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Drug Induced Changes in Ventricular Defibrillation Threshold

Charles F. Babbs
Purdue University

DRUG INDUCED CHANGES IN VENTRICULAR DEFIBRILLATION THRESHOLD

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Charles Frederick Babbs

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ABSTRACT

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A theory is developed that the minimal current required
for electrical ventricular defibrillation (the defibrilla-
tion threshold) is proportional to the gap between the
resting transmembrane potential and the threshold trans-
membrane 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 de-
fibrillation with successive damped sinusoidal shocks of
diminishing current intensity, each 10 percent less than
the preceding shock. The lowest shock intensity that de-
fibrillated 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, pCO_2, and pO_2 averaged 7.38, 34 mmHg, and 72 mmHg, respectively. The rates of change of pH, pCO_2, and pO_2 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.

Treatment	Delivered Energy	Peak Current
Quinidine (50 mg/kg, i.v.)	272	145
Lidocaine (3 mg/kg, i.v.)	148	126
Lidocaine (0.5 mg/kg/min i.v., 40 mg/kg total dose)	199	145
Elevation of plasma K to 7.5 mEq/l by KCl infusion	65	82
Elevation of plasma K to 16.6 mEq/l by KCl infusion	0	0
Pentobarbital only (controls)	101	104

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 ventricules for 2-30 msec will simultaneously
stimulate most ventricular muscle cells, causing poten-
tially 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 de-fibrillation 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 re-fractoriness 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,
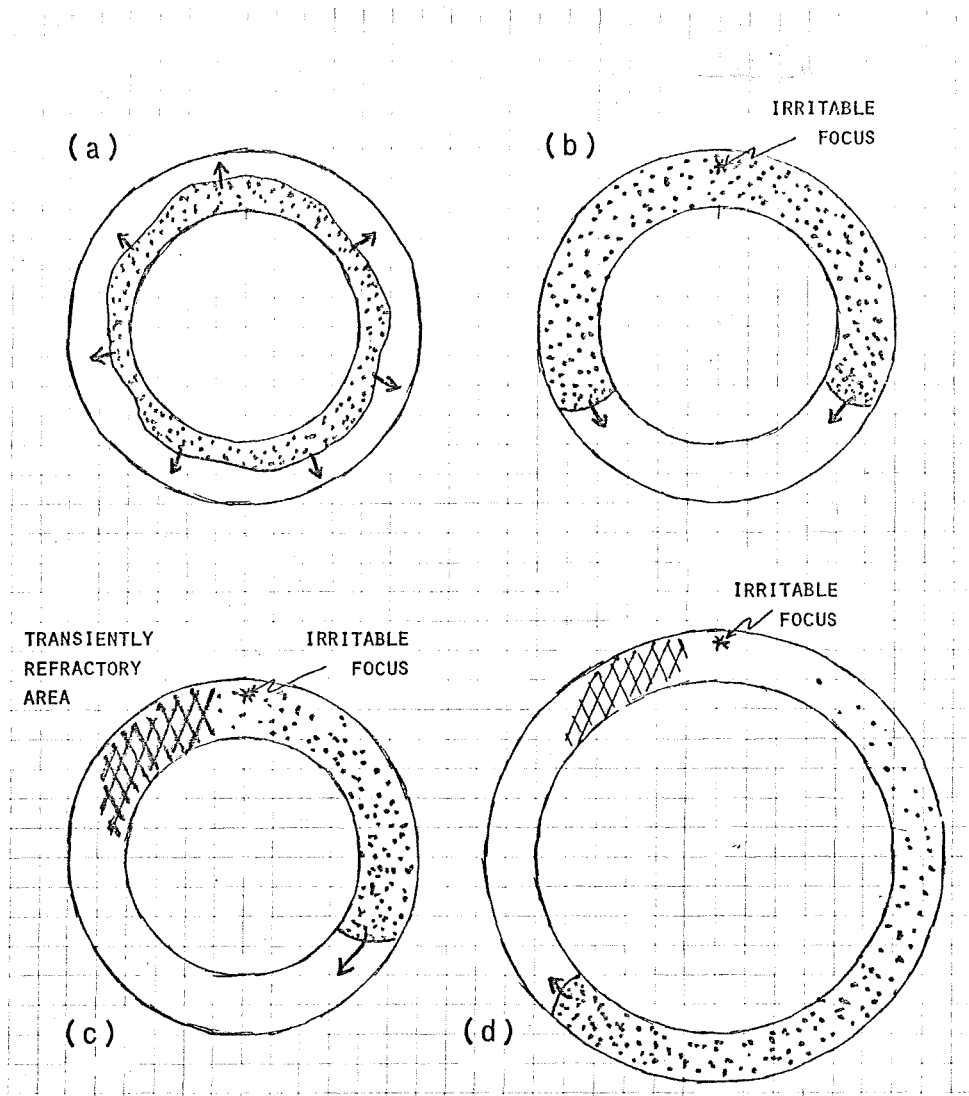
Figure 1-1. Development of circus motions in rings of
ventricular myocardium. (a) Normal excitation
via subendocardial Purkinje fibers. (b) Ex-
citation during a typical PVC, originating at
an irritable focus. (c) Excitation by a PVC
originating at the edge of a transiently re-
fractory area, leading 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, convuluted, 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.

Mechanisns 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,

$CaCl_2$ 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 fibrilla-
tion. After over a decade, the technique of 60 Hz alterna-
ting 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, com-
pared 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 de-
fibrillation, 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
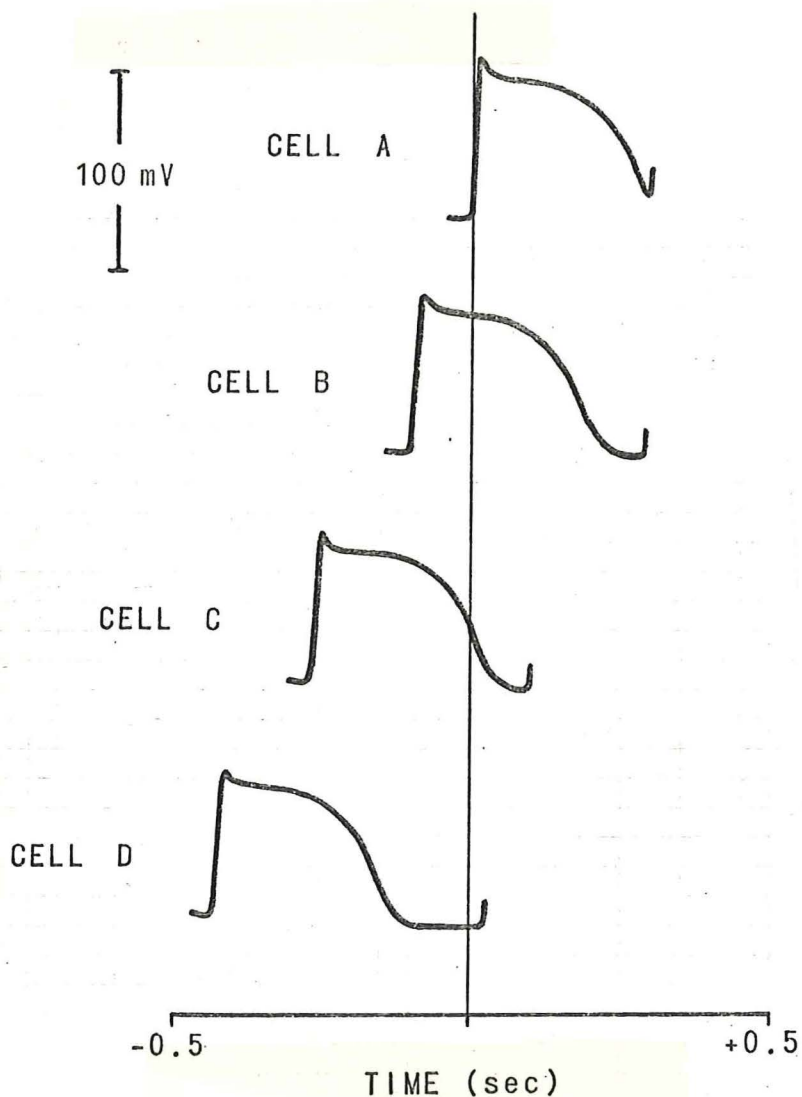
Figure 1-2. Temporal dispersion of action potentials in
fibrillating myocardium. Action potentials of 4
hypothetical cells, A, B, C, and D are indicated as
functions of time. During fibrillation cells may be
found in any stages of polarization at any instant
in time. During fibrillation Phase 4 is usually
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 supra-
threshold 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,
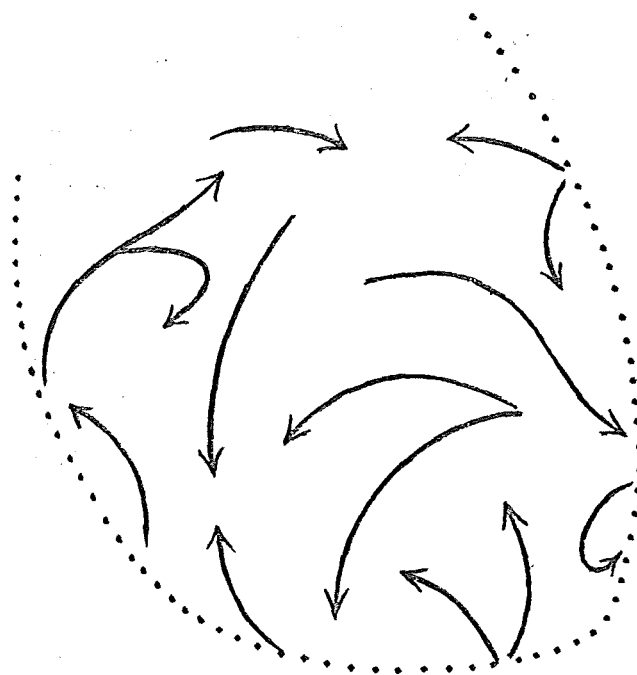
VENTRICULAR SURFACE

(VENTRAL ASPECT)

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 propaga-
        tion. Tails of arrows indicate length of refractory
        tissue strips trailing each wavefront. When a wave-
        front 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 defibrilla-
tion (Figure 1-4(a)). Consider a very thin section of
this block of tissue 15µ thick and 1cm^2 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 1cm^2
versus 0.3 ohms for 1cm^2) that membrane resistance can be
ignored for the present discussion and the membranes con-
sidered 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
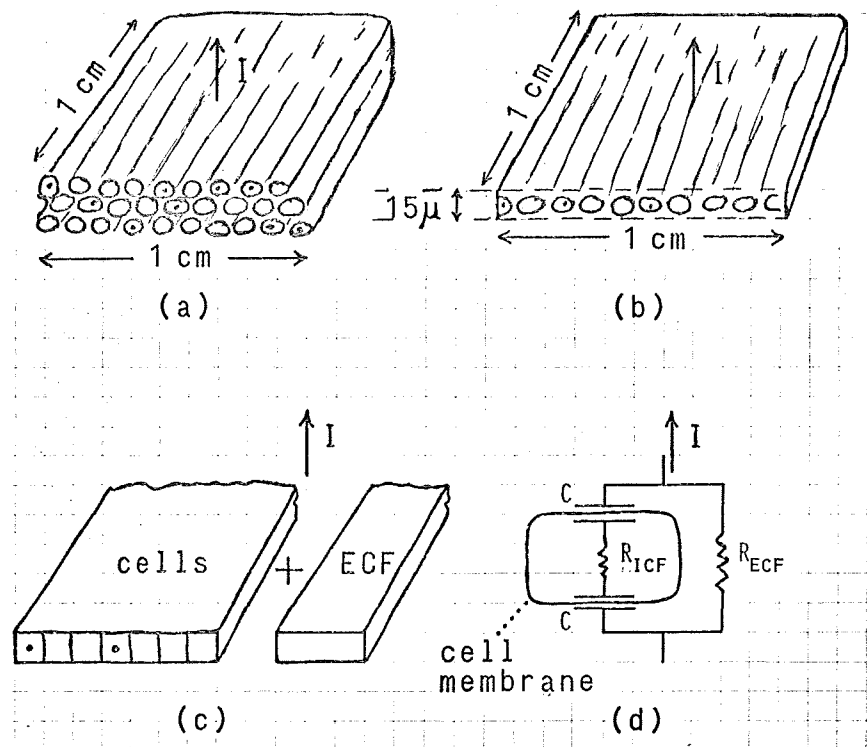
Figure 1-4. Scheme for analysis of the action of de-
fibrillating current upon myocardial cells. (a)
Bundle of myocardial fibers oriented perpendicular
to electric current field. (b and c) Hypothetical
tissue element 1 cm^2 in cross-sectional area and
one cell diameter in thickness, containing cells
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 sub-

stituted into the equivalent circuit of Figure 1-4(d) in

order to estimate the gross electrical effects of the

passage of a 100 ma/cm^2 threshold pulse of defibrillating

current through the hypothetical 15μ x 1 cm^2 slice of

myocardium. The estimate of 100 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 10μF for 1cm^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 ohm-cm x 0.0015 cm/0.3 cm^2 or
0.3 ohm. The final voltage to which both series membrane
capacitors are charged by a 100 ma/cm^2 defibrillating shock
is 100 ma x 0.3 ohm or 30 mV.

Charging the membrane capacitors results in hyper-
polarization of the anodal side and depolarization of the
cathodal side of the typical 15μ diameter cell, shown in
Figure 1-5(b). If 30 mV potential difference is divided
equally across the series membrane capacitors, the anodal
side of the 15 micron cell is depolarized by 15 mV and the
cathodal side hyperpolarized 15 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 per-
pendicular 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

(a)

(b)
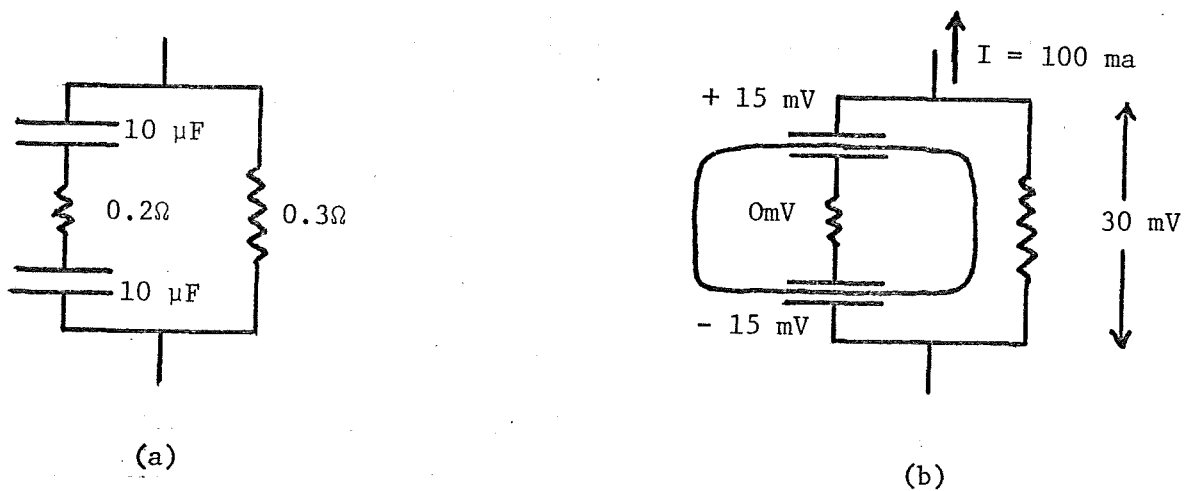
Figure 1-5.   Equivalent circuit for a hypothetical slice
      of myocardium 1 cm^2 in cross-sectional area and one
      cell diameter in thickness.   (a) Approximate values
      of the circuit elements.   (b) Steady state voltage
      differences caused by the passage of an electric
      current 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 x 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

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

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 temp-
erature selectively permeable to the membrane. The ionic

conductance, g(ion), is a function of both E_m and of time. The time dependence of g(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 gNa at the time of the transition between Phase 4 and Phase 0 is a rapidly increasing (concave upward) function of E_m; whereas gK is assumed to be approximately constant. More rigorous theoretical expressions for gNa and gK 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 gK during Phase 0. However, compared to the very large increase in gNa during excitation, gK 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 gK as a constant.*

Given the assumptions that gNa is an accelerated

function of E_m and that gK is essentially constant at the

time of excitation, the transmembrane currents involved may

be illustrated as shown in Figure 1-6(a). This figure illus-

trates 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 gNa 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

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*If gK is considered more exactly as an increasing function
of E_m with a derivative significantly less than that of the
gNa versus E_m curve, the predictions of the present theory
would be qualitatively the same with only minor quantita-
tive differences.
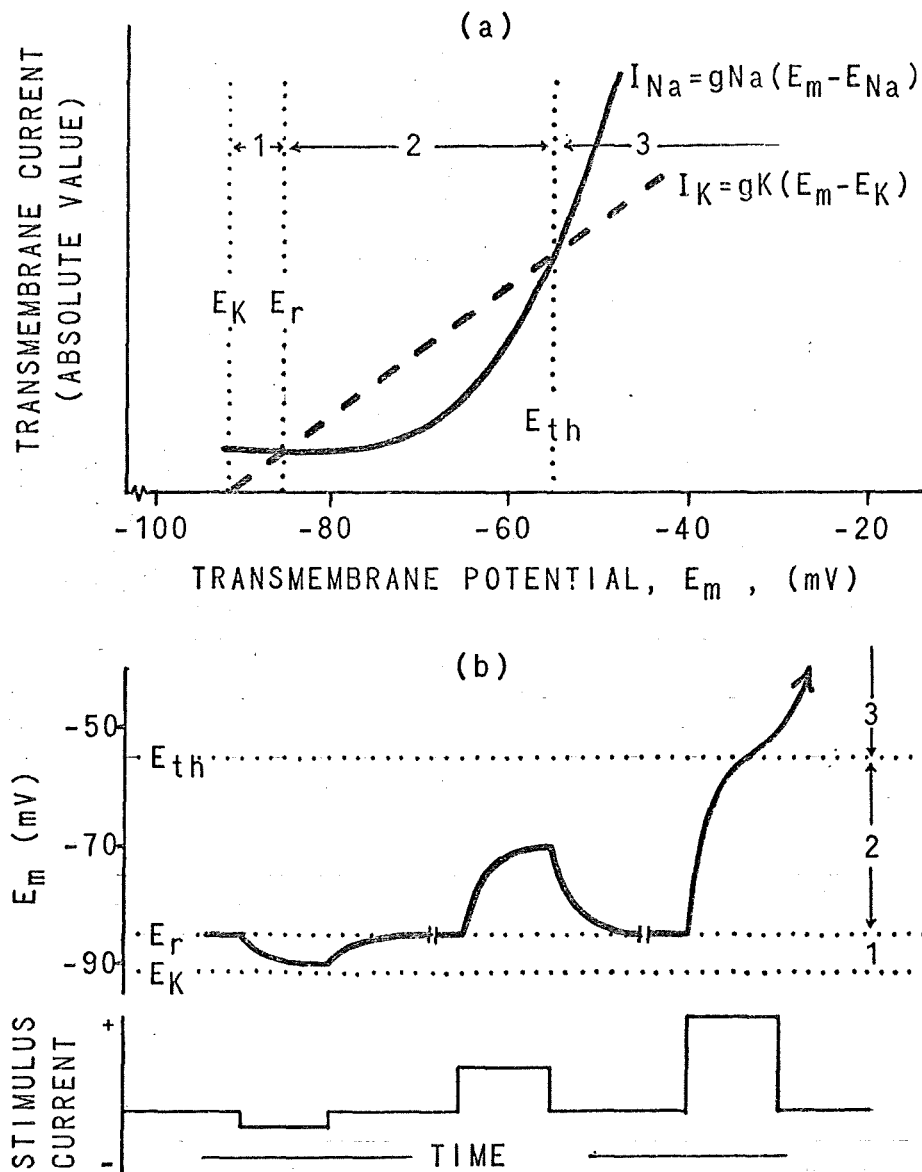
Figure 1-6.   Balance of inward sodium and outward potassium
currents in ventricular myocardial cells during Phase
4 and early Phase 0.   (a) Absolute values of sodium
and potassium currents are plotted as a function of
transmembrane potential, E_m.   Zones 1, 2, and 3 of
the E_m domain are identified. (b) Effects of altera-
tion of E_m by electrical stimuli.   If E_m is tran-
siently 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 gK,
alteration of the gNa, alteration of the E_K, and alteration
of the E_{Na}.

For example, if a drug increased gK 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 gNa 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 stimula-
tion threshold would occur. Conversely, if gK were de-
creased, gNa 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 in-
directly 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.

	gNa		
	decreased	normal	increased
gK increased	↑	↑	↑ or ↓
gK normal	↑		↓
gK decreased	↑ or ↓	↓	↓

↑ = 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 de-
fibrillation threshold.

Alteration of Myocardial gNa and gK 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 bun-
dles, 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 antiarrhyth-
mic drug action in cardiac muscle using preparations analo-
gous 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 up-stroke (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 in-crease inward sodium current in the presence of depressed gNa, as predicted by the expression $I_{Na} = gNa(E_m - E_{Na})$.

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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, Δt, later; where Δt is the propagation time required for depolarization to spread from the subendocardial to the subepicardial fibers. The time Δt is related to the propagation velocity, c, of the wavefront of depolarization and the distance, Δx, 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, ΔV, between these two areas of tissue. It follows that

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

Noting that the propagation time, Δt, is small compared to the action potential duration, and passing to the derivative,

$$\text{ECG} \propto \left(\frac{dV}{dt}\right) \cdot \frac{\Delta x}{c} \quad . \tag{1}$$

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 trans-membrane 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, Δx, 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, Δx, 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

<u>Lidocaine.</u>

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

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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/l) 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 con-
centrations 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

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*In this and the following discussions, square brackets
denoting molar concentrations of ions are omitted for
simplicity of notation.

$$E_K = -61.5 \log \frac{K_i}{K_o} \quad .$$

first with respect to K_o and then with respect to K_i:

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

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

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

1 KG OF DOG

1/3 dry	2/3 water

TBW

1/3	2/3

ECF ———— ICF

220 ml	440 ml

4 mEq/L	100 mEq/L

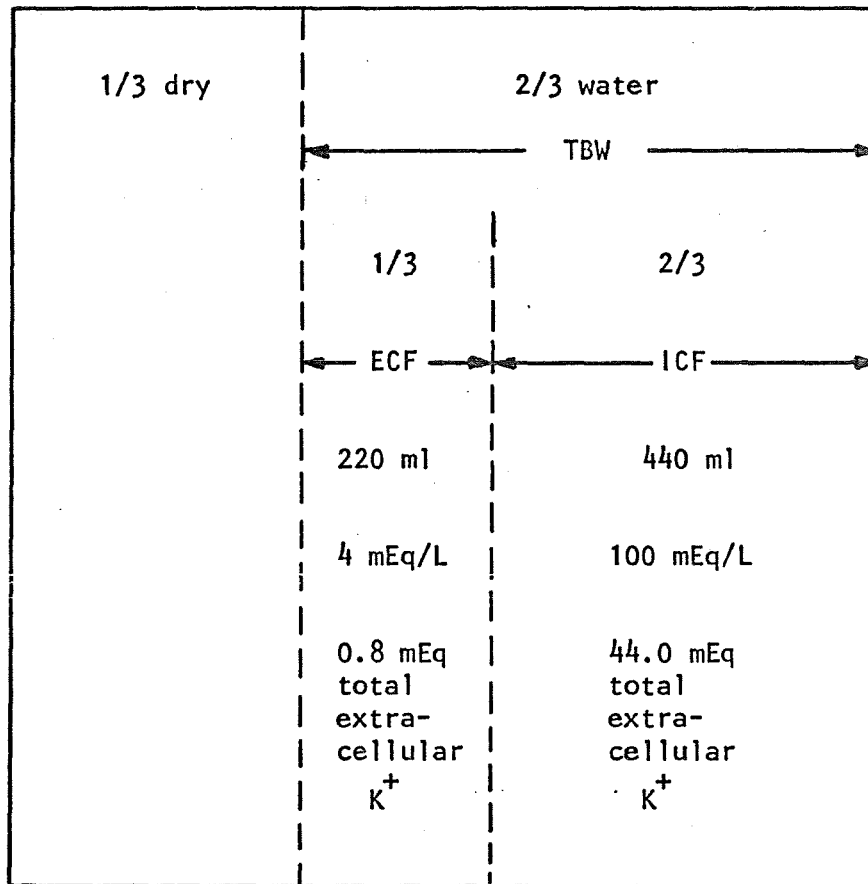| 0.8 mEq total extra- cellular K^+	44.0 mEq total extra- cellular K^+

Figure 1-7. Approximate normal distribution of potassium
ions in body fluid compartments. TBW = total body
water, ECF = extracellular fluid, ICF = intra-
cellular 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:

$$K_t = \sigma_o K_o + \sigma_i K_i \; ; \text{ where}$$

K_t = overall potassium concentration of myocardial tissue

σ_o = volume fraction of the extracellular space

σ_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 σ_o, the volume fraction of the extracellular space is known. Classically σ_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. Calcula-
tions 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_o/K_i ratio. K_o 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_o 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 pento-barbital 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[R], 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 de-
fibrillation threshold was determined before and after
induction of anesthesia with pentobarbital. These investiga-
tions 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 $\pm$ 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 pento-
barbital sodium (25-30 mg/kg), was given to produce
surgical anesthesia and the defibrillation threshold
measurement was repeated with the animal in dorsal recum-
bency. 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 pento-
barbital 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
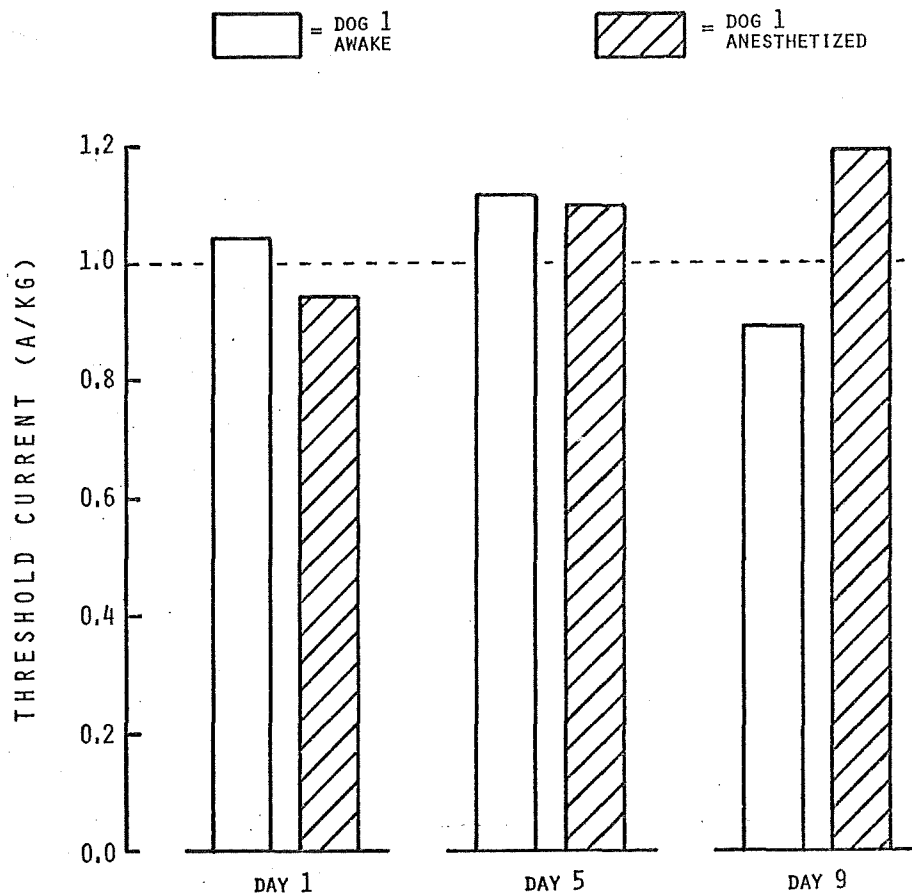
Figure 2-1.   Threshold peak current for ventricular de-
fibrillation in unanesthetized and anesthetized
states on successive trials in the same animal.   On
three successive trials the threshold current in
the unanesthetized animal was greater than, equal
to, and less than the threshold current after
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.
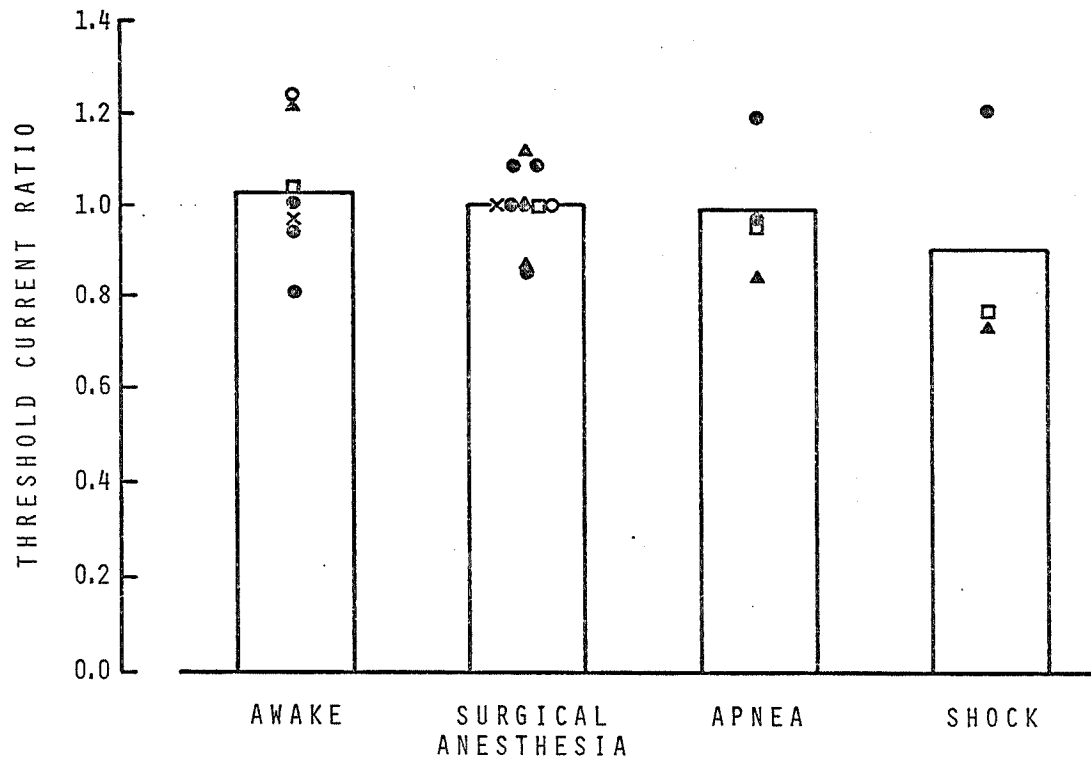
Figure 2-2. Relative values of threshold peak current for ventricular defibrillation at four levels of anesthesia. Awake = no anesthesia, Surgical anesthesia = spontaneous respiration but no response to surgical stimulation (25-30 mg/kg pentobarbital), Apnea = no spontaneous respiration (42-51 mg/kg 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

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

*+ 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 recombency 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 rep-
resents 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, pCO_2, and pO_2 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 electro-cardiogram with random waves and the fall of aortic blood pressure toward zero.

The output circuit of the damped sine wave defibrilla-tor 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-defibrilla-
tion 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
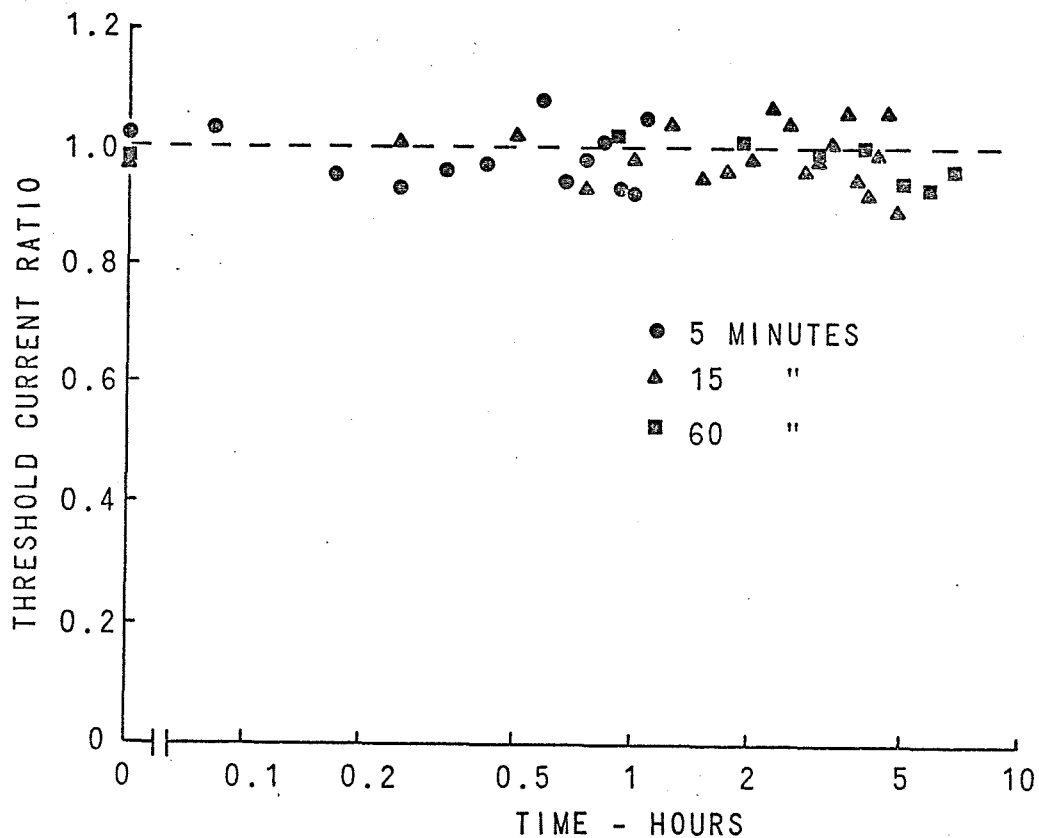different (F = 2.49, p = 0.12).   The time scale is
logarithmic.

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-defibrilla-
tion 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
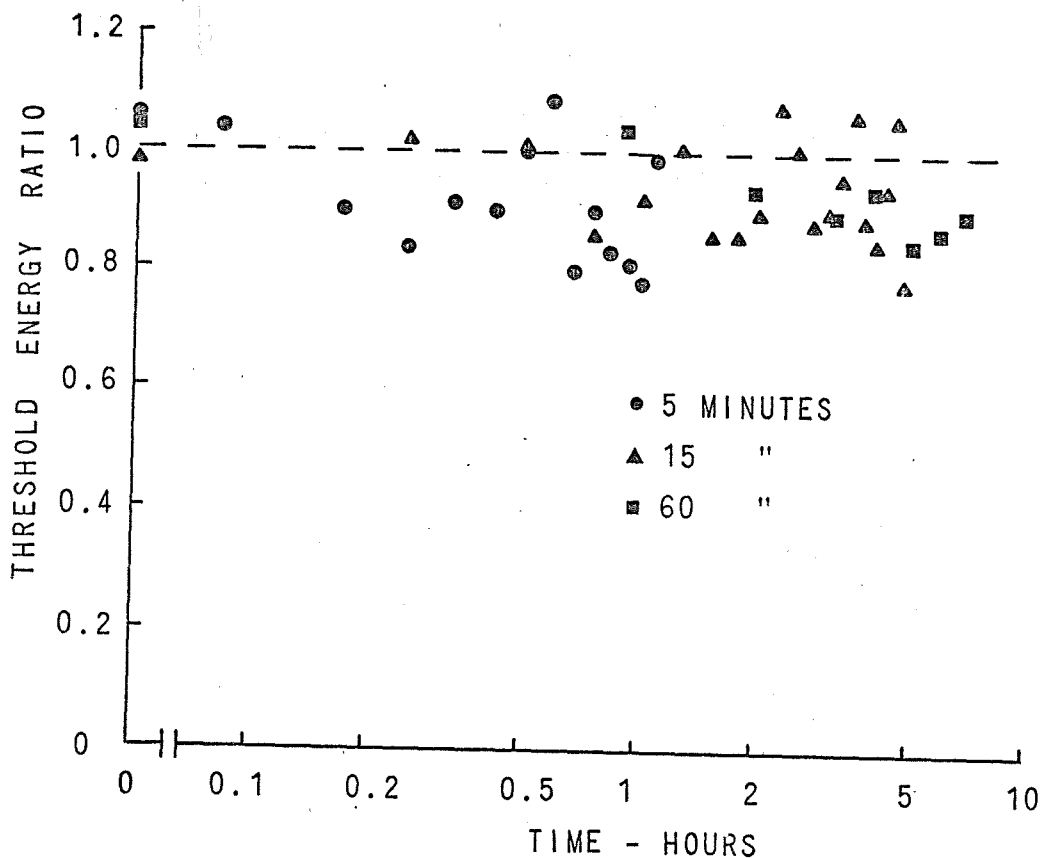different (F = 2.34, p = 0.14). The time scale is
logarithmic.

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 transchest electrical impedence, calculated by dividing peak voltage by peak current (Figure 2-5).

Arterial blood pH, pCO_2, and pO_2 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, pCO_2, and pO_2 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, pCO_2, and pO_2,
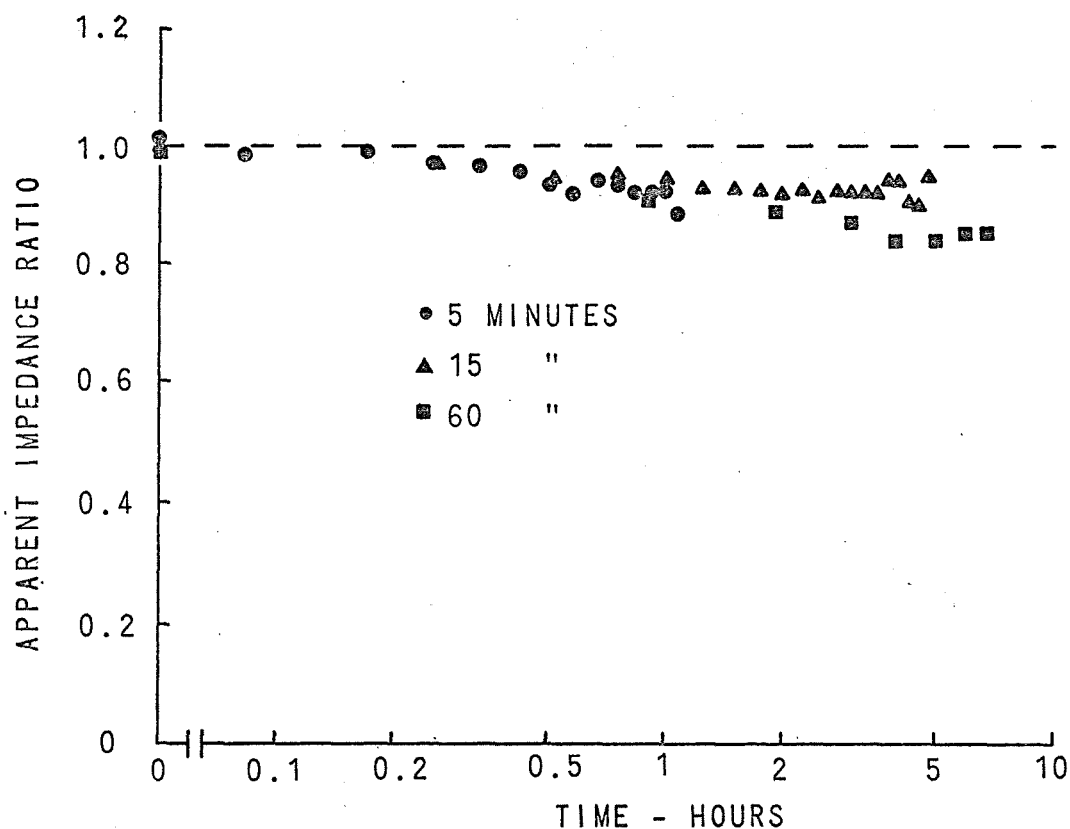
Figure 2-5. Stability of transchest electrical impedance.
Data points represent mean values of the ratio Z/Z_0
of transchest impedance, Z, at various times after
the first fibrillation-defibrillation trial to the
initial impedance value, Z_0, at time zero. The
apparent impedance Z, in ohms between the defibrilla-
ting 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.

Series	Threshold Interval (min)	pH		pCO_2		pO_2	
		Initial	Rate of Change (hr^{-1})	Initial (mmHg)	Rate of Change (mmHg/hr)	Initial (mmHg)	Rate of Change (mmHg/hr)
1	60	7.37	-0.003	35	-0.5	71	-0.2
2	15	7.38	0.006	34	-1.4	71	0.1
3	5	7.39	-0.03	34	1.7	79	-6.3
grand mean		7.38	-0.007	34	-0.067	73	-1.8
F		0.31	3.27	0.04	1.16	0.67	2.40
P		0.74	0.09	0.96	0.36	0.54	0.15
Student's t			-1.29		0.03		-1.26
P			0.22		0.98		0.24

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 x^2 = 0.20, p = 0.90 for current; Bartlett's x^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
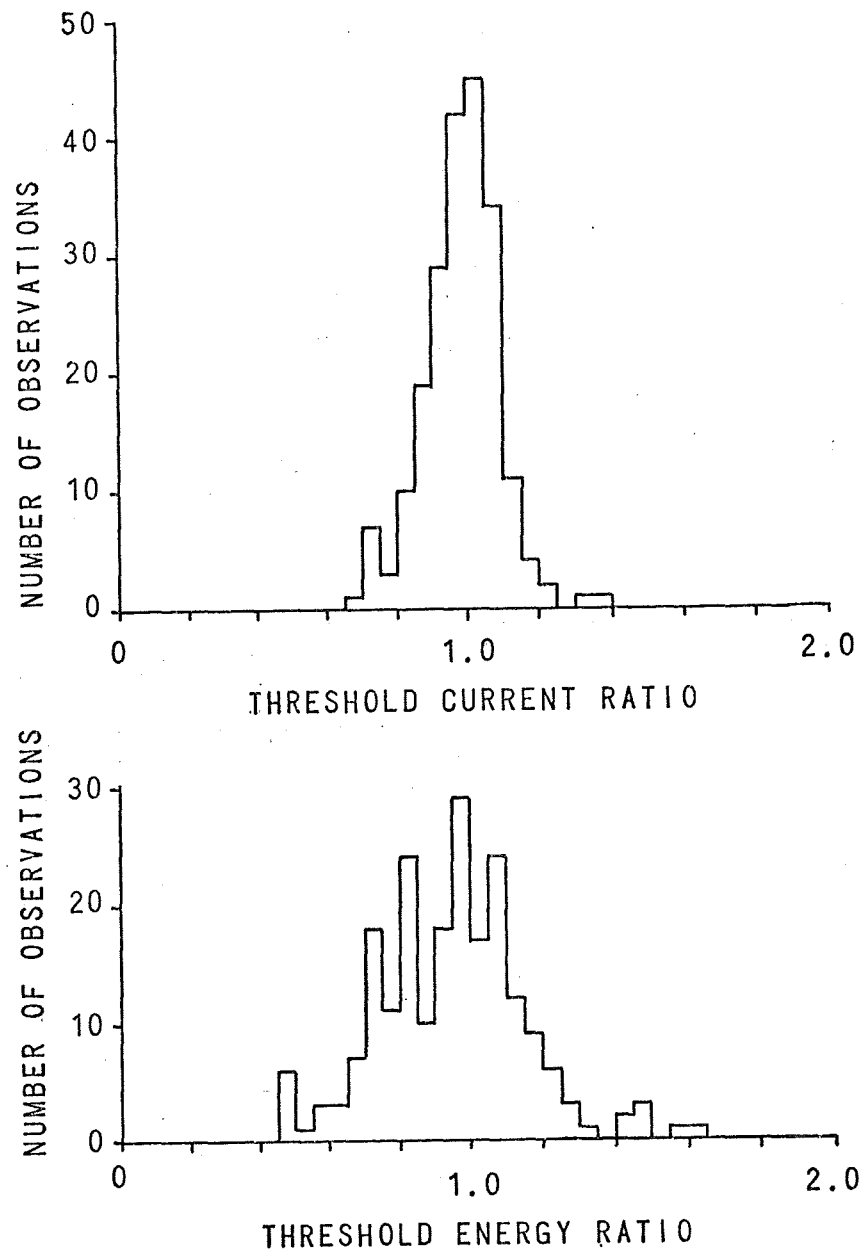
Figure 2-6. Histograms of threshold current and energy
ratios obtained in 15 control dogs. The width of
each class interval is 0.05. The value 1.00 on
the horizontal axes represents the average of the
first three threshold values obtained for each
animal. Variance represented by the histograms
therefore 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, pCO_2,
and pO_2.

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 percent 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 percent 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 σ_I. If $W = aI^2$ for any constant, a, then

$$\frac{\sigma_W}{m_W} = \frac{\dfrac{\sigma_I}{m_I} \sqrt{2 \dfrac{\sigma_I^2}{m_I^2} + 4}}{\dfrac{\sigma_I^2}{m_I^2} + 1}$$

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

$$\frac{\sigma_W}{m_W} \cong 2\,\frac{0.107}{0.984} = 0.217$$

The observed uncertainty, σ_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 determina-
tion 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_o and that the distribution of measured thresholds shown in Figure 2-7 is uniform within the interval I_o - $1.1I_o$. 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:

$$\sigma^2_{sampling} = \frac{10}{I_o} \int_{I_o}^{1.1\ I_o} I^2\ dI - (1.05\ I_o)^2 = 0.00083\ I_o^2 .$$

Since the mean of the measured values overestimates true threshold by 5 percent ($M_I = 1.05\ I_o$), one may express the sampling variance in terms of the mean <u>measured</u> threshold as

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

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

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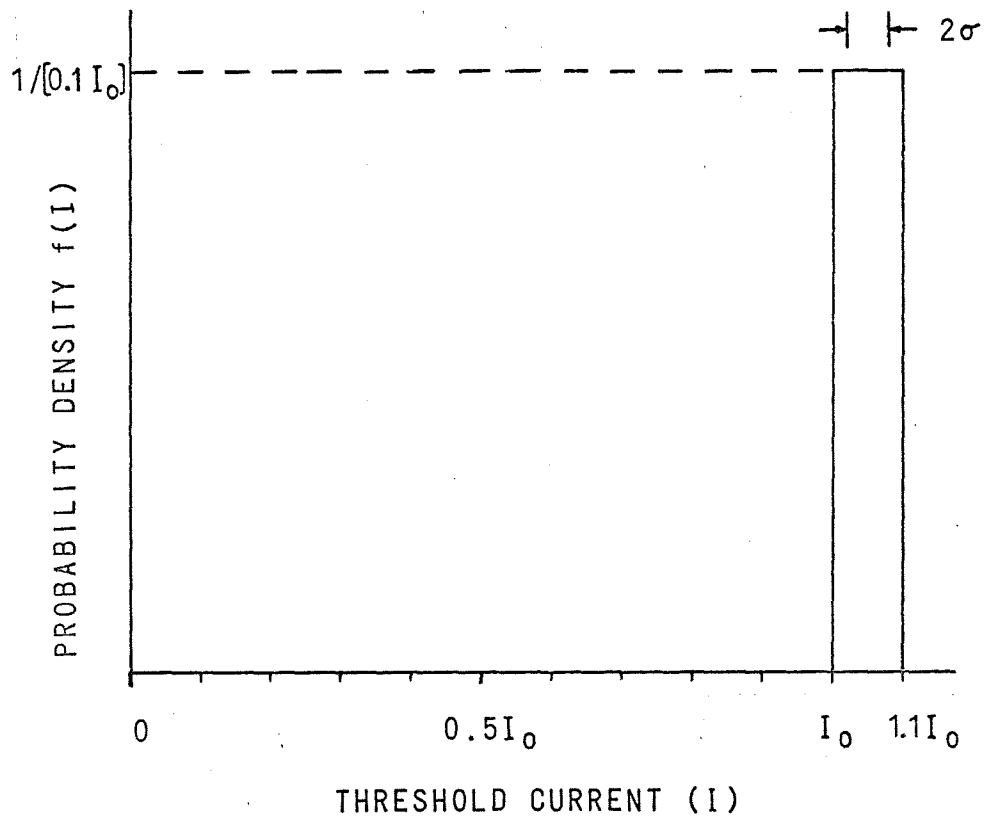
Figure 2-7. Uniform distribution of measured threshold
currents expected if physiologic variance were
zero. Probability density is scaled such that the
total area under the distribution function is unity.
For a given experiment of n observations, the
expected number of observations in class interval,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

defibrillation threshold current may be estimated as:

$$\sigma^2_{physiologic} = \sigma^2_{observed} - \sigma^2_{sampling} = 0.01188M_I^2 - 0.00076M_I^2$$

$$= 0.01112M_I^2$$

and

$$\sigma_{physiologic} = 0.105M_I \ .$$

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 pento-barbital 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 anti-
cipated 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 transchest defibrillation, each with a damped sinusoidal defibrillator shock of peak current amplitude 10 percent less than the amplitude of the preceding 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 defined 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 recorded 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. Lidocaine 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
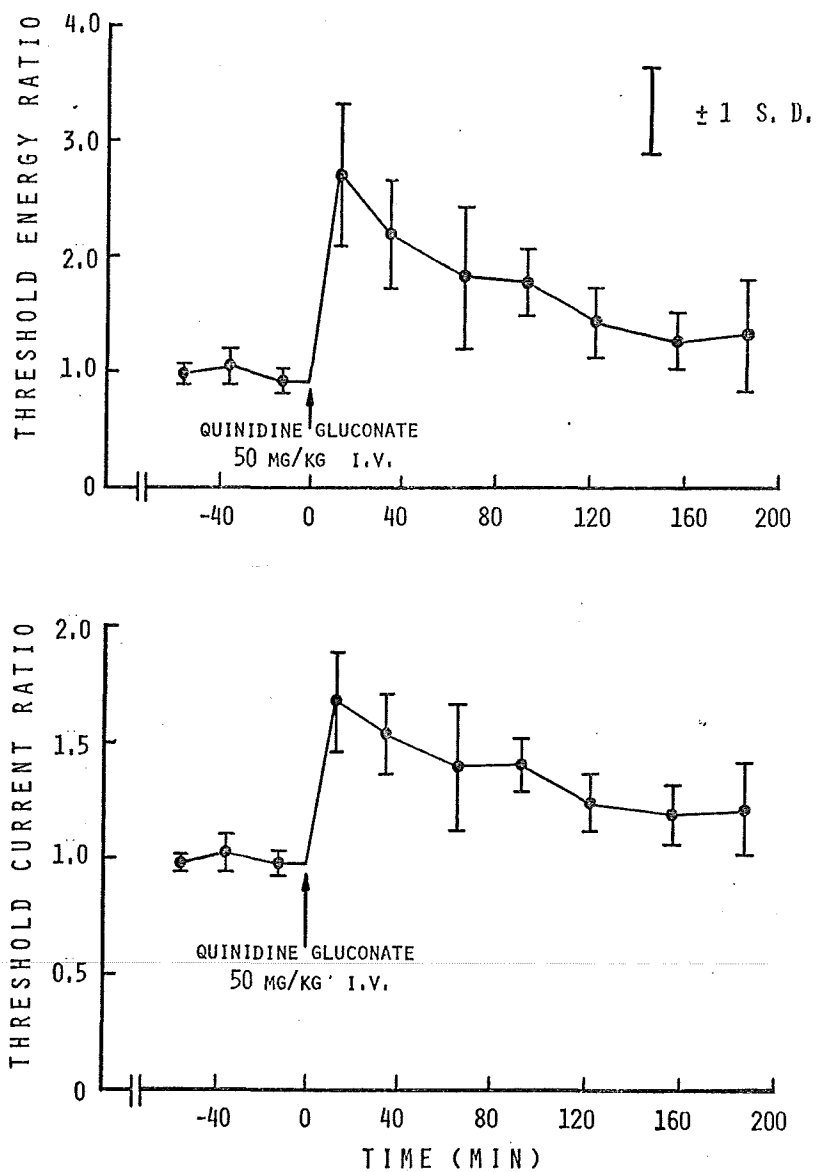defibrillation threshold in 5 dogs.   All threshold
elevations after quinidine injection are statistically
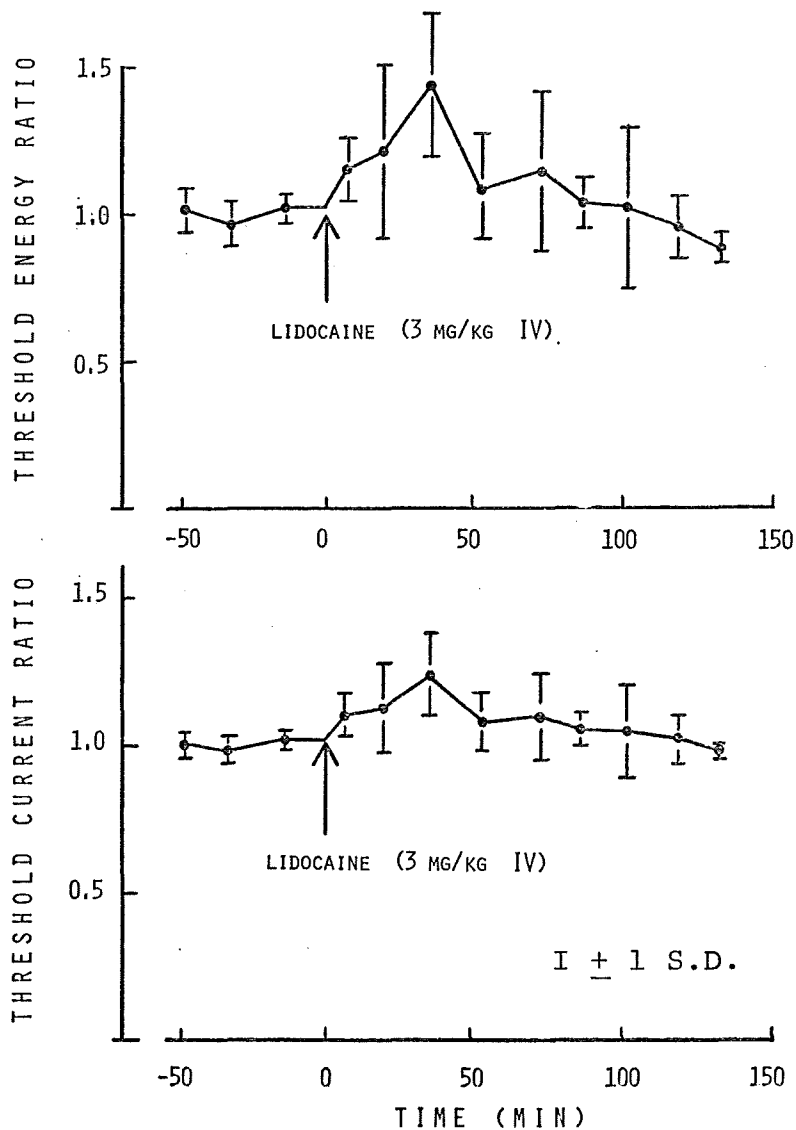significant (U < 11, p < 0.01) except the final data
point at 187 min.

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 in-
fusion (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
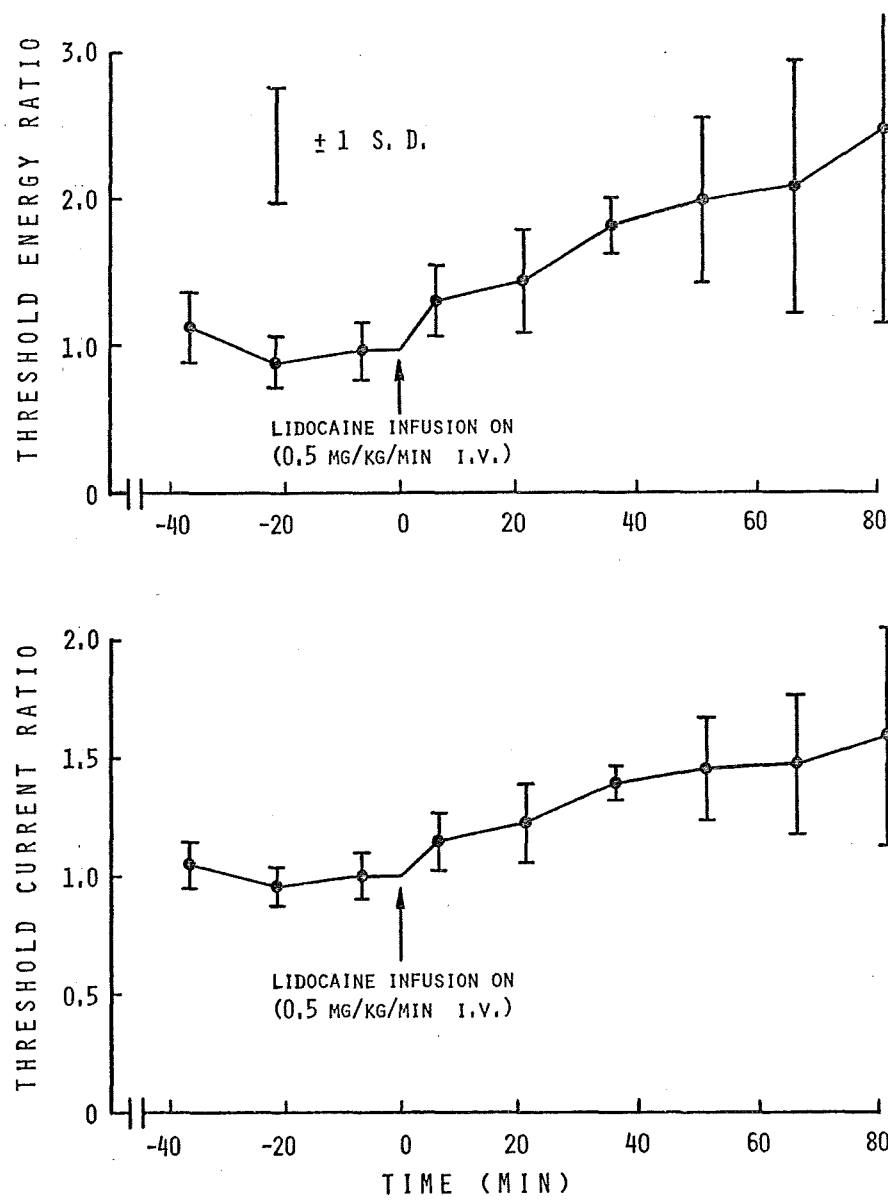
Figure 3-3. Effect of lidocaine infusion on ventricular
defibrillation threshold. All threshold elevations
after onset of the infusion are statistically sig-
nificant (U < 14, p < 0.05). After 30 min of
infusion threshold elevations are highly significant
(U < 11, p < 0.01).
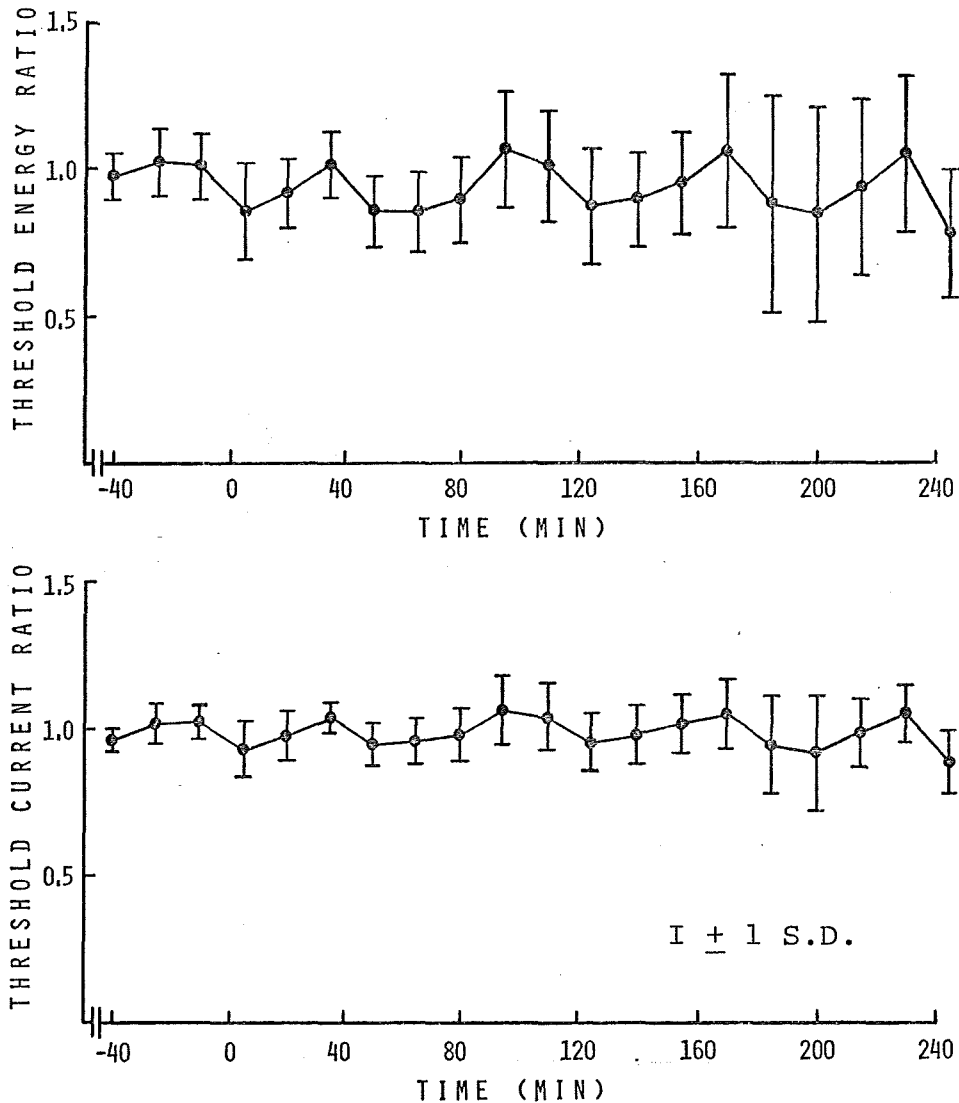
Figure 3-4. Effect of pentobarbital anesthesia only on
ventricular defibrillation threshold in 5 dogs.
These animals served as controls. The slight, periodic
variations in these threshold data were not reproduci-
ble in other control series.

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 potentialswhich must be overcome by the action of de-fibrillating 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 electrocardio-graphic 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_o) 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
  $E_K = -61.5 \log(K_i/K_o)$.

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 electro-
cardiogram 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 bracheocephalic 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 H_2SO_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 H_2SO_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, Na_t, is given by the expression

$$Na_t = \sigma_o Na_o + \sigma_i Na_i$$

where σ_o = volume fraction of the extracellular space

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

Na_i = intracellular sodium concentration

Na_o = 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, σ_o may be calculated from measurable quantities as

$$\sigma_o = \frac{\Delta Na_t}{\Delta Na_o} = \frac{Na_t(\text{Ringer's}) - Na_t(\text{dextrose})}{Na_o(\text{Ringer's}) - Na_o(\text{dextrose})} .$$

Calculation of Intracellular Potassium Concentration.

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

$$K_i = \frac{K_t - \sigma_o K_o}{1 - \sigma_o} .$$

<u>Investigation of Higher Levels of K_o.</u>

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_o 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, pCO_2, and pO_2 were
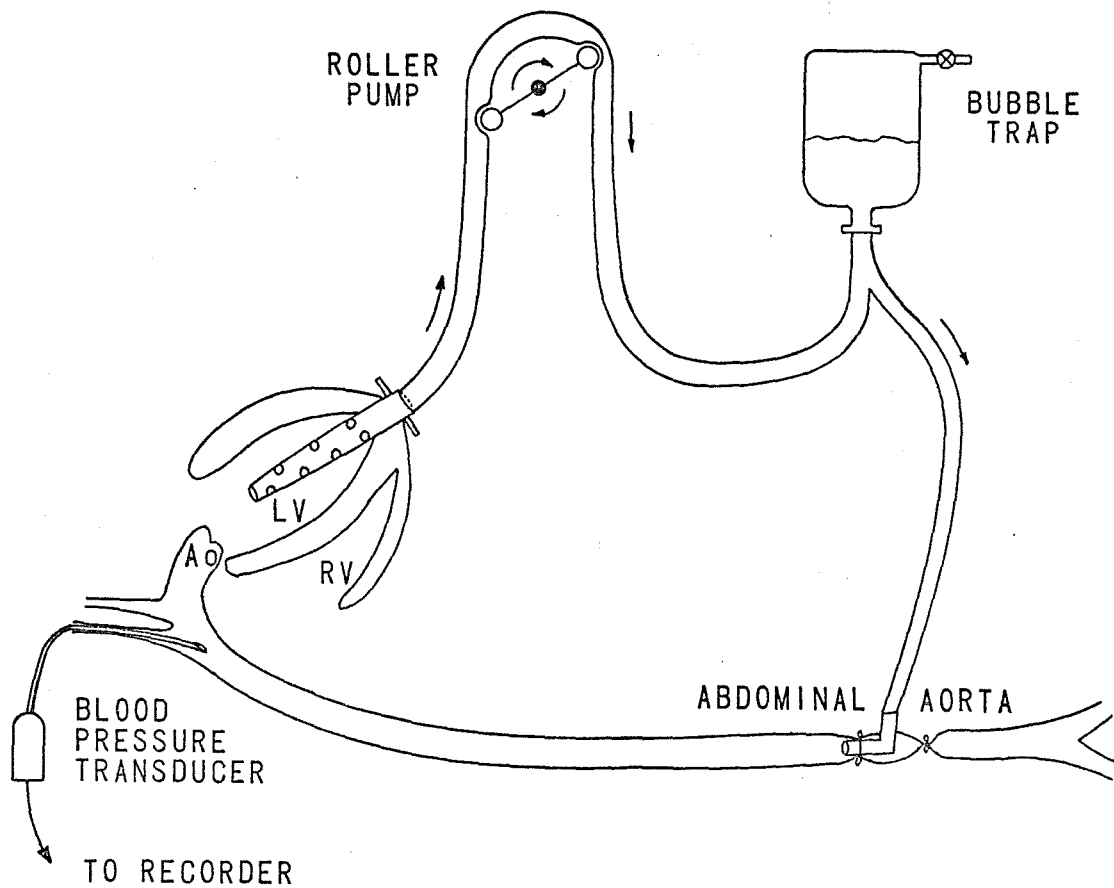
Figure 3-5. Principle of open-chest left ventricular
bypass. The left ventricle, LV, is catheterized
via a stab wound in the cardiac apex. The roller
pump provides an artificial left ventricular
output, which is returned to the abdominal aorta.
The negative pressure created in the left ventricle
and 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.
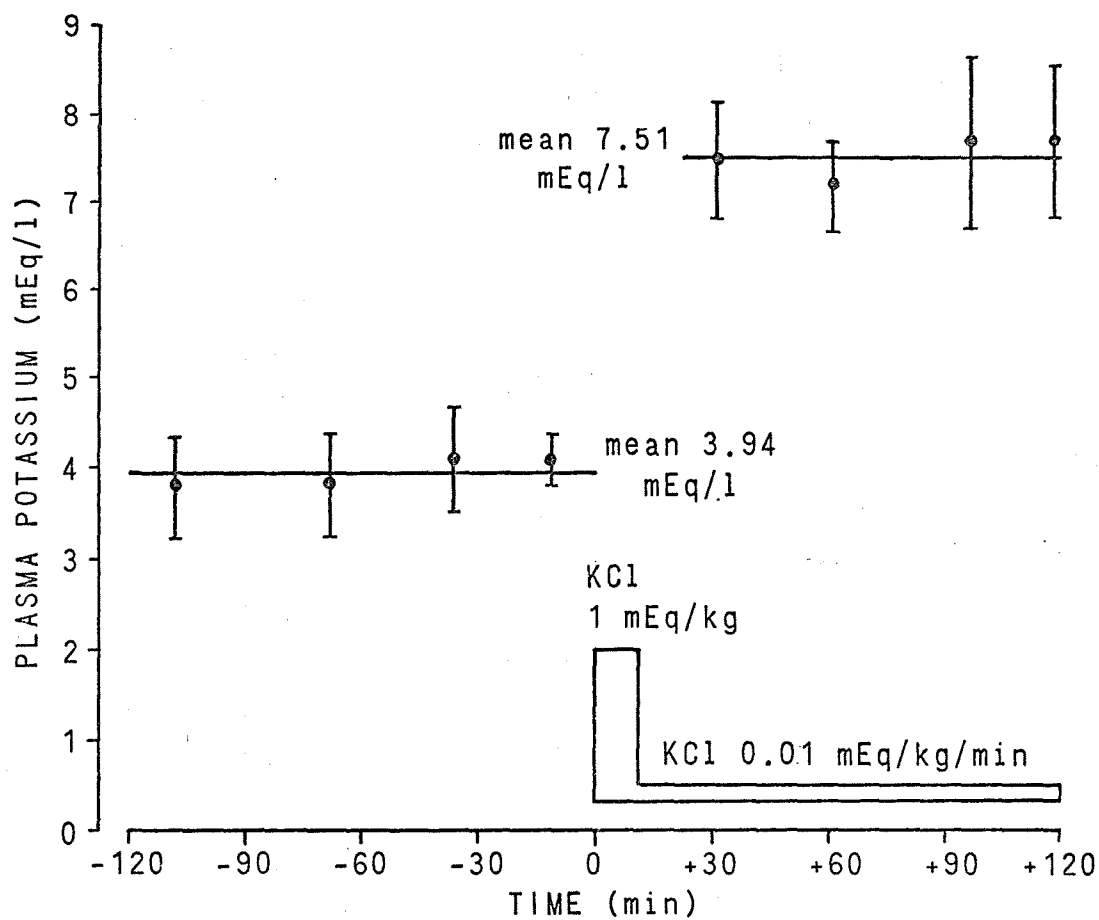
Figure 3-6. Elevation of plasma potassium in 10 dogs
produced by a slow intravenous injection of
potassium chloride, 1.0 mEq/kg, followed by a
constant infusion of potassium chloride,
0.01 mEq/kg/min.

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_O 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
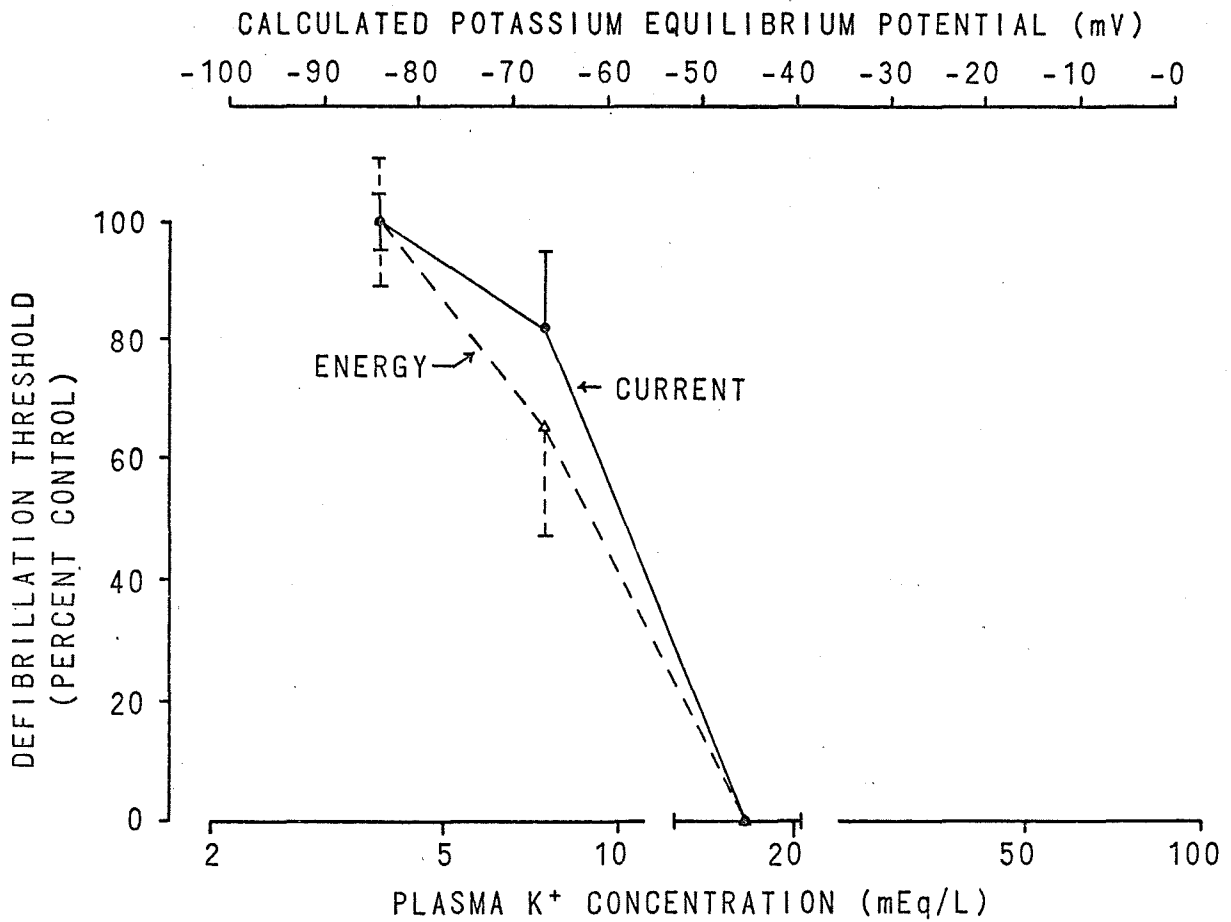
Figure 3-7. Effect of elevated extracellular potassium
concentration on ventricular defibrillation
threshold in dogs.

Table 3-1. Ionic concentrations in canine ventricular muscle. σ_i=volume fraction of extracellular space; Na_t=tissue sodium concentration; K_t=tissue potassium concentration; Na_i=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.

Dog #	Prior KCl	σ_i	Na_t mEq/l	K_t mEq/l	Na_i mEq/l	K_i mEq/l
1	no	0.27	37	54	16	77
2	no	0.26	45	82	15	109
3	no	0.15	31	71	14	83
4	no	0.20	36	69	11	85
5	yes	0.26	40	75	7	99
6	yes	0.18	29	73	6	88
7	yes	0.17	34	76	17	90
8	yes	0.24	40	74	8	97
Mean		22	37	72	12	91
S.D.		4.7	5.2	8.1	4.3	10.2
t		0.66	0.38	−0.95	1.63	−0.66
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 anti-arrhythmic 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 defibrilla-
tion 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 concen-
tration may also explain the recent (unpublished) observa-
tion 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-de-
fibrillation 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 re-
quired 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 $(dV/dt)_0$ 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 (gNa). The curve relating
gNa 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 trans-membrane 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: gNa, gK, 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 gNa, gK, 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.

BIBLIOGRAPHY

BIBLIOGRAPHY

Arnsdorf, M.F. and Bigger, J.T., "The Effect of Lidocaine on Membrane Conductance in Mammalian Cardiac Purkinje Fibers," J. Clin. Invest., 51, 2252-2263, 1972.

Arnsdorf, M.F. and Bigger, J.T., "Effect of Lidocaine on Components of Excitability in Long Mammalian Cardiac Purkinje Fibers," J. Pharmacol. Exp. Ther., 195, 206-215, 1975.

Arnsdorf, M.F., "Electrophysiologic Properties of Antiarrhythmic Drugs as a Rational Basis for Therapy," Medical Clinic of North America, 60, 213-232, 1976.

Babbs, C.F. and Whistler, S.J., "Evaluation of the Operating Internal Resistance, Inductance, and Capacitance of Damped Sine Wave Defibrillators," Medical Instrumentation, January, 1978 (in press).

Bassett, A.L. and Wit, A.L., "Recent Advances in Electrophysiology of Antiarrhythmic Drugs," Progr. Drug. Res. 17, 34-58, 1973.

Beck, C.S., Pritchard, W.H., Fiel, H.S., "Ventricular Fibrillation of Long Duration Abolished by Electric Shock," JAMA 135, 985-986, 1947.

Beeler, G.W. and Reuter, H., "Voltage Clamp Experiments on Ventricular Myocardial Fibres," J. Physiol. (Lond.) 207, 165-190, 1970.

Bigger, J.T. and Mandel, W., "The Effect of Lidocaine on the Electrophysiologic Properties of Ventricular Muscle and Purkinje Fibers," J. Clin. Invest. 49, 63-77, 1970.

Brodie, B.B., Boms, J.J., Morc, L.C., Lief, P.A., Burnstein, E., and Papper, E.M., "The Fate of Pentobarbital in Man and Dog and a Method for its Estimation in Biological Material," J. Pharm. Exp. Ther. 109, 26-34, 1953.

Chambers, W., Miles, R., and Stratbucker, R,, "Human Chest Resistance During Successive Countershocks,"Medical Instrumentation, January, 1978 (in press).

Collins, R.E., Giuliani, E.R., Tacker, W.A. and Geddes, L.A., "Transthoracic Ventricular Defibrillation: Success and Body Weight," Medical Instrumentation, January, 1978 (in press).

Davis, L.D. and Temte, J.V., "Electrophysiological Actions of Lidocaine on Canine Ventricular Muscle and Purkinje Fibers," Circ. Res. 24, 639-655, 1969.

deJong, R.A., Physiology and Pharmacology of Local Anesthesia, Charles C. Thomas, Springfield, Illinois, 1970.

Deck, K., Kern, A., and Trautwein, W., "Voltage Clamp Technique in Mammalian Cardiac Fibres," Pflügers Arch. ges. Physiol., 280, 50-62, 1964.

Dresel, P.E.,"Cyclopropane-epinephrine cardiac arrhythmias," in Price, H.L., and Ohen, P.J., Effects of Anesthetics on the Circulation, Charles C. Thomas, Springfield, Illinois, 1964.

Effendi, H., Versprille, A., and Wise, M.E., "The Negative Inotropic Effect of Barbiturates on the Heart of Newborn and Adult Guinea-pigs," Arch. Int. Pharmacodyn. 209, 127-143, 1973.

Ehrenstein, G., "Ion Channels in Nerve Membranes," Physics Today, 33-39, October, 1976.

Etsten, B., and Li, T.H.,"Hemodynamic Changes During Thiopental Anesthesia in Humans: Cardiac Output, Stroke Volume, Total Peripheral Resistance, and Intrathoracic Blood Volume," J. Clin. Invest. 34, 500, 1955.

Flacke, W., and Alper, M.H., "Actions of Halothane and Norepinephrine In the Isolated Mammalian Heart," Anesthesiology 23, 793-801, 1962.

Fozzard, H.A. and Beeler, G.W., "The Voltage Clamp and Cardiac Electrophysiology," Circulation Research 37, 403-413, 1975.

Frank, J.S. and Langer, G.A. "The Myocardial Interstitium: Its Structure and Its Role in Ionic Exchange," J. Cell Biol. 60, 586-601, 1974.

Frankenhaeuser, B., and Hodgkin, A.L., "The Action of Calcium on the Electrical Properties of Squid Axons," J. Physiol. 137, 218-244, 1957.

Friedberg, C.K., Diseases of the Heart, Vol. 1, Phila-delphia, Pa., W.B. Saunders Company, 1966.

Garrey, W.E., "The Nature of Fibrillary Contraction of the Heart: Its Relation to Tissue Mass and Form," Am. J. Physiol. 33, 397-406, 1914.

Geddes, L.A., Tacker, W.A., McFarlane, M.D., Bourland, J.D., "Strength-Duration Curves for Ventricular Defibrillation in Dogs," Circ. Res., 27, 551-560, 1970.

Geddes, L.A., Tacker, W.A., Rosborough, J.P., Moore, A.G., Cabler, B.S., Bailey, M., McCrady, J.D., Witzel, D., "The Electrical Dose for Ventricular Defibrillation with Electrodes Applied Directly to the Heart," J. Thoracic Cardiovasc. Surg., 68, 593-602, 1974.

Geddes, L.A., and Baker, L.E., Principles of Applied Biomedical Instrumentation, Second Ed., John Wiley and Sons, New York, 1975.

Geddes, L.A., Tacker, W.A., Cabler, P., Chapman, R., Rivera, R., and Kidder, H., "The Decrease in Transthoracic Impedance During Successive Ventricular Defibrillation Trials," Medical Instrumentation, Vol. 9, No. 4, July-August, 1975.

Geddes, L.A., 1977 Personal Communication.

Gettes, L.S., Surawicz, B., and Shive, "Effect of High K, Low K, and Quinidine on QRS Duration and Ventricular Action Potential, Am. J. Physiol., 203, 1175, 1962.

Gibbons, W.R. and Fozzard, H.A., "Slow Inward Current and Contraction of Sheep Cardiac Purkinje Fibers," J. Gen. Physiol., 65, 367-385, 1975.

Goldstein, A., and Aronow, L., "The Duration of Action of Thiopental and Pentobarbital," J. Pharm. Exp. Ther. 128, 1-6, 1960.

Grubbs, S. and Wilcos, P., Unpublished observations, Spring 1975.

Guide for the Care and use of Laboratory Animals, U.S. Department of Health, Education and Welfare, DHEW Pub. No. (NIH) 73-23, Revised 1972.

Gurvich, N.L. and Yuniev, G.S., "Restoration of the Heart Rhythm During Fibrillation by a Condenser Discharge," Am. Rev. Soviet Med., 4, 252-256, 1947.

Hardman, H.F., Moore, J.I., and Lum, B.K.B., "A Method for Analyzing the Effect of pH and the Ionization of Drugs Upon Cardiac Tissue with Special Reference to Pentobarbital," J. Pharmacol. Exp. Therap. 126, 136-142, 1959.

Heissenbuttel, R.A. and Bigger, J.T., "The Effect of Oral Quinidine on Intraventricular Conduction in Man: Correlation of Plasma Quinidine with Changes in QRS Duration," Am. Heart J., 80, 453-462, 1970.

Hochrein, H., Hunsmann, G., and Stoepel, K., "Changes of Intracellular Myocardial Electrolytes in Experimental Hypertension," Cardiology 56, 96-99, 1971/72.

Hodgkin, A.L. and Huxley, A.F., "A Quantitative Description of Membrane Current and Its Application to Conduction and Excitation in Nerve," J. Physiol., 117, 500-544, 1952.

Hoffman, B.F. and Cranefield, P.F., Electrophysiology of the Heart, McGraw-Hill, New York, 1960.

Hooker, D.R., "On the Recovery of the Heart in Electric Shock," Am. J. Physiol. 91, 305-328, 1930.

Hooker, D.R., Kouwenhoven, W.B. and Langworthy, O.R., "The Effect of Alternating Electrical Current on the Heart," Am. J. Physiol. 103, 444-454, 1933.

Hurst, J.W., Logue, R.B., Schlant, R.C. and Wenger, N.D., Eds. The Heart Arteries and Veins, 3rd Edition, McGraw-Hill Book Company, New York, 1974.

Kabela, E., "The Effects of Lidocaine on Potassium Efflux from Various Tissues of Dog Heart," J. Pharmacol. Exp. Ther., 184, 611-618, 1973.

Koning, G., Charbon, G.A., and Schneider, H., "The Influence of Magnesium and Calcium on Defibrillation of the Canine Heart," Proceedings of the 1st International Symposium on Magnesium Deficit in Human Pathology, Villel, France, 361-363, 1973.

Kouwenhoven, W.B. and Milnor, W.R., "Treatment of Ventricular Fibrillation Using a Capacitor Discharge," J. Appl. Physiol. 7, 253-257, 1954.

Lown, B., Neuman, J., Amarasingham, R., et al., "Comparison of Alternating Current with Direct Current Electroshock Across the Closed Chest," Am. J. Cardiol., 10, 223-233, 1962.

Lown, B., Kleiger, R., and Williams, J., "Cardioversion and Digitalis Drugs: Changed Threshold to Electric Shock in Digitalized Animals," Circulation Res., 17, 519-531, 1965.

Langer, G.A. and Serena, S.D., "Effects of Strophanthidin upon Contraction and Ionic Exchange in Rabbit Ventricular Myocardium: Relation to Control of Active State," J. Mol. Cell Cardiol. 1, 65-90, 1970.

Lehr, D., and Chau, R., "Changes of the Cardiac Electrolyte Content During Development and Healing of Experimental Myocardial Infarction," in Dhalla, N.S. (Ed.) Recent Advances in Studies on Cardiac Structure and Metabolism, Vol. 3, University Park Press, Baltimore, MD, 1973.

Mandel, W.J. and Bigger, J.T., "Electrophysiologic Effects of Lidocaine on Isolated Canine and Rabbit Atrial Tissue," J. Pharmacol. Exp. Ther., 178, 81-93, 1971.

McCall, D., "Effect of Quinidine on Cation Exchange in Cultured Cells," J. Pharmacol. Exp. Ther. 197, 605-614, 1976.

Mines, G.R., "On Dynamic Equilibrium in the Heart," J. Physiol. 44, 349, 1913.

Miura, D.S., Hoffman, B.F. and Rosen, M.R., "The Effect of Extracellular Potassium on the Intracellular Potassium ion Activity and Transmembrane Potentials of Beating Canine Cardiac Purkinje Fibers," J. Gen. Physiol., 69, 463-474, 1977.

Morrow, D.H., Haley, J.V. and Logic, J.R., "Anesthesia and Digitalis VIII. The Effect of Pentobarbital, Halothane, and Methoxyflurane on the A-V Conduction and Inotropic Responses to Ouabain, Anesthesia and Analgesia 51, 430-438, 1972.

Pantridge, J.F., Adgey, A.A.J., Geddes, J.S. and Webb, S.W., The Acute Coronary Attack, Grune and Stratton, New York, 1975.

Prevost, J.L. and F. Batelli, Death by Electric Currents (Alternating Current), C.R. Acad. De. Sci. 128, 668-670, 1899.

Prevost, J.L. and Batelli, F., "Death by Electric Current (Constant Current)," C.R. Acad. De. Sci. 128, 842-844, 1899.

Prevost, J.L. and Batelli, F., "Some Effects of Electric Discharge on the Hearts of Mammals," C.R. Acad. De. Sci., 129, 1267-1268, 1899.

Prevost, J.L. and Batelli, F., "Death by Electric Discharge," C.R. Acad. De. Sci., 129, 651-654, 1899.

Priano, L.L., Traber, D.L., and Wilson, R.D., "Barbiturate Anesthesia: An Abnormal Physiologic Situation," J. Pharm. Exp. Ther. 165, 126-135, 1969.

Price, H.L., and Helrich, M., "The Effect of Cyclopropane, Diethyl Ether, Nitrous Oxide, Thiopental, and Hydrogen Ion Concentration on the Myocardial Function of the Dog Heart-Lung Preparation," J. Pharmacol. Exp. Therap. 115, 206-216, 1955.

Price, H.L., Kounat, P.J., Safer, J.N., Conner, E.H., and Price, M.L., "The Uptake of Thiopental by Body Tissues and Its Relation to the Duration of Narcosis," Clin. Pharmac. Ther. 1, 16-22, 1960.

Prinzmetal, M., Ishikawa, K., Oishi, H., Ozkan, E., Wakayama, J., and Baines, J.M. "Effects of Quinidine on Electrical Behavior in Cardiac Muscle," J. Pharmacol. Exp. Ther. 157, 659-644, 1970.

Rawlings, M.S., "Acute Myocardial Infarction" in Conn, H.F., Ed., Current Therapy 1976: Latest Approved Methods of Treatment for the Practicing Physician, W.B. Saunders Company, Philadelphia, PA, 1976.

Regulations for Animal Facilities and Care, Purdue University, May 1972.

Rosen, M.R. and Hoffman, "Mechanisms of Action of Antiarrhythmic Drugs," Circulation Research, 32, 1-8, 1973.

Sano, T., Tsuchihashi, H. and Shimamoto, T., "Ventricular Fibrillation Studied by the Microelectrode Method," Circ. Res. 6, 41-46, 1958.

Scherf, D. and Terranova, R., "Mechanism of Auricular Flutter and Fibrillation," Am. J. Cardiol., 159, 137-141, 1949.

Schumann, R.E., Geddes, L.A. and Hoff, H.E., "Prolonged Left Ventricular Bypass by Transvalvular Aortic Catheterization I. Physiologic Effects and Rationale of Surgical Concept," Surgery 67, 957-968, 1970.

Singh, B.N. and Vaughan- Williams E.M., "Effect of Altering Potassium Concentration on the Action of Lidocaine and Diphenylhydantoin on Rabbit Atrial and Ventricular Muscle," Circulation Research 29, 286-297, 1971.

Singh, C.M., Flear, C.T.G., Nandra, A., and Ross, D.N. "Electrolyte Changes in the Human Myocardium After Anoxic Arrest," Cardiology, 56, 128-135, 1971/72.

Singh, B.W. and Hauswirth, O., "Comparative Mechanisms of Action of Antiarrhythmic Drugs," Am. Heart J., 87, 367-382, 1974.

Singh, B.N., "Antiarrhythmic Effects of Local Anesthetics and Calcium Antagonists," Pharmac. Ther. C., 2, 125-150, 1977.

Smith, S.L., Webb, W.R., Sabian, L.W., Hagaman, V.D., "Cardiac Excitability in Ether, Cyclopropane and Halothane Anesthesia," Anesthesiology, 23, 766-775, 1962.

Stephensen, H.E., Cardiac Arrest and Resuscitation, C.V. Mosby Company, St. Louis, 1974.

Tacker, W.A., Galioto, F.M., Giuliani, E., Geddes, L.A., McNamara, D.G., "Energy Dose for Human Transchest Electrical Ventricular Defibrillation," N. Eng. J. Med., 290, 214-215, 1974.

Tacker, W.A., Geddes, L.A., Kline, B., and Borton, C., "Alteration of Electrical Defibrillation Threshold by the Cardiac Glycoside, Ouabain," Proceedings of the Cardiac Defibrillation Conference, Purdue University, West Lafayette, Indiana, 129-133, 1975.

Trautwein, W., "Membrane Currents in Cardiac Muscle Fibers," Physiol. Rev. 53, 793-835, 1973.

Weld, F.M. and Bigger, J.T., "Effect of Lidocaine on Kinetics of the Fast Sodium Current in Cardiac Purkinje Fibers,"(Abstract) Circulation, 48, IV-108, 1973.

Welt, L.G., "Agents Affecting Volume and Composition of Body Fluids," in The Pharmacological Basis of Therapeutics, Goodman, L.S. and Gilman, A., Eds., The Macmillan Company, New York, 1970.

Woodbury, W.J., "Cellular Electrophysiology of the Heart," in Handbook of Physiology Vol. I, Section 2, "Circulation" WF Hamilton, Ed., American Physiological Society, Washington, DC, 1962.

Woolfolk, D.I., Chaffee, W.R., Cohen, W., Neville, J.F. and Abildskov, J.A., "The Effect of Quinidine on Electrical Energy Required for Ventricular Defibrillation," Am. Heart J., 72, 659-663, 1966.

Yeh, J.Z. and Narahashi, T., "Mechanism of Action of Quinidine on Squid Axon Membranes," J. Pharmacol. Exp. Ther., 196, 62-70, 1976.

Vassalle, M., "Generation and Conduction of Impulses in the Heart Under Physiological and Pathological Conditions," Pharmac. Ther. B, 3, 1-39, 1977.

Wagner, J.G., A Safe Method for Rapidly Achieving Plasma Concentration Plateaus, Clin. Pharmacol. Ther., 16, 691-700, 1974.

Weidmann, S., "Electrical Constants of Purkinje Fibers," J. Physiol. 118, 348, 1952.

Weidmann, S., "Effects of Calcium Ions and Local Anesthetics on Electrical Properties of Purkinje Fibers," J. Physiol. 129, 568-582, 1955.

Zipes, D.P., "Ventricular Fibrillation: Mechanisms of Initiation, Maintenance and Termination," Proceedings of Cardiac Defibrillation Conference, October 1-3, 1975, Purdue University, West Lafayette, Indiana.

Zoll, P.M., Linenthal, A.J., Gibson, W. et al., "Termination of Ventricular Fibrillation in Man by Externally Applied Electric Countershock," New Eng. J. Med. 254, 727-732, 1956.

VITA

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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.