depolarization, and refractoriness.

The hypothesis presented in this thesis is that the essential requirement for defibrillation is depolarization of one side of cardiac cells by a voltage equal to the "gap" $E_r - E_{th}$, between the resting membrane potential and the
cellular firing threshold for a sufficient time to allow activation of sodium conductance. Since the amount of depolarization is proportional to the current density delivered by the shock, drugs could conceivably alter the current required for defibrillation by altering either the firing threshold, $E_{th}$, or the resting membrane potential, $E_r$.

**Possible Mechanisms of Drug Action**

Agents which raise the cellular firing threshold, hyperpolarize resting cells, or both are predicted to increase the $E_r - E_{th}$ gap and the current required electrical stimulation or defibrillation of the heart. Agents which decrease the cellular firing threshold, hypopolarize resting cells, or both are predicted to decrease the gap and the current required for stimulation or defibrillation of the heart.

The likely ways in which drugs might produce such changes may be appreciated with reference to established principles of cardiac membrane physiology for cells in Phase 4 and Phase 0.

The transmembrane potential, $E_m$, is the voltage to which the cell membrane capacitance is charged at any instant in time. $E_m$ is determined by the balance of ionic currents across the membrane. Although the importance of calcium currents in maintaining $E_m$ have been recently
identified for ventricular muscle cells during Phase 2 (Beeler and Reuter, 1970; Gibbons and Fozzard, 1975), the ions involved in Phase 4 and Phase 0 are almost exclusively sodium and potassium for both ventricular muscle and for nerve (Hoffman and Cranefield, 1960; Vassale, 1977). The net ionic current from one side of the cell membrane to the other depends upon the membrane conductance (g) of the ion and the electrical driving force impelling the ion. The driving force is defined as the difference between the equilibrium potential for the ion ($E_{ion}$) and the instantaneous membrane potential ($E_m$). The resultant net ionic current may be predicted by the ohmic relationship

$$I_{ion} = g_{ion} (E_m - E_{ion}).$$

The equilibrium or reversal potential, $E_{ion}$, is determined by the ratio of intracellular to extracellular concentration of the ion by the Nernst equation

$$E_{ion} = \frac{RT}{F} \ln \frac{[ion]_i}{[ion]_o};$$

where square brackets indicate molar concentrations, and the subscripts $i$ and $o$ denote "inside and "outside" the cell. Evaluating the physical constants and converting to common logarithms, the Nernst equation becomes $E_{ion}$ (in mV) = 61.5 $\log([ion]_i/[ion]_o)$, for monovalent cations at body temperature selectively permeable to the membrane. The ionic
conductance, \( g(\text{ion}) \), is a function of both \( E_m \) and of time. The time dependence of \( g(\text{ion}) \) reflects the kinetics by which presumed ionic channels traversing the membrane open and close following a change in \( E_m \).

During Phase 4 and Phase 0, the membrane potential is determined by the balance between the transmembrane sodium current, \( I_{Na} \), and the transmembrane potassium current, \( I_K \). Since \( E_{Na} \) is positive (typically +80 mV) and greater than \( E_m \), and since \( E_K \) is negative (typically -90 mV), the sodium current is inward, tending to depolarize the cell, and the potassium current is outward, tending to hyperpolarize the cell. The \( g_{Na} \) at the time of the transition between Phase 4 and Phase 0 is a rapidly increasing (concave upward) function of \( E_m \); whereas \( g_K \) is assumed to be approximately constant. More rigorous theoretical expressions for \( g_{Na} \) and \( g_K \) of nerve-cell membranes as functions of voltage and time have been described elsewhere (Ehrenstein, 1976; Hodgkin and Huxley, 1952), which indicate that there is a measurable voltage dependent increase in \( g_K \) during Phase 0. However, compared to the very large increase in \( g_{Na} \) during excitation, \( g_K \) remains relatively stable just before and after the onset of Phase 0. Only later, after Phase 0 has irrevocably begun, does potassium conductance markedly increase (Hodgkin and Huxley, 1952). The present discussion is concerned only with events just before and after the rapid sodium influx which initiates Phase 0, so it is
reasonable as a first approximation to treat $g_K$ as a constant.*

Given the assumptions that $g_{Na}$ is an accelerated function of $E_m$ and that $g_K$ is essentially constant at the time of excitation, the transmembrane currents involved may be illustrated as shown in Figure 1-6(a). This figure illustrates hypothetical transmembrane sodium and potassium currents, as conceived by the author, at different levels of $E_m$. $I_K$ is a linear function of $E_m$, increasing as the membrane potential is made more positive than the potassium equilibrium potential. $I_{Na}$ is an accelerated function of $E_m$, indicating the voltage dependent increase in $g_{Na}$ as the membrane potential is made less negative. To permit easy comparison of the magnitudes of the ionic currents in opposite directions across the membrane, the absolute values of $I_{Na}$ and $I_K$ are plotted. The straight line for potassium current and the curved line for sodium current intersect at two points for which $I_{Na} = I_K$. The left-hand point is a stable equilibrium and indicates the resting membrane potential. The right-hand point is an unstable equilibrium and indicates the cellular firing threshold. This feature of Figure 1-6(a) may be appreciated by considering the effects of hyperpolarizing and depolarizing electrical

*If $g_K$ is considered more exactly as an increasing function of $E_m$ with a derivative significantly less than that of the $g_{Na}$ versus $E_m$ curve, the predictions of the present theory would be qualitatively the same with only minor quantitative differences.
Figure 1-6. Balance of inward sodium and outward potassium currents in ventricular myocardial cells during Phase 4 and early Phase 0. (a) Absolute values of sodium and potassium currents are plotted as a function of transmembrane potential, $E_m$. Zones 1, 2, and 3 of the $E_m$ domain are identified. (b) Effects of alteration of $E_m$ by electrical stimuli. If $E_m$ is transiently driven into Zone 1 or Zone 2 it will return to the stable equilibrium value, $E_r$. If $E_m$ is driven into Zone 3, an action potential will be initiated.
stimuli which might be delivered via an intracellular microelectrode connected to a constant current source. The results of such hypothetical stimulation are shown in Figure 1-6(b). Suppose a hyperpolarizing current is used to drive the $E_m$ more negative than $E_r$ into the zone denoted (1). After the current is terminated, the inward sodium current will be greater than the outward potassium current, and the cell will depolarize until $I_{Na} = I_K$ at the resting membrane potential. If a low amplitude, depolarizing current is delivered, driving the $E_m$ into zone (2) and then terminated, the outward potassium current will be greater than the inward sodium current, again driving the $E_m$ back toward the $E_r$. Such a current would constitute a subthreshold stimulus. However, if a stronger depolarizing current were to drive the $E_m$ into zone (3), the inward sodium current would exceed the outward potassium current, causing further depolarization of the cell and initiating Phase 0. Such a current would constitute a suprathreshold stimulus. The right-hand intersection of the sodium and potassium current functions, therefore, represents the cellular firing threshold. The voltage gap $E_r - E_{th}$ to which the membrane capacitance of the cell must be charged to initiate an action potential is represented by the horizontal distance between the intersections of the sodium and potassium current functions.
**Prediction of Drug Effects**

Using this graphical representation of the critical ionic currents involved in excitation of the cell, it is easy to identify four general mechanisms by which drugs could alter the strength of the electrical stimulus required to excite the cell. These include alteration of the $g_K$, alteration of the $g_{Na}$, alteration of the $E_K$, and alteration of the $E_{Na}$.

For example, if a drug increased $g_K$ by a factor $a > 1$, the slope of the $I_K$ line in Figure 1-6(a) would be increased. As a result, $E_r$ would become slightly more negative, $E_{th}$ more positive, and the voltage gap, $E_r - E_{th}$, would increase; so that a stronger stimulus would be required to excite the cell. Similarly, if $g_{Na}$ were decreased by a factor $a < 1$, the gap between $E_r$ and $E_{th}$ would also increase. If potassium conductance were increased and sodium conductance decreased simultaneously, then an even greater increase in the stimulation threshold would occur. Conversely, if $g_K$ were decreased, $g_{Na}$ were increased, or both, the $E_r - E_{th}$ gap would decrease together with the stimulation threshold. These possibilities are summarized in Table 1-1.

In addition to altering the relationship between sodium and potassium conductance of the membrane, drugs might also influence the stimulation threshold by directly or indirectly altering the sodium or potassium equilibrium potentials. Since the difference $E_m - E_{Na}$ is large (about
Table 1-1 Predicted effects on cardiac stimulation or defibrillation threshold caused by changes in transmembrane ionic conductances during diastole.

<table>
<thead>
<tr>
<th>gNa</th>
<th>decreased</th>
<th>normal</th>
<th>increased</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td>gK</td>
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↑ = increased threshold  ↓ = decreased threshold
-160 mV) relatively large changes in $E_{Na}$ would be required to cause large percentage changes in $I_{Na} = gNa(E_m - E_{Na})$. However, in the case of potassium, $E_m - E_K$ is relatively small (about 10 mV). Hence smaller changes in the $E_K$ caused by disturbances in the ratio of local extracellular to intracellular potassium concentration could more easily produce large percentage changes in the stimulation threshold. Such changes would be represented graphically in Figure 1-6(a) as a parallel shift in the potassium current line. For example, increased extracellular K would cause the potassium current line to shift to the right, narrowing the $E_r - E_{th}$ gap and reducing the stimulation threshold.

Summary of the Theory

The theory of defibrillation developed in this chapter assumes that fully recovered and almost fully recovered cells in the fibrillating heart must be brought to the cellular firing threshold, excited, and hence rendered refractory to achieve defibrillation. The critical variable in determining the strength of the stimulus required is the voltage difference or "gap" between the firing threshold and the minimal (resting) membrane potential of completely recovered cells. The magnitude of this voltage gap is determined by the balance of inward sodium current and outward potassium current across the cell membrane. According to accepted principles of membrane physiology,
the factors which affect this balance include the potassium conductance of the membrane, the sodium conductance of the membrane, and the equilibrium potentials for sodium and especially for potassium. Since all of these factors may be altered by selected drug actions, it is highly likely that drugs may alter the threshold for electrical ventricular defibrillation.

**Rationale**

To demonstrate drug-induced alterations of the ventricular defibrillation threshold experimentally, it is necessary to choose a species of animal with hearts large enough to sustain fibrillation. The hearts of small, inexpensive laboratory animals, such as rats, will not sustain fibrillation, probably because the impulse wavelength in mammalian myocardium exceeds the length of conduction pathways in such small hearts.

In the studies to be described, the dog was selected as the experimental animal. These studies were carried out in intact animals using transchest defibrillating electrodes in order to ensure that any pharmacological effects observed were physiologically important. Three drugs were selected for initial study: quinidine, lidocaine, and potassium chloride. These agents are well known. They produce selective effects upon cardiac electrophysiology in the intact animal at dose levels which do not produce
profound systemic toxicity involving other organ systems, and are thus appropriate for transchest defibrillation studies. Each produces reasonably well-characterized alterations in either sodium conductance, potassium conductance, or potassium equilibrium potential, and hence is likely on a theoretical basis to influence the defibrillation threshold.

Alteration of Myocardial $g_{Na}$ and $g_K$ by Quinidine and Lidocaine

The literature concerning the mechanisms of action of antiarrhythmic drugs has been recently reviewed (Singh, 1977; Arnsdorf, 1976; Hauswirth, 1974; Bassett and Wit, 1973; Rosen and Hoffman, 1973). This literature is complicated by the study of drug action using diverse tissue preparations, including atrial muscle, Purkinje fiber bundles, ventricular muscle, motor nerve, and squid axon; diverse species including frog, rat, guinea pig, dog, and human; and diverse extracellular potassium concentrations. Direct investigation of the ionic mechanisms of antiarrhythmic drug action in cardiac muscle using preparations analogous to the voltage-clamped squid axon has been technically difficult due to the small size and contractility of cardiac muscle cells. Recent applications of voltage-clamp techniques to cardiac muscle (Beeler and Reuter, 1970; Fozzard and Beeler, 1975) have produced promising results.
However, this approach remains limited in cardiac muscle, especially by capacitance-induced artifacts during the upstroke (Phase 0) of the action potential. As a result, conclusions about the ionic mechanisms of antiarrhythmic drug action on excitation of cardiac muscle fibers must be drawn from indirect evidence.

**Quinidine.**

Most authorities believe that quinidine acts primarily by decreasing transmembrane sodium conductance. Virtually all investigators since Weidmann (1955) have found that quinidine decreases the rate of rise of Phase 0 of the action potential ($dV/dt)_0$ recorded with intracellular electrodes. This effect is associated with a decreased slope and increased duration of the QRS complex of the electrocardiogram, which is readily demonstrated in the experimental animal and in human patients (Gettes, 1962; Prinzmetal, 1970; Heissenbuttel and Bigger, 1970). Such a correlation of changes in $(dV/dt)_0$ and the QRS complex are predicted by the interference theory of electrocardiography (Geddes and Baker, 1975)*. These quinidine-induced changes are antagonized by hyperpolarization (Weidmann, 1955; Hoffman and Cranefield, 1960) which would increase inward sodium current in the presence of depressed $g_{Na}$, as predicted by the expression $I_{Na} = g_{Na}(E_m - E_{Na})$.

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*The interference theory states that the electrocardiogram (ECG) is derived from the instantaneous difference between the excursion in transmembrane potential of two adjacent areas of myocardium which are activated sequentially by the same wavefront of depolarization. For example, in mammals the subendocardial tissue of the ventricles is first
Quinidine elevates the cellular firing threshold as measured with intracellular electrodes (Weidmann, 1955; Yeh, 1976). The major effect of quinidine is thus usually attributed to decreased sodium conductance of the membrane. At higher concentrations of quinidine, secondary effects attributable to decreased potassium conductance occur. These include prolongation of the action potential duration, refractory period, and QT interval of the electrocardiogram (Rosen and Hoffman, 1970; Heissenbuttel and Bigger, 1970).

Depression of both sodium and potassium conductance by quinidine to a roughly equal degree has been demonstrated by direct measurements of ionic currents in voltage-clamped squid axons (Yeh, 1976). However, McCall (1976), using \(^{42}\)K and \(^{24}\)Na radioisotope tracer techniques in cultured human heart cells, found that the percent decrease in the calculated sodium permeability coefficient (pNa) of the cell activated by Purkinje fibers. A wavefront of depolarization then spreads to the subepicardial fibers which are activated a time, \(\Delta t\), later; where \(\Delta t\) is the propagation time required for depolarization to spread from the subendocardial to the subepicardial fibers. The time \(\Delta t\) is related to the propagation velocity, \(c\), of the wavefront of depolarization and the distance, \(\Delta x\), between the sequentially activated areas of myocardium by the expression \(\Delta t = \Delta x / c\). According to the interference theory, the ECG amplitude is proportional to the instantaneous difference in transmembrane potential, \(\Delta V\), between these two areas of tissue. It follows that

\[
\text{ECG} \propto \Delta V = \frac{\Delta V}{\Delta t} \cdot \Delta t = \left(\frac{\Delta V}{\Delta t}\right) \cdot \frac{\Delta x}{c} .
\]

Noting that the propagation time, \(\Delta t\), is small compared to the action potential duration, and passing to the derivative,

\[
\text{ECG} \propto \left(\frac{dV}{dt}\right) \cdot \frac{\Delta x}{c} . \tag{1}
\]
membranes was approximately twice the percent decrease in calculated potassium permeability coefficients of the cell membranes after exposure to $10^{-6}$ to $10^{-3}$ molar quinidine.

Assuming that quinidine acts by decreasing transmembrane sodium conductance greater than potassium conductance, one may predict its effect on defibrillation threshold. On the basis of the theoretical analysis summarized in Figure 1-6(a) one would expect quinidine to shift the sodium current curve downward and to the right. Such a shift would slightly lower the resting membrane potential and raise the cellular firing threshold. The resultant increased "gap" between these two equilibrium voltages would, in theory, cause an increase in the stimulation or defibrillation threshold. The same net effect on the gap voltage would be expected if the sodium conductance were decreased by a factor greater than that for potassium conductance.

Thus the electrocardiographic signal is directly proportional to the derivative of the cellular transmembrane potential and the distance between the sequentially activated areas of myocardium (in this case ventricular wall thickness) and inversely proportional to propagation velocity. For example, in left ventricular hypertrophy, the amplitude of the QRS complex is greater than normal due to increased ventricular wall thickness, $\Delta x$, in accordance with equation (1). The amplitude of premature ventricular contractions in the ECG may be greater than normally conducted beats because the distance between sequentially activated areas of muscle, $\Delta x$, is larger and because the effective propagation velocity, $c$, is smaller due to bypass of Purkinje fibers penetrating the ventricular wall.

Assuming that the major electrophysiologic effect of quinidine at the cellular level is to decrease $(dV/dt)_0$ and prolong Phase 0, without altering the final amplitude of the action potential, the interference theory predicts two
**Lidocaine.**

Lidocaine appears to act by increasing transmembrane potassium conductance, probably to a greater degree in Purkinje fibers than in working myocardial cells (Davis and Temte, 1969; Arnsdorf and Bigger, 1972). In therapeutic concentrations, lidocaine, unlike quinidine, has little effect on $(dV/dt)_0$ (Davis and Temte, 1969; Bigger and Mandel, 1970), indicating that blockade of sodium conductance is not the most important mechanism of lidocaine action.

Positive physiological correlates of lidocaine action include decreased rate of Phase 4 diastolic depolarization of pacemaker cells (Davis and Temte, 1969; Bigger and Mandel, 1970), which has been attributed to a progressively decreasing potassium conductance (Trautwein, 1973). Increased potassium conductance during Phase 4 in response to lidocaine changes in the QRS complex of the electrocardiogram. The first is a decrease in the amplitude of the QRS complex due to decreased $dV/dt$. The second is an increase in the duration of the QRS complex, since $dV/dt$ will remain positive for the longer time required for complete depolarization. (Both of these effects occurred in the quinidine studies reported in Chapter 3). The first effect may be antagonized by the concomitant decrease in conduction velocity produced by quinidine, since propagation velocity appears in the denominator of equation (1). Hence the second effect, prolongation of the QRS complex, is a more reliable sign of quinidine effect in the electrocardiogram.
would thus explain this aspect of its antiarrhythmic action. Lidocaine also may decrease the action potential duration and refractory period of cardiac cells, a phenomenon consistent with increased potassium conductance during Phase 3 repolarization (Mandel and Bigger, 1971). In Purkinje fibers depolarized by injury, exposure to lidocaine may cause a return of the resting membrane potential toward normal (Arnsdorf and Bigger, 1972). This phenomenon is consistent with the expectation that increased potassium conductance, gK, would cause a greater stabilizing current, 

\[ I_K = gK(E_m - E_K) \]

when \( E_m \) is farther from the \( E_K \) in depolarized cells. Recently Arnsdorf and Bigger (1975), using multiple microelectrodes and cable theory applied to long cardiac Purkinje fibers, have measured a 64 percent increase in membrane potassium conductance after exposure to therapeutic concentrations (5 mg/1) of lidocaine. Kabela has reported increased \( ^{42}K \) efflux from dog heart tissues after exposure to lidocaine. This body of evidence strongly suggests increased potassium conductance as the therapeutic mechanism of lidocaine action upon the heart.

At higher concentrations, or in the presence of higher extracellular potassium levels (Singh and Vaughan Williams, 1971), lidocaine begins to exert "quinidine-like" effects. These include decreased amplitude, decreased rate of rise and prolonged duration of the action potential (Mandel and Bigger, 1971), and are attributable to decreased sodium
conductance. This quinidine-like action at higher concentrations has been proposed as the principle local anesthetic mechanism of procaine and lidocaine in peripheral nerves (deJong, 1970).

The analysis of Figure 1-6(a) predicts that lidocaine would increase stimulation and defibrillation threshold by raising the potassium current line and, at higher doses, lowering the sodium current curve. These shifts would widen the voltage gap between the equilibrium points for the resting membrane potential and the cellular firing potential, and proportionally increase the current required for stimulation or defibrillation.

Alteration of $E_K$ by Potassium

The dependence of the potassium equilibrium potential, $E_K'$, and resting membrane potential, $E_m'$, upon the ratio of intracellular to extracellular potassium concentration $(K_i/K_o)^*$ has been well described by Hoffman and Cranefield (1960) and recently reinvestigated in terms of ionic activities by Miura (1977). These reports clearly indicate that the equilibrium potential for potassium is very sensitive to changes in $K_o'$. This result may be appreciated by differentiating the Nernst equation

---

*In this and the following discussions, square brackets denoting molar concentrations of ions are omitted for simplicity of notation.
\[ E_K = -61.5 \log \frac{K_i}{K_o} . \]

First with respect to \( K_o \) and then with respect to \( K_i \):

\[ \frac{d(E_K)}{dK_o} = \frac{+26.7}{K_o} \quad \text{and} \quad \frac{d(E_K)}{dK_i} = \frac{-26.7}{K_i} ; \quad \text{so that} \]

\[ \left| \frac{d(E_K)}{dK_o} \right| \cdot \left| \frac{d(E_K)}{dK_i} \right| = \frac{K_i}{K_o} \approx 20-40 \]

Hence the transmembrane potential is normally 20-40 times more sensitive to changes in \( K_o \) than to changes in \( K_i \).

Small changes in extracellular potassium concentration may cause large changes in the potassium equilibrium potential and in turn the threshold current for defibrillation.

Mathematical Feasibility of Varying \( K_o \) and Calculated \( E_K \)
While Keeping \( K_i \) Essentially Constant.

Because measurement of intracellular potassium concentrations in the myocardium requires sacrifice of the experimental animal, it is desirable to keep \( K_i \) levels essentially constant during the course of an experiment. Then a single determination of myocardial \( K_i \) at the end of the experiment may be interpreted with some validity. As illustrated in Figure 1-7, the overwhelming majority of total body potassium (about 50 mEq/kg body weight) is found
Figure 1-7. Approximate normal distribution of potassium ions in body fluid compartments. TBW = total body water, ECF = extracellular fluid, ICF = intracellular fluid. Roughly 98 percent of total body potassium is contained within cells.
intracellularly, whereas only about 1 mEq/kg is found in the extracellular fluid. If 1.0 mEq/kg of potassium is infused intravenously over 3-5 minutes, $K_o$ will increase roughly 4 mEq/l -- enough to double normal plasma levels. In practice, the intravenous dose of 1.0 mEq/kg produces about a 3.5 mEq/l rise in plasma potassium levels in our laboratory. However, even if this entire potassium dose enters the cells, $K_i$ will be changed by only 2 percent. Thus it is possible to significantly raise $K_o$ by potassium infusion while keeping $K_i$ essentially constant.

A "bolus plus infusion" dosage schedule permits repeated determination of the defibrillation threshold at a specified $K_o$ level. The mathematical rationale for the use of a combined bolus plus infusion dosage schedule to produce a "square" step-up in the plasma levels of a drug was described by Wagner (1974). Using this technique in dogs with bilateral ureteral ligation to prevent renal excretion, the maintenance of a stable elevation in $K_o$ for 100 minutes requires the administration of 2.0 mEq/kg KCl. This total dose represents a 4 percent increase in total body potassium. Since plasma levels remain constant from the beginning to the end of the 100 minute period, about half the total dose of 2 mEq/kg must be transported into cells during 100 minutes of infusion. As a consequence, overall intracellular potassium levels increase by approximately 1 mEq/kg, or only about 2 percent at the end of 100 minutes.
Measurement of Intracellular Potassium Concentration.

Because it is physically impossible to separate the intracellular and extracellular fluid compartments of solid tissues, intracellular potassium concentration must be calculated indirectly. The calculation can be made from measurements of total tissue and extracellular potassium concentrations on the basis of the following relation:

\[ K_t = \sigma_o K_o + \sigma_i K_i \]

where

- \( K_t \) = overall potassium concentration of myocardial tissue
- \( \sigma_o \) = volume fraction of the extracellular space
- \( \sigma_i \) = volume fraction of the intracellular space = (1-\( \sigma_o \)) for heart muscle. The intracellular potassium concentration is calculated as

\[ K_i = \frac{K_t - \sigma_o K_o}{1 - \sigma_o} \]

provided \( \sigma_o \), the volume fraction of the extracellular space is known. Classically \( \sigma_o \) is measured as the volume of distribution of an indicator substance which is permeable to capillaries but which is excluded from cells. \(^{24}\)Na, thiosulfate, and manitol have been used as indicators for this purpose (Welt, 1970). The method developed by the author for the present studies employs nonisotopic sodium as the indicator substance. The sodium indicator is subtracted rather than added to the extracellular space as
the myocardium is perfused with two different isotonic solutions, the first (lactated Ringer's solution) containing physiologic sodium concentration and the second (5 percent dextrose in water) containing zero sodium concentration. Tissue samples are analyzed for total sodium and potassium content by flame photometry after each perfusion. Calculations are made as described in Chapter 3.

In this manner it is feasible to study defibrillation threshold as a function of $E_K$, by using a regulated KCl infusion to alter the $K_0/K_i$ ratio. $K_0$ may be determined from samples of blood plasma, and $K_i$ may be measured terminally in the same animal with confidence that it has remained essentially constant during the experiment. With knowledge of both $K_0$ and $K_i$, $E_K$ may be calculated from the Nernst equation and related to defibrillation threshold.

**Importance of the Stability of the Animal Model**

Before undertaking the drug studies, however, certain critical questions concerning the validity and the stability of the animal model must be addressed. These questions concern the effect of anesthesia and the reproducibility of control data obtained when no drug other than the anesthetic is administered. Attention to these questions, as described in Chapter 2, ensured that presumed effects of cardiac drugs on the defibrillation threshold would be correctly interpreted.
Objectives of the Investigation

According to the preceding rationale, the objectives of the investigation described in this thesis were as follows:

- To determine the effects of the induction of pentobarbital anesthesia on ventricular defibrillation threshold.
- To determine the stability and precision of control defibrillation threshold data in pentobarbital anesthetized dogs.
- To determine the effect of intravenous quinidine gluconate on ventricular defibrillation threshold.
- To determine the effect of intravenous lidocaine on ventricular defibrillation threshold.
- To determine the effect of elevated extracellular potassium concentration and potassium equilibrium potential on ventricular defibrillation threshold.
- To compare observed drug effects with theoretical predictions.
CHAPTER 2
EVALUATION OF THE ANIMAL MODEL FOR
PHARMACOLOGIC STUDIES

Pentobarbital Anesthesia

All controlled experimental studies of electrical ventricular defibrillation reported to date have used anesthetized animals as subjects -- in most cases barbiturate anesthetized dogs. In contrast, virtually all clinical ventricular defibrillation outside the operating room is carried out in unanesthetized patients in settings such as the coronary care unit or emergency room. Recently the barbiturate anesthetized dog has been criticized as a model of normal cardiovascular physiology (Priano, 1969). Since no study can be found in the literature reporting the influence of anesthesia on the efficacy of electrical defibrillation, a reasonable question may be raised about the validity of anesthetized animal models used for defibrillation studies.

Unquestionably, anesthetic agents of all kinds have direct effects upon excitable biologic membranes. Although the central nervous system is the most important site of action of general anesthetic agents; many anesthetics, including pentobarbital, are known to affect the mechanical
and electrical performance of cardiac muscle. The amplitude and strength of myocardial contraction are depressed by cyclopropane, diethyl ether, nitrous oxide, and halothane, as well as by barbiturates including pentobarbital, secobarbital, and thiopental (Price, 1955; Flacke, 1962; Hardman, 1959; Effendi, 1973; and Etsten, 1955). Hydrocarbon anesthetics may depress the rate of the sinus node pacemaker as well as the speed of atrioventricular and intraventricular conduction (Flacke, 1962; Hardman, 1959; Effendi, 1973; Etsten, 1955; Smith, 1962). Significant differences in the response of the dog heart to the atrioventricular blocking and arrhythmogenic actions of digitalis glycosides have been reported for animals anesthetized with pentobarbital versus halothane, versus methoxyflurane (Morrow, 1972). Cyclopropane, halothane, and to a lesser extent, thiopental, are known to sensitize the myocardium to the arrhythmogenic effects of epinephrine (Dressel, 1964). Thus, it is quite conceivable that anesthetics could alter those parameters of cardiac electrophysiology which determine the success or failure of electrical defibrillation.

Accordingly, the following study was undertaken to determine if the induction of anesthesia with intravenous pentobarbital sodium in the dog alters transchest defibrillation threshold. In this study, threshold was determined in the same animals in both the awake, unanesthetized state and after the induction of various levels of pentobarbital anesthesia.
Method

Five dogs of mixed breed, weighing 6 to 14 kg served as subjects. Initially each dog was anesthetized with injectable pentobarbital sodium (Nembutal®, 50 mg/ml 10% alcohol, 40% propylene glycol vehicle, 25-30 mg/kg i.v.). No preanesthetic medication was given. A bipolar catheter electrode was placed in the right ventricle of the heart via a right jugular venous cut-down, using sterile technique. Position of the catheter electrode within the heart was verified by recording the catheter tip electrogram and comparing its timing with the electrocardiogram (ECG) Lead II. The catheter was stabilized in the jugular vein and the wound closed with 2-0 silk sutures. The external portion of the catheter was protected with an adhesive elastic bandage placed around the neck and a soft collar 8 cm in width. After a recovery period of 36-72 hours, the defibrillation threshold was determined before and after induction of anesthesia with pentobarbital. These investigations in unanesthetized and anesthetized subjects were carried out in accordance with National Institutes of Health and institutional guidelines for the use of laboratory animals ("Guide", 1972; "Regulations", 1972).

Defibrillation threshold in awake, unrestrained animals was measured as follows: ECG Lead II electrodes were applied to the limbs and the position of the catheter electrode was confirmed by recording the catheter tip electrogram.
Defibrillating electrodes, held in position with rubber straps, were applied to the shaved skin of the thorax with electrolytic jelly, one centered over the apex beat area and the other in the opposite position on the right chest wall. The defibrillating electrodes were stainless steel discs, 2 mm thick and 8-10 cm in diameter (20 percent of the animal's chest circumference ± 1cm). The standard location of each electrode was outlined in ink on the thorax.

Ventricular fibrillation was produced by the application of a 1 sec train of 60 Hz, 2 msec duration rectangular electrical pulses of 5-15 volts intensity via the right ventricular catheter. Ventricular fibrillation was confirmed by the presence of random waves in the electrocardiogram and by the descending level of consciousness of the subject. As the animal lost consciousness, it was placed in dorsal recombency.

The defibrillator employed contained a 16 μF capacitance, a 44 millihenry inductance, and a 7 ohm internal resistance in series with the subject. A 1.00 ohm, 100 watt resistor in series with one electrode was used for measuring current output. The peak output voltage of the defibrillator could be varied continuously from 0 to 8000 volts. The duration of the delivered current pulse, slightly dependent upon subject resistance, was typically 4-5 msec. The waveform of the current pulse was a heavily damped sinusoid.
As soon as possible after the confirmation of ventricular fibrillation (15-45 sec after endocardial stimulation), a defibrillator shock, calculated to be adequate for defibrillation on the basis of the dog's body weight as described by Geddes (1974), was delivered at the time of end-expiration. The voltage and current applied to the subject were measured using a Tektronics model D-11 dual channel storage oscilloscope. Defibrillation was confirmed by palpation of the femoral pulse and QRS complexes in the electrocardiogram. With return of consciousness, the animal was allowed to right itself. After a recovery period of about 2 min, the animal was refibrillated and defibrillation was attempted with a voltage setting 5-10 percent less than that of the previous trial. This procedure was repeated until the animal was not defibrillated by the first shock, and then a stronger shock was applied immediately to restore cardiac pumping action. Threshold voltage and current were defined as the lowest values able to defibrillate the ventricles. Only data from the first shock delivered after the onset of fibrillation were used in calculation of threshold. In this study threshold values were considered adequately precise if they differed no more than 10 percent from values unable to defibrillate the ventricles. Delivered energy and charge were calculated as described by Babbs and Whistler (1978).
Twenty minutes after the defibrillation threshold was determined in the unanesthetized animal, intravenous pentobarbital sodium (25-30 mg/kg), was given to produce surgical anesthesia and the defibrillation threshold measurement was repeated with the animal in dorsal recumbency. After a three-day recovery period, another set of threshold determinations was made in the awake and anesthetized states.

On the final day of testing the defibrillation threshold was determined following larger doses of pentobarbital. After the routine threshold determination under surgical anesthesia, sufficient intravenous pentobarbital was given to produce apnea and the threshold measurement repeated. Then sufficient intravenous pentobarbital was given to produce circulatory shock (defined as systolic blood pressure less than 50 mmHg measured via a catheter placed in the abdominal aorta) and a final threshold determination made within 10 minutes. During apnea and shock the animal was maintained using mechanical ventilation sufficient to produce a respiratory minute volume, measured with a Wright respirometer, roughly equal to that measured under surgical anesthesia.

Results

In all 5 dogs comparisons could be made between defibrillation thresholds in the awake and the anesthetized
states. In one dog, three successive comparisons of awake versus anesthetized threshold values were made during a twelve-day period. Threshold current data for this animal are plotted in Figure 2-1. The ratios of the threshold peak current for all dogs at all levels of anesthesia to the average threshold under surgical anesthesia for each animal are plotted in Figure 2-2. No consistent effect of pentobarbital anesthesia on the ventricular defibrillation threshold is evident. The slight downward trend in Figure 2-2 is not statistically significant.

Mean values of threshold shock strength, in terms of peak current, and delivered energy per kilogram body weight, are given in Table 2-1. One-way analyses of variance indicate that the observed effects of anesthesia level upon threshold current, and energy are far from statistically significant, as indicated by the p values in the table.

The response of unanesthetized dogs to the fibrillation-defibrillation procedure is worthy of mention. Typically, the dogs were not alarmed by the intracardiac electrical stimulation used to induce fibrillation. The loss of cerebral blood flow due to ventricular fibrillation produced initial excitation, lasting 5-15 sec, which rapidly diminished as the animal lost consciousness. Delivery of defibrillating current caused a brief, forceful contraction of thoracic and abdominal musculature, resulting in
Figure 2-1. Threshold peak current for ventricular defibrillation in unanesthetized and anesthetized states on successive trials in the same animal. On three successive trials the threshold current in the unanesthetized animal was greater than, equal to, and less than the threshold current after induction of pentobarbital anesthesia. Mean threshold before anesthesia = 1.02 A/kg; mean threshold after anesthesia = 1.08 A/kg. Threshold data for the unanesthetized dog were reproducible within ±10 percent limits.
Figure 2-2. Relative values of threshold peak current for ventricular defibrillation at four levels of anesthesia. Awake = no anesthesia, Surgical anesthesia = spontaneous respiration but no response to surgical stimulation (25-30 mg/kg pentobarbital), Apnea = no spontaneous respiration (42-51 mg/kg pentobarbital, cumulative dose), Shock = aortic blood pressure less than 50 mmHg systolic (61-77 mg/kg pentobarbital, cumulative dose). Mean threshold current under surgical anesthesia = 1.0 for each animal. Dog 1, solid circles; Dog 2, solid triangles; Dog 3, open circles; Dog 4, open squares; Dog 5, crosses.
Table 2-1. Mean Defibrillation Threshold* at 4 Levels of Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>Surgical Anesthesia</th>
<th>Apnea</th>
<th>Shock</th>
<th>F Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Current (amps/kg)</td>
<td>1.25+ .28</td>
<td>1.22+ .17</td>
<td>1.21+ .18</td>
<td>1.13+ .21</td>
<td>0.21</td>
<td>0.89</td>
</tr>
<tr>
<td>Delivered Energy (joules/kg)</td>
<td>1.55+ .77</td>
<td>1.35+ .46</td>
<td>1.28+ .42</td>
<td>1.11+ .17</td>
<td>0.51</td>
<td>0.68</td>
</tr>
<tr>
<td>Number of Observations</td>
<td>7</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*+ 1 S.D.
vocalization. Animals for whom the total circulatory arrest time was less than 30 sec rapidly regained consciousness, and resumed a sitting or standing position. Animals for whom the total circulatory arrest time was 30-60 sec did not regain consciousness as soon after defibrillation. These animals remained in dorsal recumbency after resuscitation and appeared dazed or tranquilized.

Conclusion

The data indicate that defibrillation threshold is negligibly affected by the induction of anesthesia with pentobarbital sodium. Hence this anesthetic was selected for use in further defibrillation studies.

Stability and Precision of Control Data

The question of the stability and reproducibility of control data is especially pertinent because of the intrinsic nature of the defibrillation studies in which the experimental animal literally is rescued from impending death on repeated occasions. Each fibrillation-defibrillation sequence represents a stress to the animal subject, including transient circulatory arrest, possible tissue hypoxia and acidosis, and the electric shock itself, any of which might effect the measured defibrillation threshold.

Accordingly, the following studies were undertaken to determine (1) to what extent defibrillation threshold is stable and reproducible with time in pentobarbital
anesthetized dogs and (2) to what extent the stability of the baseline threshold level is dependent upon the recovery interval between threshold measurements.

Method

Fifteen mongrel dogs of both sexes, weighing 4 to 16 kg and anesthetized with pentobarbital sodium (30 mg/kg, i.v.), served as subjects. No other drugs except 0.9 percent saline were administered at any time. The trachea of each dog was intubated and the animal placed in dorsal recumbency for the duration of the study. The urinary bladder was catheterized with a #8 French filiform catheter connected to a closed volumetric drainage bottle. Aortic blood pressure was recorded using a P23DB Statham transducer. Respiratory minute volume was measured with a Wright respirometer. Arterial blood pH, pCO₂, and pO₂ were monitored using an Instrumentation Laboratories Model 213 blood-gas analyzer. Disk electrodes, 8, 10, or 12 cm in diameter were applied to the shaved skin of the right and left hemithoraces with electrolytic jelly and sutured in place. The diameter of the electrodes was standardized to 20 percent of the chest circumference, measured at the mid-sternal level. One electrode was centered over the apex beat area and the other at a corresponding position on the right chest wall, 3 cm cephalad of the left electrode.
Mean aortic blood pressure, respiratory minute volume, urine output, arterial blood gases, and esophageal temperature were recorded at half hour intervals. A stable level of surgical anesthesia was maintained in each animal by intravenous doses of pentobarbital sodium 2-5 mg/kg each hour. Saline solution, 0.9 percent, was given at a rate of 1-2 ml/kg/hr by vein to maintain hydration. Esophageal temperature was maintained in the range of 36-39°C with the aid of warm overhead lights.

Ventricular fibrillation was initiated by 2-10 volt 60 Hz electrical stimulation of the right ventricle delivered via a bipolar electrode catheter inserted through the right jugular vein. The position of the electrode catheter in the right ventricle had been previously verified by recording the cardiac electrogram from the catheter electrodes. Ventricular fibrillation was confirmed by replacement of the QRS-T complexes of the electrocardiogram with random waves and the fall of aortic blood pressure toward zero.

The output circuit of the damped sine wave defibrillator employed contained a capacitance of 16 μF, an inductance of 44 mH, and an internal resistance of 7 ohms, as determined by the method of Babbs and Whistler (1978). The voltage on the capacitor could be varied continuously from 0 to 8000 volts. The maximum stored energy available was 512 joules. A 1.00 ohm, 100 watt resistor in series with one electrode was used for measuring the current.
In a typical trial a defibrillator shock calculated to be adequate for defibrillation on the basis of the dog's body weight was delivered at the time of end-expiration, less than 15 sec after the onset of fibrillation. The voltage across the electrodes and current passing through the subject were recorded on a Tektronix model D-11 dual-channel storage oscilloscope. Defibrillation was confirmed by return of pulsatile blood pressure and QRS complexes in the electrocardiogram. After restoration of aortic blood pressure to a stable level, the animal was refibrillated and defibrillation was attempted with a voltage setting approximately 10 percent less than that of the previous trial. This procedure was repeated until defibrillation was not achieved, whereupon a stronger shock was applied immediately to restore cardiac pumping action. At no time did fibrillation persist for more than 30 sec.

Threshold voltage and current were defined as the lowest values able to defibrillate the ventricles. In this study threshold values were considered adequately precise if peak current differed no more than 10 percent from a value unable to defibrillate the ventricles. Only data from the first shock delivered after the onset of fibrillation were used in calculations of threshold. Delivered energy was calculated as described previously (Babbs and Whistler, 1978).

Three series of five dogs were studied. In Series 1, threshold was measured every hour for 8 hours. In Series 2,
threshold was measured every 15 min for 5 hours. In Series 3, threshold was measured every 5 min for 1 hour. This last series represents the closest spacing of threshold measurements consistently possible when only first-shock data are acceptable.

Results

The stability of ventricular defibrillation threshold is demonstrated by Figures 2-3 and 2-4, which present mean threshold current and energy ratios as a function of time, for animals in all three series. The threshold current and energy ratios were calculated by dividing the individual threshold values by the average of the first three "baseline" threshold values obtained for each animal. Hence the threshold energy and current ratios may be interpreted as the relative values obtained in experiments in which each animal served as its own control.

Threshold peak current remained stable in all three series. Decreasing the recovery interval between threshold measurements from 60 to 15 to 5 minutes did not cause a discernible upward or downward drift of threshold current. Threshold current stability was further assessed by computing the linear regression function relating the threshold current dose to time for each animal. The slopes of the regression lines so obtained give sensitive estimates of the overall rate of change of threshold current.
Figure 2-3. Stability of defibrillation threshold current. Data points represent mean values of the threshold current ratio for the 5 dogs in each series at various times after the first fibrillation-defibrillation trial. Average baseline values of threshold current (1.00 on the vertical axis) were 1.40 amp/kg for Series 1, threshold interval = 60 min; 1.10 amp/kg for Series 2, threshold interval = 15 min; and 1.13 amp/kg for Series 3, threshold interval = 5 min. The baseline values are not statistically different (F = 2.49, p = 0.12). The time scale is logarithmic.
Figure 2-4. Stability of defibrillation threshold energy. Data points indicate mean values of the threshold energy ratio for the 5 dogs in each series at various times after the first fibrillation-defibrillation trial. Average baseline values of threshold energy (1.00 on the vertical axis) were 1.23 joules/kg for Series 1, threshold interval = 60 min; 0.87 joules/kg for Series 2 threshold interval = 15 min; and 1.06 joules/kg for Series 3, threshold interval = 5 min. The values are not statistically different (F = 2.34, p = 0.14). The time scale is logarithmic.
with time. The slopes were positive for 7 of 15 dogs, negative for 8 of 15 dogs, and not significantly different from zero (mean slope -0.008 amp/kg/hr, n=15, Student's t=0.69, p=0.50).

Threshold delivered energy data were more variable than the current data and appeared to drift slightly downward during the first hour. In all three series, defibrillation threshold energy after one hour was about 10 percent less than the initial threshold energy. The observed decrease in threshold energy was associated with a corresponding decrease in transthoracic electrical impedance, calculated by dividing peak voltage by peak current (Figure 2-5).

Arterial blood pH, pCO₂, and pO₂ remained stable in all control series, averaging 7.38, 34 mmHg, and 72 mmHg respectively. To evaluate subtle changes in blood-gas values during the course of experimentation, linear regression functions relating pH, pCO₂, and pO₂ values to time were computed for each animal. The mean regression coefficients for each series are presented in Table 2-2. One-way analyses of variance reveal no significant differences in the regression coefficients for the three experimental groups, indicating that increasing the frequency of threshold measurements from 1 to 12 per hour did not cause a deterioration in arterial blood gas status. The observed rates of change in arterial blood pH, pCO₂, and pO₂,
Figure 2-5. Stability of transchest electrical impedance. Data points represent mean values of the ratio $Z/Z_0$ of transchest impedance, $Z$, at various times after the first fibrillation-defibrillation trial to the initial impedance value, $Z_0$, at time zero. The apparent impedance $Z$, in ohms between the defibrillating electrodes was calculated as peak voltage/peak current for shocks delivered at the time of end expiration. Absolute values of $Z_0$ for the three series of dogs were 57 ohms for Series 1; 60 ohms for Series 2; and 52 ohms for Series 3. These values are not statistically different ($F = 0.72$, $p = 0.51$).
Table 2-2. Linear regression analysis of the stability of arterial blood gas data. Regression coefficients $a_0$ and $a_1$ of equations of best fit of the form $y = a_0 + a_1t$ are presented as "initial" values and "rate of change" for blood gas variables $y = pH$, $pCO_2$, or $pO_2$ as a function of time, $t$. Coefficients $a_0$ and $a_1$ were computed for each animal. Table entries represent the mean values of the coefficients for the animals in each series.

The F ratios for one-way analyses of variance and associated p values test the null hypotheses that the coefficients for the three series are the same. The Student's $t$ statistics and associated p values test the null hypotheses that the mean values of the regression coefficients $a_1$ are zero for the population of all 15 animals. The regression coefficients for the three series are not significantly different, and the coefficients, $a_1$, are not significantly different from zero.

<table>
<thead>
<tr>
<th>Series</th>
<th>Threshold Interval (min)</th>
<th>pH</th>
<th>$pCO_2$</th>
<th>$pO_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
<td>Rate of Change (hr$^{-1}$)</td>
<td>Initial</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>7.37</td>
<td>-0.003</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>7.38</td>
<td>0.006</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>7.39</td>
<td>-0.03</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>grand mean</td>
<td>7.38</td>
<td>-0.007</td>
<td>34</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>0.31</td>
<td>3.27</td>
<td>0.04</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.74</td>
<td>0.09</td>
<td>0.96</td>
</tr>
<tr>
<td>P</td>
<td>Student's $t$</td>
<td>-1.29</td>
<td>0.03</td>
<td>-1.26</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.22</td>
<td>0.98</td>
<td>0.24</td>
</tr>
</tbody>
</table>
indicated by the slopes of the linear regression functions, were not statistically different from zero.

The precision of defibrillation threshold data may be appreciated with reference to Figure 2-6, which illustrates the frequency distributions of the 209 threshold energy and current ratios obtained in all three series. The distributions of the three series were pooled since all have means of 0.97-0.99 and variances which are not significantly different (Bartlett's $\chi^2 = 0.20, \ p = 0.90$ for current; Bartlett's $\chi^2 = 2.84, \ p = 0.24$ for energy). These histograms illustrate the relative dispersion of threshold data about the baseline established for each animal at the beginning of each experiment. The standard deviations of the distributions are a measure of the reproducibility of the threshold data. Under control conditions the precision of threshold current data is greater than the precision of threshold energy data.

Discussion

In the absence of pharmacologic or pathologic intervention, the threshold current for ventricular defibrillation remains stable in pentobarbital anesthetized dogs. Even though the animal is repeatedly rescued from impending death, there appears to be no cumulative influence of repeated trials of fibrillation and defibrillation upon the threshold current, provided no more than 30 sec of
Figure 2-6. Histograms of threshold current and energy ratios obtained in 15 control dogs. The width of each class interval is 0.05. The value 1.00 on the horizontal axes represents the average of the first three threshold values obtained for each animal. Variance represented by the histograms therefore reflects only variability of individual subjects. The standard deviation of the threshold current distribution is 11 percent of the mean. The standard deviation of the threshold energy distribution is 22 percent of the mean.
fibrillation is permitted on any trial. This conclusion is valid even if threshold is measured as frequently as every five min, under which circumstances there is loss of pulsatile blood pressure for 10-20 percent of the elapsed time. This stability in threshold current is associated with comparable stability in the arterial blood pH, pCO₂, and pO₂.

The approximate 10 percent decrease in threshold delivered energy during the first hour of testing is associated with a corresponding decrease of the apparent impedance between the defibrillating electrodes. Geddes (1975) and Chambers (1978) have reported similar decreases in transthoracic impedance during successive ventricular defibrillation trials in animals and in man. These reports imply that the critical variable associated with decreasing impedance is the number of fibrillation-defibrillation trials. In our studies, however, time appears to be a better predictor of subject impedance than trial number. The decrease in transchest impedance during the first hour of testing averaged 4.64 ohms/hour for the dogs of Series 1 and 5.21 ohms/hour for the dogs of Series 3. These values are not statistically different (Student's t = -0.28, p = 0.79) even though threshold was obtained 12 times in Series 3 and only 2 times in Series 1. Accordingly factors other than the number of fibrillation-defibrillation trials, such as impregnation of high resistivity skin with
electrolytic jelly, may be responsible for the slight initial fall in transchest impedance and threshold energy.

Using the method described in this thesis, defibrillation threshold current may be measured with a precision of \( \pm 10.9\% \) of the mean, as indicated by the standard deviation of a large population of repeated threshold measurements in stable animal preparations. The comparable precision of threshold energy measurements is \( \pm 21.8\% \) of the mean. The two-fold greater uncertainty in threshold energy is a direct result of the fact that delivered energy is proportional to the square of the peak current. As reported in detail elsewhere (Babbs and Whistler, 1978), the energy, \( W \), delivered by a damped sine wave defibrillator may be calculated from the peak current, \( I \), by an expression of the form \( W = aI^2 \), where the factor, \( a \), contains terms relating to the internal resistance, inductance, and capacitance of the defibrillator and the transchest impedance of the subject. However, if "\( a \)" is taken as a simple constant, all of the observed variance in threshold energy, \( W \), may be explained. Consider Gaussian random variable, \( I \), with mean value, \( m_I \), and standard deviation \( \sigma_I \). If \( W = aI^2 \) for any constant, \( a \), then

\[
\frac{\sigma_W}{m_W} = \sqrt{\frac{\sigma_I}{m_I} \left( \frac{\sigma_I}{m_I^2} + 4 \right) \frac{\sigma_I}{m_I} + 1}
\]
For the special case \( \sigma_{I}^2 / m_{I}^2 \ll 1 \), indicating relatively small variations in \( I \), \( \sigma_{W} / m_{W} \approx 2 \sigma_{I} / m_{I} \). If \( I \) is taken as the threshold current ratio in defibrillation experiments one would therefore expect

\[
\frac{\sigma_{W}}{m_{W}} = 2 \frac{0.107}{0.984} = 0.217
\]

The observed uncertainty, \( \sigma_{W} / m_{W} \), in the threshold energy ratio was 0.218. Thus the greater uncertainty of threshold energy, compared to threshold current, may be explained by the necessary mathematical relationship between energy and current. The slight decrease in transchest impedance which was observed does not contribute significantly to the variability in threshold energy data.

One additional factor which may be quantitated at this time contributes to the variability in defibrillation threshold data. Some of the variability in measured threshold values is due to the method of threshold determination in which discrete current values differing by approximately 10 percent are tested, rather than due to variation in the animal's true threshold. In a discussion of the precision of defibrillation threshold data, it is worthwhile to identify the magnitude of this sampling variance in order to assess how much of the observed variance in threshold data is due to the experimental animal and how
much of the observed variance is due to the experimental protocol.

Suppose the true, physiologic value of the defibrillation threshold current remained absolutely constant at a value $I_0$ and that the distribution of measured thresholds shown in Figure 2-7 is uniform within the interval $I_0 - 1.1I_0$. This distribution of measured thresholds would occur if the first suprathreshold shock tested were selected "blindly" with no fixed relation to the true threshold, a situation which exists in practice. In this case, the mean measured threshold would overestimate the true threshold by 5 percent, and the variance of the distribution of measured thresholds may be calculated analytically as:

$$
\sigma_{\text{sampling}}^2 = \frac{10}{I_0} \int_{I_0}^{1.1I_0} I^2 \, dI - (1.05I_0)^2 = 0.00083 I_0^2.
$$

Since the mean of the measured values overestimates true threshold by 5 percent ($M_I = 1.05 I_0$), one may express the sampling variance in terms of the mean measured threshold as

$$
\sigma_{\text{sampling}}^2 = 0.00076 M_I^2 \quad \text{or} \quad \sigma_{\text{sampling}} = 0.027M_I.
$$

Further, since sampling and physiologic variance are independent phenomena,* the physiologic variance in

*That is, the variability of the experimenter and the variability of the animal are not correlated.
Figure 2-7. Uniform distribution of measured threshold currents expected if physiologic variance were zero. Probability density is scaled such that the total area under the distribution function is unity. For a given experiment of \( n \) observations, the expected number of observations in class interval, \( I \pm (\Delta I)/2 \), would be \( n f(I) \Delta I \).
defibrillation threshold current may be estimated as:

\[
\sigma_{\text{physiologic}}^2 = \sigma_{\text{observed}}^2 - \sigma_{\text{sampling}}^2 = 0.0118M^2 - 0.00076M^2
\]

\[
= 0.0112M^2
\]

and

\[
\sigma_{\text{physiologic}} = 0.105M
\]

That is, if only physiologic variation were present, the standard deviation of measured threshold currents would be 10.5 percent of the mean. This figure is hardly different from the 10.9 percent standard deviation observed using the method described in this thesis. The sampling variance introduced by testing discrete defibrillator currents differing by 10 percent in amplitude is negligible compared to the physiologic variance. Therefore there appears to be little justification for testing defibrillator currents differing by less than 10 percent in the routine measurement of defibrillation threshold.

In summary, these studies show repeated fibrillation and defibrillation are well tolerated by pentobarbital-anesthetized dogs which fibrillate for less than 30 sec. The experimental manipulations inherent in defibrillation studies as described in this thesis do not in themselves alter the phenomena under investigation. The precision of threshold data obtained by the method reported here is
limited only by physiologic variability of the animal subject and, in the case of threshold energy, by the mathematical relationship of energy to current. Accordingly the pentobarbital anesthetized dog, prepared as described in this chapter, is a suitable model for pharmacologic studies of ventricular defibrillation.
CHAPTER 3
ALTERATION OF VENTRICULAR DEFIBRILLATION THRESHOLD BY DRUG TREATMENT

This phase of the investigation was conducted to determine if selected cardiac drugs which in theory alter the ventricular defibrillation threshold produce the anticipated effects in the intact animal.

Treatments Which Alter Sodium and Potassium Conductance

The following studies were conducted to determine the effect on ventricular defibrillation threshold of quinidine, which acts primarily by decreasing sodium conductance, and of lidocaine, which acts primarily by increasing potassium conductance. These ionic mechanisms of action are anticipated to cause an increase in defibrillation threshold.

Method

Twenty pentobarbital anesthetized mongrel dogs served as subjects. This anesthetic was chosen because it does not alter the defibrillation threshold. Details of the anesthesia and monitoring have been described in Chapter 2. In brief, threshold was determined by repeated trials of
fibrillation and transthoracic defibrillation, each with a
damped sinusoidal defibrillator shock of peak current
amplitude 10 percent less than the amplitude of the pre-
ceding shock. The lowest intensity shock able to achieve
defibrillation, and differing no more than 10 percent in
amplitude from a shock which did not defibrillate, was de-
ined as threshold.

The animals were never permitted to fibrillate more
than 30 sec prior to defibrillation and never refibrillated
until arterial blood pressure had returned to a stable level.
The peak voltage and peak current for each shock were re-
corded on a storage oscilloscope. Only data from the first
shocks applied after the onset of ventricular fibrillation
were used in the calculation of threshold. Delivered
energy was calculated as described by Babbs and Whistler
(1978).

The antiarrhythmic drugs used in this study were
quinidine gluconate, injection, U.S.P. (Lilly), 80 mg/ml
in water vehicle, and lidocaine hydrochloride (Astra),
20 mg/ml, in a water vehicle, pH 6-7. Quinidine was given
as a single intravenous bolus (50 mg/kg) to 5 dogs. Lido-
caine was given as an intravenous bolus (3 mg/kg) to 5
dogs and as a constant infusion (0.5 mg/kg/min) to another
5 dogs. The 5 dogs in the control group received no drug
other than pentobarbital. Ventricular defibrillation
threshold was determined at 15 min intervals. Three
pre-drug control threshold determinations served to establish a stable baseline for each animal. The mean of the first three threshold values was defined as 100 percent of control and served as the reference for drug effect in each animal. Drug induced changes in the ECG were also noted.

Results

Figure 3-1 shows the dramatic elevation of the threshold current and energy caused by an intravenous bolus of quinidine gluconate (50 mg quinidine/kg) in 5 dogs. The data points in Figure 3-1 represent mean threshold energy and current ratios. The threshold energy and current ratios were calculated by dividing the individual threshold values by the average of the first three "baseline" threshold values for each animal. The period of negative time on the abscissa represents this baseline. Threshold peak current was increased by 70 percent and threshold delivered energy was increased by 172 percent by 50 mg/kg of intravenous quinidine gluconate. This dose was sufficient to cause systolic blood pressure to fall initially from 170 to 95 mmHg, and diastolic blood pressure to fall initially from 128 to 60 mmHg. Thereafter the magnitude of blood pressure depression gradually diminished at approximately the same rate as the magnitude of defibrillation threshold elevation.

Figure 3-2 illustrates a similar elevation of defibrillation threshold by an intravenous bolus of lidocaine
Figure 3-1. Effect of intravenous quinidine on ventricular defibrillation threshold in 5 dogs. All threshold elevations after quinidine injection are statistically significant ($U < 11, p < 0.01$) except the final data point at 187 min.
Figure 3-2. Effect of intravenous lidocaine on ventricular defibrillation threshold in 5 dogs. The peak elevation in defibrillation threshold is statistically significant (U < 11, p < 0.01).
in a dose of 3 mg/kg. The maximal elevation of threshold current was 26 percent and the maximal elevation of threshold energy was 48 percent. In contrast to the threshold elevation observed after intravenous quinidine, the effect of lidocaine appeared slower in onset. Administration of lidocaine by continuous intravenous infusion (0.5 mg/kg/min) also caused threshold to rise continuously in another group of 5 dogs (Figure 3-3) to a maximum of 199 percent of control energy and 145 percent of control current after 80 min. Mean blood pressure fell from 150 mmHg at the beginning to 110 mmHg at the end of the lidocaine infusion.

Figure 3-4 illustrates mean threshold energy and current in the control animals which received no drug other than pentobarbital anesthesia. These animals were studied for a longer period of time than any drug treatment group. In control animals, threshold energy decreased by about 10 percent during the first hour of testing and thereafter remained stable. Mean threshold current did not change over a period of 280 minutes.

Discussion

Elevation of ventricular defibrillation threshold by quinidine and lidocaine confirms the predictions of the theory of defibrillation presented in Chapter 1. The scheme of Figure 1-6 predicts that a decrease in sodium conductance
Figure 3-3. Effect of lidocaine infusion on ventricular defibrillation threshold. All threshold elevations after onset of the infusion are statistically significant ($U < 14, p < 0.05$). After 30 min of infusion threshold elevations are highly significant ($U < 11, p < 0.01$).
Figure 3-4. Effect of pentobarbital anesthesia only on ventricular defibrillation threshold in 5 dogs. These animals served as controls. The slight, periodic variations in these threshold data were not reproducible in other control series.
will have two effects: first, a slight negative shift of the resting membrane potential, and second, a positive shift of the transmembrane potential at which the depolarizing sodium current exceeds the hyperpolarizing potassium current and generates Phase 0. As a result the theory predicts that any agent which decreases sodium conductance would cause a greater voltage gap between membrane resting and firing potentials which must be overcome by the action of defibrillating current. In fact, quinidine, a drug which decreases sodium conductance, did increase the electric current "dose" for defibrillation. Lidocaine, however, acts by increasing potassium conductance at therapeutic doses. The theory of Chapter 1 predicts that increased potassium conductance would decrease the resting membrane potential slightly and raise the firing threshold at which inward sodium current exceeds outward potassium current. In turn, defibrillation threshold would be expected to increase. This prediction, too, was confirmed by the experimental results. Hence the threshold elevation caused by antiarrhythmic drugs which alter sodium or potassium conductance can be understood in terms of the principles of membrane physiology.

The notion that quinidine and lidocaine acted by different mechanisms to raise defibrillation threshold in the present studies is confirmed by the electrocardiographic data. In theory, decreased transmembrane sodium
conductance is related to decreased \( (dV/dt)_0 \) and in turn to prolonged QRS complex duration, as explained in Chapter 1. Lidocaine in higher concentrations is known to have such a quinidine-like effect (deJong, 1970; Mandel and Bigger, 1971; Weld and Bigger, 1973). However, in the present study quinidine prolonged the QRS complex duration while lidocaine did not. Following quinidine (50 mg/kg, i.v.), the mean duration of the QRS complex increased 37 percent and then gradually returned to the control level. The mean percent increase in QRS duration was correlated with the mean percent increase in defibrillation threshold current \( (r^2=0.67, p=0.004) \). In lidocaine-treated animals, however, QRS duration remained essentially constant, and changes in mean QRS duration were not correlated with changes in mean defibrillation threshold current \( (r^2=0.06, p=0.46) \). These findings are consistent with the claim that the effect of lidocaine was produced by a different ionic mechanism than that of quinidine.

**Treatments Which Alter the Potassium Equilibrium Potential \( (E_K) \)**

Theory predicts that the defibrillation threshold will not only be altered by changes in the sodium or potassium conductance of the membrane but also by parallel shifts in the \( I_K \) versus \( E_m \) function of Figure 1-6(a), caused by changes in the potassium equilibrium potential. The
objectives of the studies reported in this section were as follows:

- To investigate changes in ventricular defibrillation threshold produced by changes in extracellular potassium ion concentration \( (K_{\circ}) \) in dogs.

- To hold total body potassium content essentially constant during the above studies.

- To measure the intracellular potassium ion concentration \( (K_{i}) \) of the ventricular myocardium.

- To plot defibrillation threshold as a function of \( E_K = -61.5 \log(K_{i}/K_{\circ}) \).

Method

Animal Preparation.

Healthy mongrel dogs weighing 17-20 kilograms served as subjects. Anesthesia was induced with intravenous pentobarbital sodium (25-30 mg/kg) and maintained with additional 2 mg/kg boluses as necessary. No other drug except potassium chloride was administered. Esophageal temperature, the electrocardiogram, aortic blood pressure, respiratory minute volume, and arterial blood pH, \( pCO_2 \), and \( pO_2 \) were monitored as described in Chapter 2. One hour before the beginning of defibrillation threshold measurements, the right and left ureters were ligated.
through a midline laparotomy and the wound closed with continuous suture. A bipolar catheter electrode was placed in the right ventricle via a jugular venous cut-down to initiate ventricular fibrillation.

Defibrillation threshold was determined three times during the 120 min period before potassium administration and three times during the 120 min period after potassium administration. Plasma levels of sodium and potassium in arterial blood were monitored at 10-20 min intervals using an Instrumentation Laboratories Model 443 flame photometer. After the first three pre-drug threshold determinations, intravenous potassium chloride in a dose of 1.0 mEq/kg was given slowly over a period of 5-10 min as the electrocardiogram was closely monitored for arrhythmias. Following this injection, a slow infusion of potassium chloride at 0.01 mEq/kg/min was begun using a motor driven syringe. After stable, elevated levels of plasma potassium were attained, three more measurements of the defibrillation threshold were made during the 120 min following the onset of potassium administration.

Measurement of Intracellular Potassium Concentration.

Following completion of the defibrillation threshold measurements, the potassium infusion was stopped and median sternotomy and pericardiotomy were performed. The heart was perfused first with lactated Ringer's solution and then with
5 percent dextrose in water via a cannula placed in the left brachiocephalic artery. All other branches of the aortic arch except of the coronary arteries were ligated. Before perfusion, the cavae and descending thoracic aorta were clamped; the atria were cut to promote drainage of blood and perfusate. After perfusion with 500 ml of lactated Ringer's solution, a 1 gram sample of right ventricular muscle nourished by the left anterior descending coronary artery was excised for assay of sodium and potassium content. Then perfusion with 500 ml of dextrose solution was carried out and a 1 gram sample of right ventricular muscle nourished by the right coronary artery was excised for assay of tissue sodium and potassium content. The assay procedure employed overnight digestion of the tissue samples in 10 volumes of 1 molar $\text{H}_2\text{SO}_4$ at 80°C. Such digestion for 1 hour or longer produced maximal recovery of sodium and potassium from the pieces of myocardium. Assay of the supernatant solution for sodium and potassium concentration was accomplished using an Instrumentation Laboratories Model 443 flame photometer, calibrated with solutions of 1 molar $\text{H}_2\text{SO}_4$ containing known concentrations of Na$^+$ and K$^+$ ions. Samples of coronary sinus effluent taken after perfusion with 400 ml of each solution provided a measure of extracellular sodium and potassium concentrations in each case. Perfusion pressure was always 80-120 mmHg.
Calculation of the Fractional Extracellular Fluid Volume.

Total tissue sodium concentration, $N_{a_t}$, is given by the expression

$$N_{a_t} = \sigma_o N_o + \sigma_i N_i$$

where $\sigma_o = \text{volume fraction of the extracellular space}$

$\sigma_i = 1 - \sigma_o = \text{volume fraction of the intracellular space}$

$N_i = \text{intracellular sodium concentration}$

$N_o = \text{extracellular sodium concentration}$.

Assuming that sodium ions cross intact cell membranes slowly, total tissue sodium is linearly related to extracellular sodium concentration, with intracellular sodium remaining constant, when the tissue is perfused with isotonic solutions of differing sodium concentrations. Hence, $\sigma_o$ may be calculated from measurable quantities as

$$\sigma_o = \frac{\Delta N_{a_t}}{\Delta N_o} = \frac{N_{a_t}(\text{Ringer's}) - N_{a_t}(\text{dextrose})}{N_o(\text{Ringer's}) - N_o(\text{dextrose})}.$$

Calculation of Intracellular Potassium Concentration.

Once $\sigma_o$ is known, intracellular potassium concentration is then calculated from total tissue and plasma potassium concentrations as

$$K_i = \frac{K_t - \sigma_o K_o}{1 - \sigma_o}.$$
Investigation of Higher Levels of $K_0$.

The potassium treatment schedule for the 10 animals just described was designed to produce stable elevations of extracellular potassium concentration near the maximal levels tolerated by the animals, without profound hypotension, paralysis of the sinoatrial or atrioventricular nodes, or intractable tachyarrhythmias.

In preliminary experiments such complications did occur with more rapid rates of potassium infusion.

To elucidate the influence of high concentrations of extracellular potassium upon defibrillation threshold, an experiment was designed to determine at what concentration of extracellular potassium the ventricles of dogs would spontaneously defibrillate, that is, at what level of $K_0$ defibrillation threshold was zero. These studies were carried out in open-chest dogs in whom cardiac output was maintained by a left ventricular bypass pump. The problem of circulatory collapse produced by very high levels of plasma potassium was thus obviated. No defibrillator was needed for the study. Neither was it necessary to establish a control level of the defibrillation threshold, since zero threshold current is equivalent to zero percent of control in any case.

Nine pentobarbital anesthetized dogs served as subjects for this study. After median sternotomy and pericardiotomy had been performed, surgical hemostasis
secured, and heparin (2 mg/kg i.v.), administered ventricular fibrillation was initiated by 60 Hz stimulation of the right ventricular surface. Each animal was immediately placed on a La Farge-type left ventricular bypass system. As shown in Figure 3-5, blood was withdrawn from the left ventricle through a large bore multiple side-hole cannula inserted through a small stab wound in the cardiac apex. Blood withdrawn from the left ventricle was led through a Travenol roller pump and reinfused into the animal via a large bore, right-angle cannula previously placed in the abdominal aorta. Prior to institution of the bypass, the tubing was filled with warmed (30-40°C) Ringer's solution. Care was taken to ensure that the left ventricular cannula was not pushed through the aortic valve from the left ventricle, since a short circuit would have been created. To promote venous return, the animal's hindquarters were elevated 30 degrees and up to 1000 ml of additional Ringer's solution infused as necessary to maintain a stable artificial cardiac output.

After the bypass system had been adjusted, potassium chloride was infused via the femoral vein at a rate of 0.2 mEq/kg/min, calculated to raise the extracellular potassium concentration by approximately 1 mEq/L/min. Esophageal temperature, the electrocardiogram, arterial blood pressure, and arterial blood pH, pCO₂, and pO₂ were
Figure 3-5. Principle of open-chest left ventricular bypass. The left ventricle, LV, is catheterized via a stab wound in the cardiac apex. The roller pump provides an artificial left ventricular output, which is returned to the abdominal aorta. The negative pressure created in the left ventricle and left atrium is sufficient to draw systemic venous blood through the pulmonary vasculature.
monitored as described in Chapter 2. Two arterial blood samples were taken at the time of spontaneous, chemical defibrillation for analysis of plasma potassium concentration. The first sample was taken at the moment fibrillation appeared to cease, as judged by the electrocardiogram and direct visual inspection of the heart. The second sample was taken when defibrillation was confirmed by electrical pacing of the ventricles by single 10 volt, 2 msec stimuli applied to the ventricular surface with hand-held bipolar electrodes. Generation of ventricular ectopic beats in the electrocardiogram was taken as confirmation of ventricular defibrillation. The average plasma potassium concentration of the first and second samples was taken as the level required for defibrillation with zero current and energy.

Results

The stable elevation of plasma potassium concentration produced by the "bolus plus infusion" technique in ten dogs is illustrated in Figure 3-6. The technique described produced a stable plateau of extracellular potassium concentration for defibrillation studies. The overall mean control potassium level was 3.9 mEq/L and the overall post potassium infusion level was 7.5 mEq/L. Calculated levels of intracellular potassium concentration in 4 of these animals and in 4 animals which did not receive prior potassium infusions are given in Table 3-1.
Figure 3-6. Elevation of plasma potassium in 10 dogs produced by a slow intravenous injection of potassium chloride, 1.0 mEq/kg, followed by a constant infusion of potassium chloride, 0.01 mEq/kg/min.
The mean value for intracellular potassium was 91 mEq/l and the standard error of the mean was 3.6 mEq/l.

Intracellular potassium concentrations of dogs which received potassium treatment were not significantly different from those of dogs which did not (t = 0.66, p = 0.53).

Figure 3-7 summarizes the effects of increased extracellular potassium concentration on ventricular defibrillation threshold. Defibrillation threshold as percent of control is plotted as a function of plasma potassium concentration and of calculated potassium equilibrium potential. The left-hand and middle data points represent mean control and post-potassium infusion threshold values. The right-hand data point represents the mean plasma potassium concentration for spontaneous defibrillation with zero current or energy. The upper scale for potassium equilibrium potential was calculated from the Nernst equation using the mean value of intracellular potassium concentration reported in Table 3-1. As extracellular potassium concentration is increased, ventricular defibrillation threshold dramatically decreased, reaching zero value when K was 16.6 mEq/l and E_K was -46 mV.

Discussion

The theory developed in Chapter 1 predicts that the defibrillation threshold should be related to the potassium equilibrium potential, E_K. As E_K is increased, the gap between the theoretical equilibria for resting
Figure 3-7. Effect of elevated extracellular potassium concentration on ventricular defibrillation threshold in dogs.
Table 3-1. Ionic concentrations in canine ventricular muscle. 

$\sigma_i$=volume fraction of extracellular space; $N_{at}$=tissue sodium concentration; $K_t$=tissue potassium concentration; $N_{ai}$=intracellular sodium concentration; $K_i$=intracellular potassium concentration. Prior KCl=KCl 1.0 mEq/kg i.v. slowly, followed by KCl 0.01 mEq/kg/min for 120 min. Student's t tests the null hypothesis that values for dogs 1-4 (no prior KCl) are equal to values for dogs 5-8 (prior KCl treatment). Prior KCl did not cause significant changes in the tabulated values.

<table>
<thead>
<tr>
<th>Dog #</th>
<th>Prior KCl</th>
<th>$\sigma_i$</th>
<th>Na$_t$ (mEq/l)</th>
<th>K$_t$ (mEq/l)</th>
<th>Na$_i$ (mEq/l)</th>
<th>K$_i$ (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no</td>
<td>0.27</td>
<td>37</td>
<td>54</td>
<td>16</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>no</td>
<td>0.26</td>
<td>45</td>
<td>82</td>
<td>15</td>
<td>109</td>
</tr>
<tr>
<td>3</td>
<td>no</td>
<td>0.15</td>
<td>31</td>
<td>71</td>
<td>14</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
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<td>69</td>
<td>11</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
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<td>0.26</td>
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<td>75</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>yes</td>
<td>0.18</td>
<td>29</td>
<td>73</td>
<td>6</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>yes</td>
<td>0.17</td>
<td>34</td>
<td>76</td>
<td>17</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>yes</td>
<td>0.24</td>
<td>40</td>
<td>74</td>
<td>8</td>
<td>97</td>
</tr>
</tbody>
</table>

Mean 22 37 72 12 91
S.D. 4.7 5.2 8.1 4.3 10.2
$\text{t}$ 0.66 0.38 -0.95 1.63 -0.66
$\text{P}$ (two-tailed) 0.53 0.72 0.38 0.15 0.53
membrane potential and cellular-firing threshold narrows. This change in turn is predicted to decrease the defibrillation threshold. At some value of $E_K$ less negative than normal, theory predicts that defibrillation threshold is zero. As indicated in Figure 3-7, the decrease in defibrillation threshold is in fact related to the increase in $E_K$, and defibrillation threshold falls to zero at half the normal negative value of $E_K$. Thus the influence upon defibrillation threshold of drugs which alter the potassium equilibrium potential may also be understood in terms of fundamental concepts of membrane physiology.

Discussion of Drug Effects on Ventricular Defibrillation Threshold

Drug effects on defibrillation threshold are of potential clinical importance because patients who fibrillate may have been placed on maintenance inotropic or antiarrhythmic drug therapy or admitted to coronary care units where antiarrhythmic drugs may be given routinely. Intravenous lidocaine by bolus injection or continuous infusion is currently recommended for hospitalized patients following acute myocardial infarction for suppression of ventricular arrhythmias (Hurst, 1974; Rawlings, 1976). Nonetheless, patients receiving lidocaine may still fibrillate (Pantridge, 1975). A variety of drugs may be given prior to defibrillation in attempts at cardiopulmonary resuscitation. Since
some authors have indicated that present commercial
defibrillators, which store 400 joules of energy, may
have marginal or inadequate output for heavyweight
patients (Tacker, 1974; Collins, 1978), the question of
whether cardiac drugs alter the electrical shock strength
required for defibrillation becomes especially pertinent.

The present studies show that members of three classes
of cardiac drugs alter the energy and current for electrical
ventricular defibrillation. Quinidine, a drug which acts
primarily by decreasing transmembrane sodium conductance,
and lidocaine, a drug which acts primarily by increasing
transmembrane potassium conductance, raise defibrillation
threshold. Potassium chloride, a drug which acts by making
potassium equilibrium potential less negative, lowers the
defibrillation threshold. These findings significantly
augment the literature concerning drug interactions with
defibrillating current.

The only previous report of the influence of anti-
arrhythmic drugs upon ventricular defibrillation threshold
is that of Woolfolk (1966), who found that quinidine
(10-60 mg/kg, i.v.) decreased the likelihood of successful
ventricular defibrillation in dogs given transchest shocks
of 30, 40, or 50 joules. The present studies confirm
Woolfolk's conclusion and also demonstrate that failure to
defibrillate in the presence of quinidine may be reversed
by the use of increased electric shock strength.
Lown (1968) reported that the mean stored energy for ventricular defibrillation by damped sinusoidal current in 5 dogs, given toxic doses of acetyl strophanthidin and ouabain, was 42 joules compared to the pre-drug value of 58 joules. In this study, digitalis glycosides appeared to decrease defibrillation threshold by 27 percent, although the difference was not statistically significant. Lown's data were obtained in animals given digitalis glycosides in doses sufficient to produce ventricular tachycardia. Fibrillation was produced by transthoracic direct current shocks delivered during the "vulnerable period" of the cardiac cycle. The post-defibrillation rhythm was always ventricular tachycardia, not sinus rhythm. However, when ventricular fibrillation was caused by higher doses of digitalis in three of these animals, the arrhythmia could not be reverted, even by multiple, high energy shocks.

Tacker (1975) found a dose-related decrease in defibrillation threshold current and energy in dogs following a single intravenous dose of ouabain. A dose of 50 μg/kg, corresponding to that used in Lown's study, produced an average maximum decrease in threshold energy of 29 percent, a finding virtually identical to that of Lown. However, at a higher dose, 80 μg/kg, Tacker reported that the lethal mechanism in 2 of 4 dogs was electromechanical dissociation following successful defibrillation rather than failure to defibrillate. Both studies, however, agree that high,
but not lethal, doses of ouabain decrease the defibrillation threshold.

These findings are consistent with the effects of potassium reported in this thesis and may be explained as an indirect effect of the well-known inhibition of membrane-bound sodium/potassium ATPase by digitalis glycosides. This cellular effect of digitalis preparations causes inhibition of active transport of sodium ions out of and potassium ions into myocardial cells. As a result, there is a net outward leakage of potassium ions (Langer and Serena, 1970) which conceivably could produce local elevations in extracellular potassium concentration with resultant depression of the defibrillation threshold.

These indirect alterations in defibrillation threshold by induced changes in local extracellular potassium concentration may also explain the recent (unpublished) observation in our laboratories that defibrillation threshold decreases following durations of fibrillation and total circulatory arrest lasting more than 2 min. In addition to depression of defibrillation threshold, we have found in preliminary experiments that the potassium concentration of blood recovered from the coronary vascular bed increases progressively as the duration of fibrillation and cardiac anoxia is lengthened. Such hearts, which have fibrillated for more than 2 min exhibit hypocontractility following defibrillation which may be reversed by calcium.
administration or several minutes of cardiac massage and ventilation ("washing out" of the coronary vascular bed). These preliminary observations lead to the hypothesis that accumulation of extracellular potassium ions may lead to depression of both defibrillation threshold and post-defibrillation cardiac contractility after prolonged durations of fibrillation. Hence, although elevations of extracellular potassium concentration as great as those reported in the present studies would never be produced for therapeutic reasons, the finding of threshold depression by potassium may be important in understanding various pathophysiologic states.

Koning and associates (1973) have reported calcium and magnesium induced changes in the shock strength required for ventricular defibrillation using dog preparations in which the coronary circulation was maintained during fibrillation by means of a bypass pump. Using a unique double pulse technique, Koning found that after doubling the plasma calcium concentration, the second of two shocks delivered 5-10 msec apart must be increased in amplitude to achieve defibrillation. Doubling of plasma magnesium concentration caused the threshold amplitude of the second shock to decrease. These results may be analogous to an increase in the single shock defibrillation threshold by calcium and a decrease in the single shock defibrillation threshold by magnesium. Such an effect would be predicted
by the theory developed in Chapter 1 to the extent that (1) calcium blocks sodium conductance and (2) magnesium acts as a calcium antagonist.

Although by no means a local anesthetic in most respects, calcium may have a local anesthetic-like action upon sodium conductance. Weidmann (1955) was the first to study the electrophysiologic properties of calcium in cardiac tissue. Using multiple microelectrodes in calf and sheep Purkinje fibers, this investigator found an increase in the cellular firing potential from -68 to -61 mV when extracellular calcium concentration was raised fourfold. However, since transmembrane resistance was unchanged or slightly decreased and since \( \frac{\text{dV}}{\text{dt}} \) was increased by added calcium, the author concluded that calcium does not decrease sodium conductance in the manner of local anesthetics.

Such a "local anesthetic" effect of calcium ions, however, has been reported by others in both nerve and ventricular muscle. Frankenhaeuser and Hodgkin (1957) studied voltage-clamped squid axons bathed by 0, 4, 22, and 112 mM Ca\(^{++}\) solutions made isotonic with choline and sodium salts. They found that increased extracellular calcium concentration decreased inward sodium current and transmembrane sodium conductance \( (g_{Na}) \). The curve relating \( g_{Na} \) to transmembrane potential was shifted 15 mV to the right (less negative) by a fivefold increase in calcium
concentration. That is, 15 mV greater depolarization was required to produce a given gNa. Calcium, like local anesthetics or quinidine, also decreased potassium current and conductance. Unlike local anesthetics, however, calcium did not decrease the maximal sodium conductance.

Beeler and Reuter (1970) developed a voltage-clamp method utilizing a sucrose gap and glass microelectrodes to study dog ventricular fiber bundles. Although these authors admitted some technical difficulties in measuring large inward sodium currents during Phase 0, they obtained curves relating peak transient (inward sodium) current to transmembrane potential (E_m) similar to those for squid axon. In these studies, ventricular muscle activation curves for gNa were shifted in a parallel fashion toward less negative voltages by increased extracellular calcium concentration. The E_m for 50 percent of maximal activation of gNa was shifted from -64 mV to -58 mV to -54 mV as extracellular calcium was increased from 0.2 mM to 1.8 mM to 7.2 mM. To the extent that such a "local anesthetic" action of calcium occurred in Koning's defibrillation studies, his finding of increased second pulse amplitude for defibrillation in hypercalcemia is consistent with the studies reported in this thesis using quinidine, a drug which also decreases sodium conductance.

Perhaps the most useful result of the present investigation is the development of a theory which relates
ventricular defibrillation threshold to four fundamental parameters of membrane physiology: \( g_{Na} \), \( g_{K} \), \( E_{Na} \), and \( E_{K} \). Such a theory readily suggests fruitful areas for further experimentation. These include both investigations of cardiac drugs known to alter \( g_{Na} \), \( g_{K} \), or both such as procaine amide, diphenylhydantoin, or propranolol, and investigations of pathophysiologic states which are known to increase potassium efflux from cells such as hypoxia (Singh, 1971/72; Lehr and Chau, 1973) or hypertension (Hochrein, 1971/72). These and similar studies, using the canine model described in this thesis, can be undertaken with confidence that the data obtained will be stable and reproducible and will demonstrate any true alterations in ventricular defibrillation threshold.


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VITA
VITA

Charles Frederick Babbs, Jr. was born July 6, 1946 in Toledo, Ohio. After preparation in public school systems, he entered Yale University in 1964 and graduated with a B.A. in psychology in 1968. He taught physics, chemistry, and general science at Montpelier High School, Montpelier, Ohio, during the subsequent year and then began studies at Baylor College of Medicine in Houston, Texas. He received the M.D. degree with honor in 1974 and an M.S. in anatomy in 1975 from this institution. During his tenure at Baylor College of Medicine he served as a teaching assistant in gross anatomy, microscopic anatomy, and neuroanatomy. Since coming to Purdue University in the fall of 1974, he has served as instructor in biology, and research associate in the Purdue Biomedical Engineering Center, while pursuing graduate study in the Department of Pharmacology and Toxicology, School of Pharmacy and Pharmacal Sciences.