Depression of canine defibrillation thresholds with amiodarone hydrochloride

by

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A Thesis Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
MASTER OF SCIENCE

Major: Biomedical Engineering

Iowa State University
Ames, Iowa

1986

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SYMBOLS AND ABBREVIATIONS

A	ampere
A. C.	alternating current
AV	atrio-ventricular
cc.	cubic centimeter
cm.	centimeter
DFT	defibrillation threshold
EKG	electrocardiogram
ERP	effective refractory period
g., gr.	gram
Hz.	hertz
I_o	leading edge (peak) current
I_f	trailing edge current
i(t)	time dependent current
kg.	kilogram
lb.	pound (weight)
ln	natural logarithm
J	joule
mA.	milliamp
mg.	milligram
ml.	milliliter
msec.	milliseconds
pH	ion concentration

pO_2	partial pressure of oxygen in arterial blood
pCO_2	partial pressure of carbon dioxide in arterial blood
r	linear correlation coefficent
SA	sino-atrial
sec.	second
T	tilt
t	time
t_f	pulse width
TED	truncated exponential defibrillator
U	energy
ug.	micrograms
V., v.	volt
V_o	leading edge voltage
V_f	trailing edge voltage
Z	impedance

INTRODUCTION

One hundred years ago, the prognosis for a patient with ventricular fibrillation was fairly straightforward. Death ensued within a matter of five or six minutes. By the turn of the 20th century, scientists were beginning to understand the electrical and electrophysiologic nature of the heart. By the 1930s patients with cardiac conduction arrhythmias were being treated with both chemical and electrical means. With the advent of the transistor, permanently implantable stimulators became a reality in treating some cardiac arrhythmias. Currently, the pacemaker technology developed in the '60s and '70s is being extended to the treatment of ventricular fibrillation by means of implantable defibrillators (Mirowski et al., 1984; Thakor, 1984). The physical size of these devices is constrained by the large capacitors and batteries needed for cardiac defibrillation.

In an effort to reduce the size of the devices, one approach has been to investigate the use of the device in conjunction with antiarrhythmic drugs. If a drug could be found that would decrease the energy needed to defibrillate the heart, the efficacy and reliability of the implantable defibrillator would improve.

This thesis was undertaken to evaluate the effect of one such antiarrhythmic agent, amiodarone hydrochloride, on the defibrillation threshold in dogs. Although anecdotal observations have been made in the clinical setting on the effect of amiodarone on other

electrophysiologic events in the heart, there has been no known quantification of the effect of the drug on defibrillation thresholds in a controlled study. The question to be answered by this study is: Does amiodarone hydrochloride significantly reduce the defibrillation thresholds in dogs?

VENTRICULAR FIBRILLATION

During a normal heartbeat, the myocardial cells depolarize in an organized, rhythmic fashion. Starting at the apex of the heart, a wave of depolarizing wave propagates upward to the base of the ventricles. This rhythmic motion reduces the intraventricular volume and forces the blood to move out of the chamber.

Ventricular fibrillation is a condition characterized by the unsynchronized depolarization of the ventricular myocardial cells. With the loss of the rhythmic compression, the pumping action of the ventricles ceases, causing a loss of blood pressure. This is a life threatening situation, and if untreated, anoxia of the brain tissue and vital organs will result in death in a matter of minutes.

Because of the suddenness of death, it is difficult to determine the exact sequence of physiologic events leading to specific cases of fibrillation (Harrison, 1972). However, it is well-established that fibrillation in general can be precipitated by myocardial infarction or disease, drug toxicity, metabolic abnormalities, hypothermia or electric shock (Geddes and Tacker, 1983).

The mechanism of ventricular fibrillation has been explained by two popular theories, circus motion and multiple pacemaker sites (Tacker and Geddes, 1980). Both theories recognize the necessity for a critical mass of myocardium to maintain fibrillation. Without this critical mass, fibrillation cannot continue. That is the underlying reason why

small warm-blooded mammals such as cats, puppies, rabbits and rats will not normally sustain fibrillation (Geddes and Tacker, 1983).

Before discussing the theories of fibrillation, it may be useful to review the normal cardiac conduction system.

Normal Cardiac Conduction

In a normal heart, the natural pacemaker site is located in the right atrium at the sino-atrial (SA) node. Rate determining P cells, or primitive cells, spontaneously depolarize. The depolarization impulse is rapidly conducted from the SA node to the atrio-ventricular (AV) node by three internodal pathways located in the atrium. The anterior, middle and posterior internodal pathways merge as they converge on the AV node (James et al., 1982). As the impulse travels from the SA to AV node, the myocardial cells depolarize and the atrium contracts. A band of nonconductive tissue at the base of the ventricles prevents propagation of the atrial myocardial depolarization wave into the ventricular myocardium. The impulse conducted by the internodal pathways does continue into the ventricles after a slight delay at the AV node. The impulse travels down the Bundle of His located in the intraventricular septum, then branches out to the right and left ventricles. The rapid conduction of the pacing impulse is then carried by the Purkinje fibers to the apex of the ventricles. A wave of depolarization spreads from the endocardium to the epicardium and progresses from the apex of the heart to the base.

The normal pacing impulse travels through this specialized conduction system much more rapidly than normal myocardial muscle tissue. Typically, the signal will be conducted through the Bundle of His at speeds of 2.5-5 meters/second, versus only 0.3-0.8 meters/second for myocardial tissue (Hamlin and Smith, 1977), with the conduction being more rapid at the apex than the base of the ventricles.

The speed of conduction through these different ventricular tissues is important in establishing a coordinated wave of depolarization. The rhythmic contraction of the ventricles forces blood out of the chamber. When the wave of depolarization meets the nonconductive base of the ventricles, the muscle tissue stops contracting and repolarizes. The cycle normally repeats with the next P cell depolarization in the SA node.

As the wave of depolarization progresses from apex to base, the cells that depolarize are refractory for a short period of time before they repolarize. It is important to note that the propagation velocity of the depolarization wave and the refractory period of the tissue are not necessarily constant throughout the heart.

Circus Motion

Circus motion refers to the condition of continuous cardiac stimulation by a wave of depolarization that takes an abnormal, unending, circuitous route through the cardiac tissue. Using rings of cardiac tissue from turtle ventricles, Garrey, 1914 (cited in Geddes and

Tacker, 1983) first described this mechanism for continuous stimulation of the ventricles.

In a ring of normal turtle cardiac tissue, if one stimulates the bottom of the ring, a wave of depolarization will progress outward from the stimulation point. Two wavefronts will develop, one progressing in a clockwise direction around the ring, and the other going counter-clockwise. As the wavefronts travel around the ring, they are "followed" by a region of refractory cells, and further back, a region of repolarized cells. If the tissue possesses uniform conductivity, the two waves will meet at a point diametrically opposite the stimulation point. As the wavefronts collide, each will encounter refractory cells from the other wavefront, and the propagation of both wavefronts will cease. If a second stimulation is initiated at the bottom of the ring, it too will split into two wavefront and travel around the ring until either encountering the refractory region from the first stimulus, or colliding at the top of the ring.

If, however, the propagation velocity of the wavefront through the tissue is not uniform, its possible for the wavefront collision to occur close to the original stimulation point, resulting in a region of refractory tissue very close to the point of stimulation. If this occurs, when a second stimulation is made, one wavefront may collide with the refractory region, leaving only the second wavefront to travel around the ring of tissue. If the length of the ring is long enough, the refractory period short enough, and the propagation velocity slow

enough, it is possible for the propagation wave to continue traveling its circuitous route uninterrupted. In Garrey's experiment, this "circus motion" continued for seven hours.

Lewis, 1920 (cited in Tacker and Geddes, 1980) described a reentrant excitation mechanism (Lewis, 1920), which is similar to Garrey's circus motion theory. As a wave of depolarization progresses, it can only travel through tissue that is excitable. If it encounters inexcitable tissue (a "block" according to Lewis), the wave will break into daughter waves and go around the block. If the block is transient, such as with a region of tissue with a prolonged refractory period, it is possible for it to become "unblocked", or excitable, before the daughter waves have circumvented it. The "unblocked" tissue can be excited and change the direction of the depolarization wave, possibly causing a continuous wave of depolarization.

The main difference between Garrey and Lewis's explanation of the mechanism for fibrillation is that the pathway for the reentrant mechanism can be different for each cycle of depolarization, whereas Garrey's model requires the same pathway each time.

Multiple Pacemaker Sites

The multiple pacemaker mechanism proposed by Scherf (Scherf and Teranova, 1949) states that fibrillation occurs when several asynchronous pacemaker sites are active simultaneously, causing the ventricles to contract continuously and without coordination.

Causes of Fibrillation

Of the mechanisms of fibrillation mentioned, the circus motion and reentrant theories are considered "sustaining" mechanisms, whereas the multiple pacemaker site theory has been referred to as a "precipitating" mechanism (Tacker and Geddes, 1980). There are several other causes of fibrillation besides the activation of multiple pacemaker sites.

Myocardial infarction will cause a localized area of inexcitable dead tissue, surrounded by a ring of poorly oxygenated tissue that is hyperexcitable and often autorhythmic (Tacker and Geddes, 1980), providing the precipitating mechanism for fibrillation. In addition, this surrounding ring of tissue's conductivity is nonuniform, permitting the sustaining mechanism of reentrant conduction.

Low frequency electrical shock can precipitate fibrillation at voltages as low as 5 millivolts, if administered directly to the cardiac tissue during the vulnerable phase of the cardiac cycle (Wiggers and Wegria, 1940). Forty years previous to that, in 1899, Prevost and Battelli reported on the effects of direct current, alternating current and capacitor-discharge current on the heart of mammals. They noted that low-voltage shocks produced ventricular fibrillation, but extremely high voltage (4800 volts) did not.

Several pharmacological agents can induce fibrillation, such as large doses of epinepherine, digitalis or calcium salts. Each of these agents, in smaller doses, increases the contractility of the heart. In

an excessive dose, or in combination with several other drugs or anesthesias, these substances will initiate fibrillation. In addition, some environmental effects can induce fibrillation, such as hypothermia.

DEFIBRILLATION

Several methods have been used successfully in the past to defibrillate the heart. Hooker, in 1930, described a chemical treatment for defibrillation. By injecting isotonic potassium chloride into the left ventricle, and forcing the solution through the coronary arteries, he was able to alter the extracellular potassium concentration to the extent that the myocardial cells spontaneously depolarized. After flushing the potassium chloride out of the coronary circulation, normal sinus rhythm was restored (Hooker, 1930). Later, he found that a subsequent injection of calcium chloride would increase the contractility of the heart, and improve the survivability of the heart.

This method for defibrillation was used clinically, but had several drawbacks. First, it necessitated the clamping of the aorta in order to force the potassium chloride into the coronary artery. This required emergency surgery to expose the aorta. Second, the concentrations of potassium chloride and calcium chloride could not be established for a large patient population. Each individual, depending on previous medication or metabolic state would require differing amounts of potassium chloride or calcium chloride. If an excess of potassium chloride were administered, the ventricles would be hypodynamic; too much calcium chloride could reinitiate fibrillation. By 1947, electrical defibrillation had replaced chemical defibrillation as the treatment of choice in the clinical setting.

In the early 1930s, Kouwenhoven and associates investigated the use of 60 Hertz current to defibrillate canine hearts (Geddes, 1984), although Prevost and Battelli had investigated electrical defibrillation in dogs as early as 1899, in Sweden. Beck et al. reported the first successful human defibrillation in 1947. Using 110 volts A.C., they defibrillated a 14 year old boy. The device they used to defibrillate with consisted of two panel lights, a switch and two resistors. The length of the defibrillating pulse was determined by how fast one opened and closed the on-off switch (Geddes and Hamlin, 1983). Currently, electrical defibrillation is the method of choice for the treatment of ventricular fibrillation.

Two main types of external defibrillators are currently employed, and are typically described by the shape of the defibrillating pulse that they produce. The capacitor-discharge devices produce an exponentially decaying waveform, and the damped sinusoid defibrillators produce either underdamped or overdamped sine waves.

The capacitor-discharge design stores electrical charge on large capacitors. When the capacitor is discharged across the heart, the voltage and current exponentially drop from the peak stored value. The drop in the current waveform is called the "tilt" of the pulse, and can be small (approximating a square wave) or large (sometimes referred to as a trapezoidal wave). This energy delivery system can result in large peak currents, which have been shown to impair myocardial contractility (Tacker et al., 1969; Geddes et al., 1970).

The second external defibrillator design incorporates an inductor in series with the output circuit. This design permits defibrillation wih less energy, voltage or current (Geddes et al., 1970). Although this appears to be a superior defibrillator design, for implantable defibrillator, the need for an inductor in the output circuit poses a serious design problem, since it is a bulky discrete component. Because of this, implantable defibrillators do not incorporate this design.

Regardless of the design, these devices are effective in defibrillating the heart because they are able to maintain a threshold current density in a critical mass of ventricular tissue for a specified time (Niebauer et al., 1983a, 1984). This is essentially the criterion for defibrillation (Geddes and Tacker, 1983).

Principles of Defibrillation

Tacker and Geddes have literally written the book on electrical defibrillation (Tacker and Geddes, 1980). Through their study of the phenomenon, they have developed what they call the five "laws" of defibrillation. These laws address five important concepts: the strength-duration curve, the threshold distribution concept, the dose relationship, the average current hypothesis and the myocardial depression phenomenon (Geddes and Tacker, 1983).

The strength-duration curve relates the length of the defibrillating pulse (the "duration") to the peak current of that pulse (the "strength"). In comparing animals of different body weights and

species, the strength is generally normalized on the basis of heart weight. The strength-duration curve for defibrillation is similar in shape to the strength-duration curves for muscle stimulation; that is, at short duration, a large amount of current is needed to defibrillate the heart. At longer durations, less current is required. The graphical relation is shown in Figure 1.

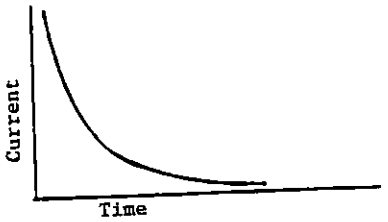

Figure 1. Strength-duration curve

Mathematically, this relation can be described by the following equation:

$$I = b + k/d$$

where I is the peak current, d is the duration of the pulse and k and b are constants dependent on heart size, electrode location and the shape of the waveform. This inverse Lapicque-type relationship exists only over a finite range of pulse durations. As the pulse duration lengthens over about 20 milliseconds, the current needed to defibrillate begins to increase. At pulse lengths greater than 30 msec., the current rises dramatically. One theory for this increase states that the cells that had depolarized prior to the beginning of the pulse come out of their refractory period and are refibrillated by the trailing edge of the

pulse (Schuder et al., 1966).

The threshold distribution concepts states that the defibrillation threshold (DFT) measured in one animal with a given heart size may not be the same for another with the same heart size. Both intraspecies and interspecies differences in DFT exist. Geddes reported that in measuring the DFT in 49 dogs, using the same pulse duration and waveform, he found thresholds ranging from 11.4 to 42.5 mA./gram of heart tissue (Geddes and Tacker, 1983). The range of thresholds, however, was normally distributed. This normal distribution of thresholds permits a statistical analysis of DFT data.

The dose relationship in defibrillation states that DFT is dependent on the size of the heart, bigger hearts requiring more energy to defibrillate than smaller hearts. This is true for both transchest defibrillation and direct defibrillation. In studying thresholds for dogs, goats, horses, calves and sheep, Geddes characterized defibrillation energy versus heart weight with an exponential equation of the form:

$$U = a\,(W)\exp b$$

where U is energy, W is heart weight and a and b are empirically derived constants (Geddes et al., 1974). Gutgesell et al. (1976) reported a linear, rather than exponential, energy/heart weight relationship in children under 50 Kg. He determined a 1 watt-sec/pound of body weight was generally needed for these patients.

The dose relationship for defibrillation is not universally

accepted. Kerber noted that in patients with left ventricular hypertrophy resulting from aortic valve disease the proposed dose relation did not hold true (Kerber et al., 1980).

The average current law of defibrillation states that for damped sine waves, square or trapezoidal waves at a given pulse duration, the average current for DFT is the same, regardless of waveform (Geddes and Tacker, 1983). This holds true for both direct and transchest defibrillation.

The myocardial depression phenomenon has been demonstrated to increase in severity with increasing shock strength, regardless of the waveform used for defibrillation (Niebauer et al., 1983b). Myocardial depression is characterized by a decrease in the peak systolic blood pressure following defibrillation. It is more severe when the defibrillation shock is shorter in duration (Niebauer et al., 1983a). It should be noted that the defibrillation shock itself is only one factor among many that contribute to myocardial depression. However, Neibauer has shown in controlled, isolated heart preparations that as current overdose increases, the percent decrease in pressure increases (Geddes and Tacker, 1983).

AMIODARONE

Amiodarone hydrochloride is a class III antiarrhythmic drug with the structure of an iodinated benzofuran derivative (Gillis and Kates, 1984). The structure of amiodarone appears below in Figure 2. Amiodarone was originally developed at Labaz Laboratories in Belgium in 1962 as an antianginal coronary dilating agent (Singh, 1983), but it was soon shown to have other pharmacological properties, including prolonging myocardial action potentials, reducing the heart rate, and decreasing myocardial oxygen demand (Canada et al., 1983). It is currently used in the treatment of ventricular and atrial arrhythmias.

The drug has been studied since the late 1960s in Europe, and more recently in South America and the United States. Many of the effects of the drug have been reported, but the underlying mechanisms are still unclear.

For example, the metabolism of the drug is not clearly characterized. Several potential metabolites have been proposed, but only desethyl amiodarone (see Figure 3) has been seen in the assays of blood from patients on long term medication (Latini et al., 1984).

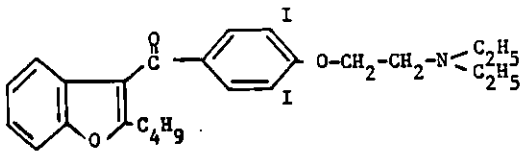

Figure 2. Amiodarone

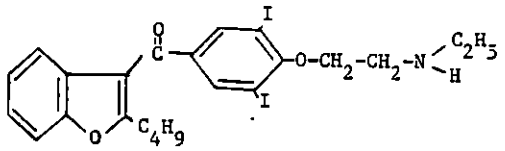

Figure 3. Desethyl amiodarone

The uptake of the drug is likewise unclear. The drug is absorbed following oral administration in an erratic and unpredictable fashion. The time to reach peak plasma concentrations measured in man have been reported to vary from 2 to 12 hours (Latini et al., 1984), and the apparent half-life of the drug has been reported anywhere from 15 to 45 days (Canada et al., 1983). One reason for the erratic uptake that has been proposed is the low solubility of amiodarone in aqueous solutions, which may cause incomplete absorption across the intestinal mucosa (Gillis and Kates, 1984). Another proposed reason, based on studies of isolated perfused rat livers by Riva et al. (1982) that showed a high extraction ratio (.49), is that much of the amiodarone in the blood is removed on the first pass through the liver. This could account in part for its low and variable bioavailability (Latini et al., 1984).

The primary electrocardiographic effect of amiodarone that contributes to its utility as an antiarrhythmic is its ability to lengthen the action potential duration, or more specifically, the effective refractory period (ERP). In measuring the 50% and 90% repolarization times, Singh noted an increase related to the length of time on medication. After 1 week, repolarization time increased 11%, after 3 weeks it increased 23% and after 6 weeks on medication, the 90% repolarization time had increased by 30% (Singh, 1983).

The increased ERP, if it occurs uniformly throughout the myocardium, is in itself an antiarrhythmic mechanism. With longer ERPs

it is more difficult for a reentrant type arrhythmia to become established, and multipacemaker sites have less opportunity to initiate an arrhythmia.

This antiarrhythmic property, along with its long half-life, make amiodarone a desirable drug to be incorporated into system that combines an implantable defibrillator and an implantable drug infusion device for the treatment of recurrent fibrillation. To date, however, no one has made a quantitative, comparative study on the effect of amiodarone on defibrillation thresholds. For this reason, the following investigation was undertaken in an attempt to validate the use of amiodarone in this type of application.

METHODS AND MATERIALS

The information on the use of animals in research and teaching was reviewed and approved by Dr. Joan Hopper of the Laboratory Animal Resources department. Two surgical procedures were performed on each animal in the study. The initial procedure was an aseptic determination of the transchest defibrillation threshold of the animal. The follow-up procedure, six weeks later, was a nonsterile determination of both transchest and direct contact cardiac defibrillation threshold. In addition, an assay for blood and tissue levels of amiodarone was developed.

Defibrillating Electrode and Stimulating Catheter Designs

Prior to the surgery, a pair of external defibrillation electrodes were constructed using aluminum mesh and backed with .050 inch thick Dow silicone rubber reinforced with Dacron mesh. The circular electrodes measured 8 cm. in diameter, the same diameter as the chest electrodes supplied for the American Optical Model 10645 external defibrillator. The mesh was secured to the silicone rubber backing by applying Dow Type A medical adhesive to the perimeter of the mesh and curing at 200 degrees Farenheit for 8 hours. An alligator clip was secured to each electrode to allow easy connection to the different type of defibrillators to be used in the procedure. A sketch of the electrodes appears in Figure 4.

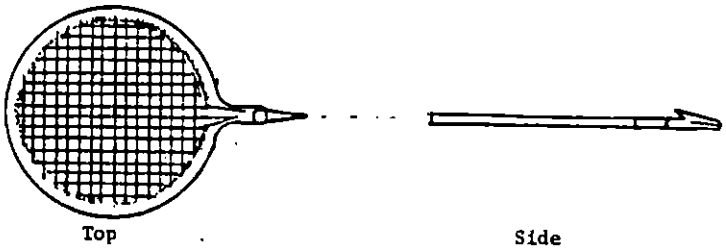

Figure 4. External defibrillation electrodes

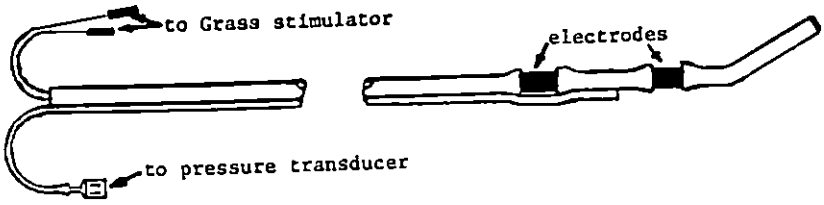

Figure 5. Stimulating catheter

A bipolar, transvenous stimulating catheter was constructed from tubing and wire (see Figure 5). Two strands of teflon coated 30 gauge wire-wrap wire were pulled through a 30" length of .044 x .065 polyvinyl tubing. Two 1/2" lengths of 18 gauge stainless steel hypodermic needle stock were cut to form the proximal and distal electrodes. One strand of wire was soldered to the proximal end of the proximal electrode, and

the other wire was pulled through the bore of the proximal electrode. An overlap joint between the polyvinyl tubing and the proximal electrode was secured with Dupont Superglue. A 1/2" section of polyvinyl tubing overlapped the distal end of the proximal electrode by 1/8" and was also glued. The second strand of wire was pulled through the distal electrode and soldered to the distal end of the electrode. The proximal end of the distal electrode was glued to the 1/2" section of tubing, and another 1" piece of tubing was glued to the distal end of the distal electrode. This piece of tubing was back-filled with Dow Type A medical adhesive to prevent blood from flowing up the catheter. A slight "lazy-L" curve was formed in this most distal piece of tubing by gently heating over a Bunsen burner. The proximal ends of the wires were stripped and crimped to two 1/2" sections of 18 gauge hypodermic needle stock to provide an electical contact point for alligator clips. A second 36" length of .023 x .038" polyethylene tubing was glued along the length of the stimulating catheter to provide a pressure monitoring line to the right ventricle. The distal end extended to the section of tubing connecting the proximal and distal electrodes. A blunt 20 gauge needle was attached to the proximal end.

Defibrillators

Two defibrillators were used during the procedures. The first, an American Optical Model 10645 defibrillator, was a commercial unit that provides a damped sinusoidal defibrillation pulse. The output is

variable from 0 to 400 watt-seconds (i.e., joules). However, the output was difficult to accurately preset, and there was no direct way to monitor the output voltage and current pulse. This unit was used only as a backup device in the event that the primary defibrillator malfunctioned.

Defibrillation thresholds were determined using a capacitor discharge defibrillator made by the Biomedical Engineering Center, Purdue University. The unit, called TED (Truncated Exponential Defibrillator), could be preset to any voltage between 0 and 1999 volts in one volt increments (see Figure 6). The tilt of the waveform could be varied, and was selected to be 63%. Provisions were made so the unit could be preset for a backup shock if the first shock was unsuccessful. Backup shocks were preset to roughly one and a half times the initial shock. Since oscilloscopes are unable to monitor the high voltages involved in defibrillation, the output pulse from the TED ran through a circuit that would scale the voltage waveform and also measure the scaled current waveform. Two outputs on the back of the unit provided voltage and current waveforms with a voltage scaling factor of 400 volts/volt, and a current scaling factor of 10 amps/volt. The voltage and current waveform outputs were connected to a Tektronic two channel differential oscilloscope, with one waveform inverted to get maximum resolution from the scope.

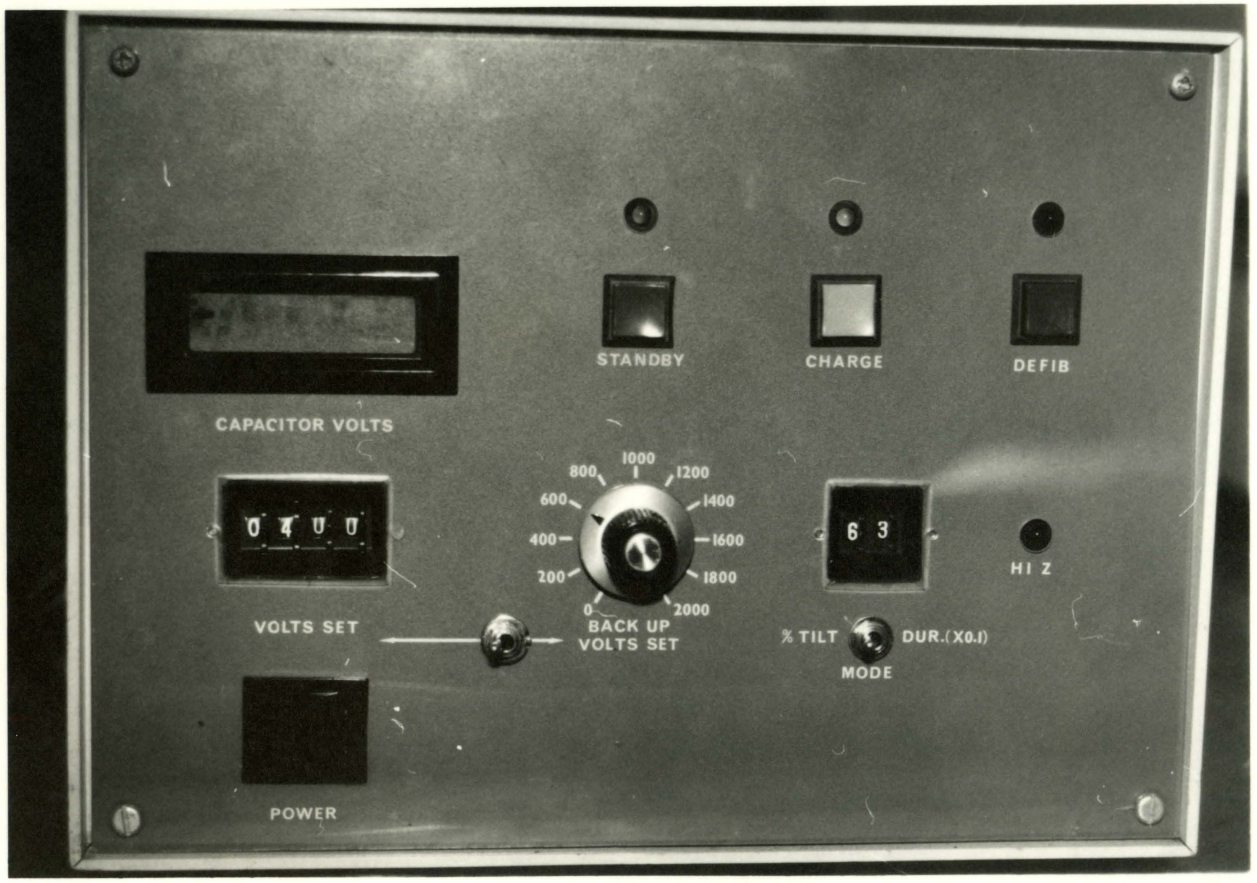

Figure 6. TED (truncated exponential defibrillator)

Transchest defibrillation thresholds were determined by using the TED with the chest electrodes. For direct defibrillation thresholds, the TED was connected to a pair of 4 cm. in diameter round, concave hand paddles. Surgical sponges soaked in normal saline were tied to the paddle faces to enhance the electrical contact and minimize the tissue damage caused by localized high current density contacts.

Initial Procedure

Prior to the initial procedure, the animals were given an oral antibacterial agent, Tribrissen (trimethoprim and sulphadiazine, 30 mg./kg.; Burroughs Wellcome) for one day. The Tribrissen was administered to prevent infections arising from the surgery. Because of lack of personnel, it was necessary to break the sterile surgical field several times during the course of the threshold determination in order to adjust equipment. The antibiotics counteracted any inadvertent contamination of the surgical site. The animals were maintained on tribrissin (30 mg./kg./day) for up to five days after surgery, if the surgical site showed signs of infection (edema, redness).

The dogs were prepared by being walked immediately before the surgery to empty the bowel and bladder. The dog's right forepaw was shaved, and an intravenous injection of 4-8 mg./lb. of Surital (sodium thiamylal) was administered. An endotracheal tube was inserted, and the animal was maintained on Metofane (methoxyflurane) anesthesia. The tops of the right and left front paws and left hind paw were shaved to accept

EKG skin electrodes. The right and left side of the chest was shaved to accept the transchest defibrillation electrodes. The neck and inner left thigh were shaved, scrubbed with Betadine soap and alcohol and sprayed with Betadine solution.

The animal was then wheeled into the surgery room, and the EKG and transchest electrodes attached. Low resistance electrode paste (Liqui-Cor) was applied to both the defibrillation and EKG electrodes. The animal was placed in a slight left lateral recumbency position. The left transchest electrode was placed on apical beat location of the left side, as described by Geddes et al. (1977). This position was determined by either listening for the loudest heartbeat with a stethoscope, or, more commonly, observing the motion of the chest wall as the heart beat against it. The right transchest electrode was placed in the corresponding apical beat position. Its position had to be ascertained by listening, as no motion was apparent. The transchest electrodes were held in place with an elastic bandage (see Figure 7).

The animal was then draped, and a femoral artery cut down made. A four-inch piece of polypropylene tubing was inserted into the femoral artery, and was connected to a Statham PR-23Dc pressure transducer. The pressure waveform was displayed on a four channel Hewlett-Packard Sanborn 780-6A Viso scope monitor.

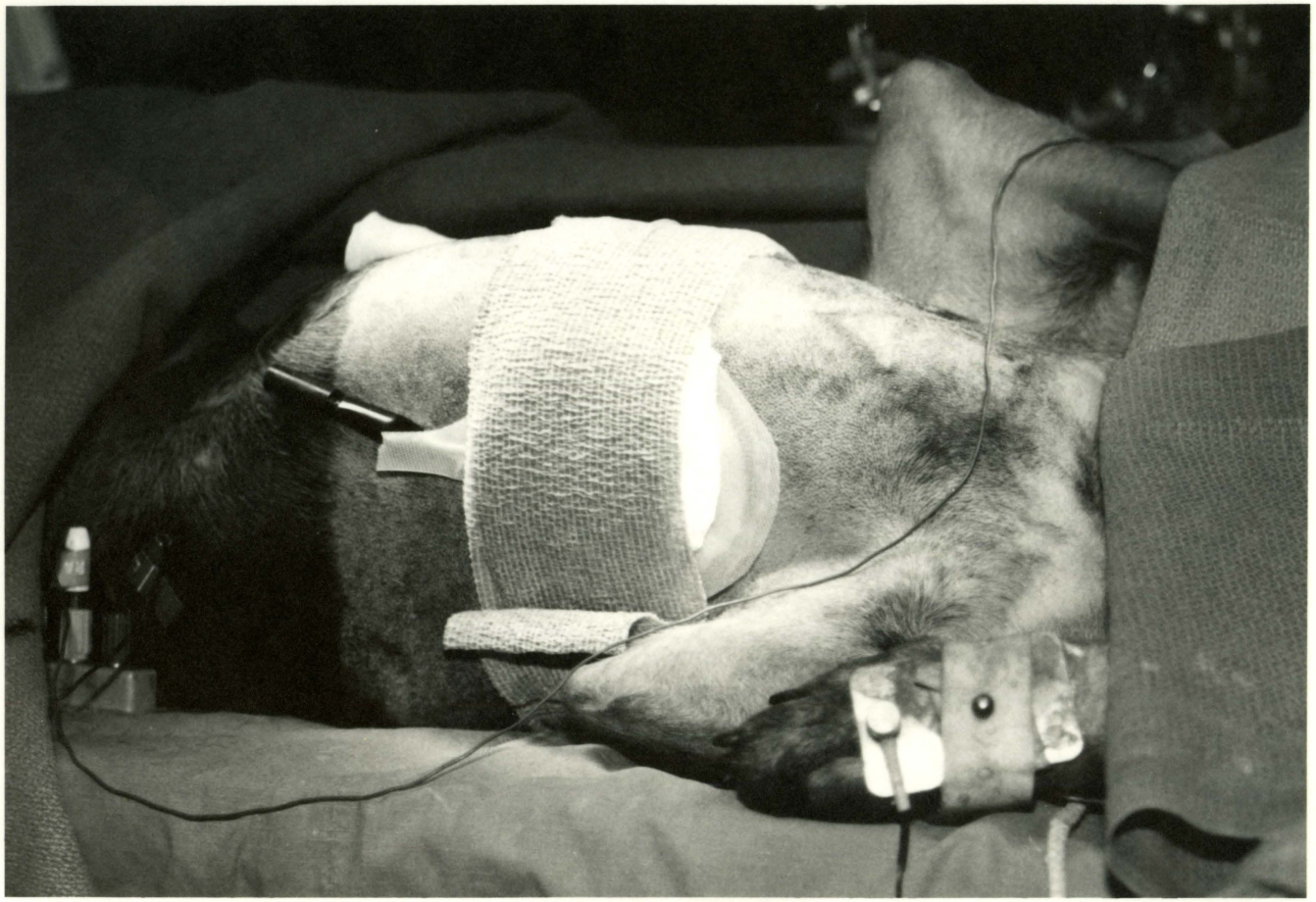

Figure 7. Transchest electrodes held in place with elastic bandage

A right jugular vein cut down was then made and a stimulating catheter was inserted into the vein. The catheter's pressure tube was connected to a Statham PR-23 pressure transducer, and the resultant pressure waveform was displayed on the Sanborn monitor. The animal was given 100 units/lb. of sodium heparin to prevent clot formation on and in the catheters. The tip of the jugular catheter was passed into the right ventricle. The position of the catheter tip was verified by viewing the distinctive pressure waveform on the monitor (see Figure 8).

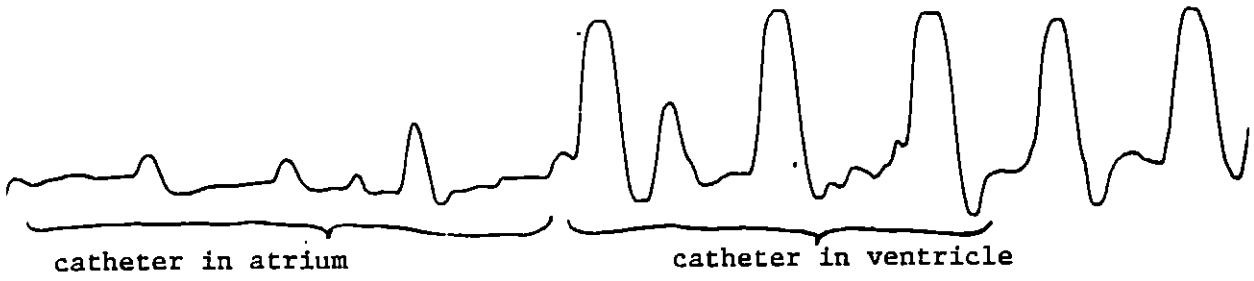

Figure 8. Typical right ventricular pressure waveform

The arterial and venous pressure and the EKG (lead II) were displayed on the Sanborn monitor, and recorded on a Hewlett-Packard Model 3960 4-channel instrumentation recorder. Fibrillation was induced with a Grass Model SD9 stimulator connected to the stimulating catheter with 18 gauge wires. The TED was connected to the chest electrodes by 18 gauge wires, and the outputs from the TED were connected to the oscilloscope.

Once the stimulating catheter was in position, a 5 ml. blood sample

was taken for blood gas analysis on an Instrumentation Lab Model 513 pH/Blood Gas Analyzer, and the threshold determination procedure commenced. A 2-5 second 5 volt peak to peak, 60 Hz. pulse from the stimulator was delivered to induce fibrillation. If the initial pulse was unsuccessful, a subsequent pulse of higher voltage was tried. If a 5 second, 10 volt pulse would not induce fibrillation, the stimulating catheter was repositioned.

Fibrillation was ascertained by both the drop in arterial pressure and the disorganized fibrillation pattern of the EKG waveform (see Figure 9). Fifteen to twenty seconds after successfully fibrillating the animal, a transchest defibrillating pulse was given. The fifteen second delay was needed to assure the animal was truly in fibrillation. Occasionally, an animal would spontaneously convert to a normal sinus rhythm immediately after the fibrillation pulse.

The defibrillation pulse was delivered at the end of expiration. Successful defibrillation was determined by the rise in right ventricular pressure and reestablishment of a coordinated EKG waveform (see Figure 10). Defibrillation pulse leading and trailing edge currents and voltages were recorded, as well as the pulse width. The percent tilt of the waveform, leading edge impedance and pulse energy were calculated with a Texas Instruments TI-58C calculator and recorded.

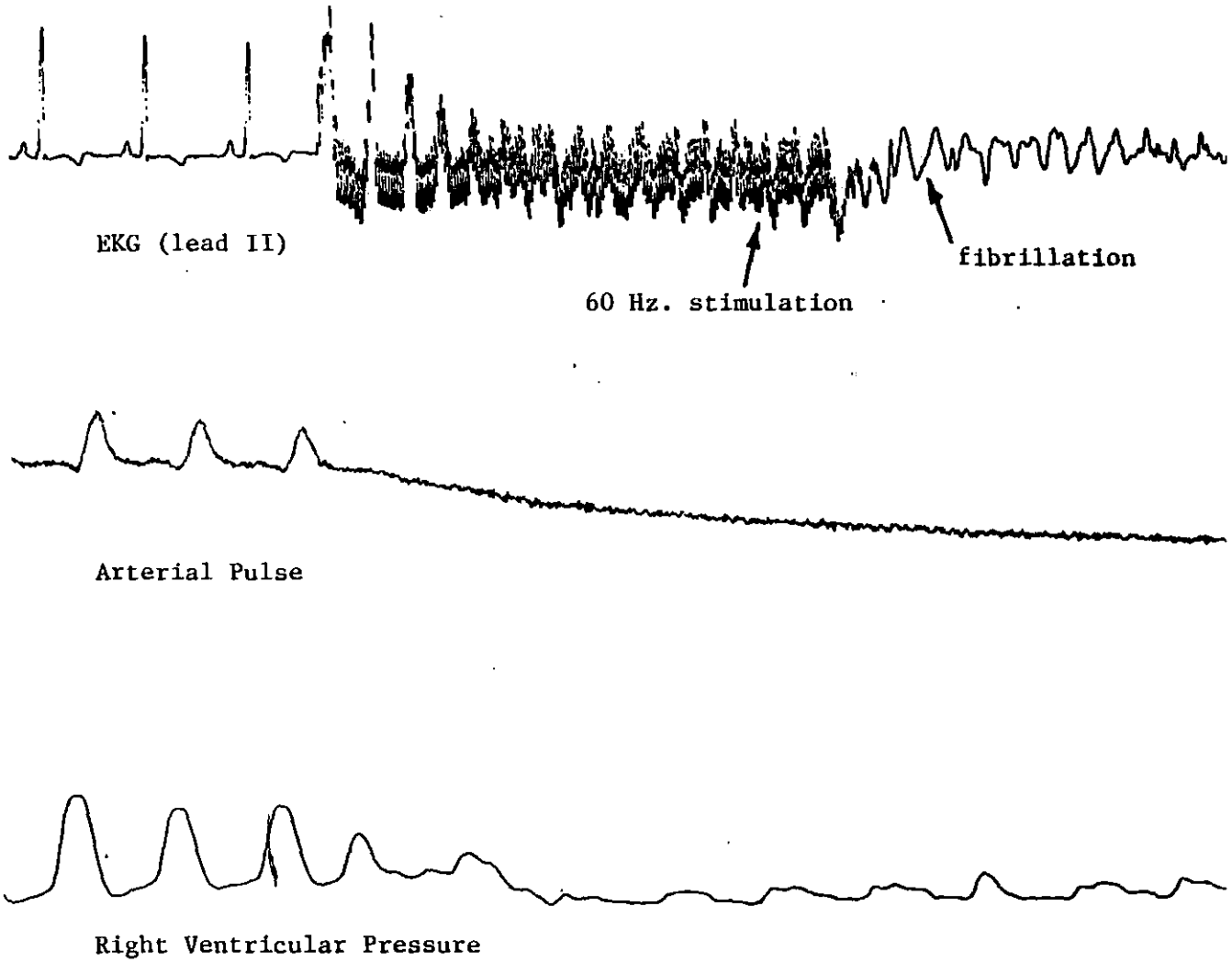

Figure 9. Fibrillation resulting from 60 Hz. stimulation

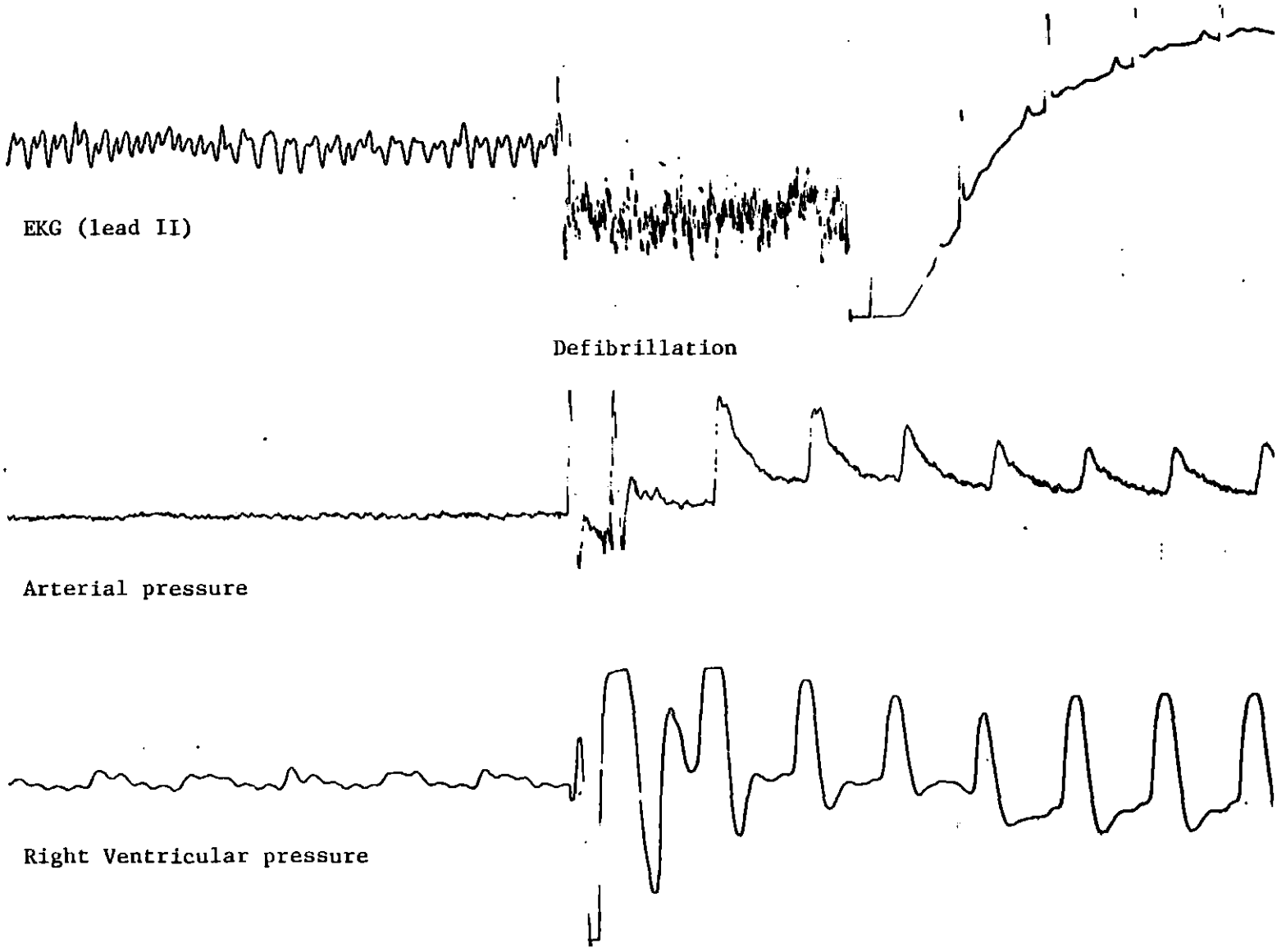

Figure 10a. Defibrillation and return of EKG and blood pressure

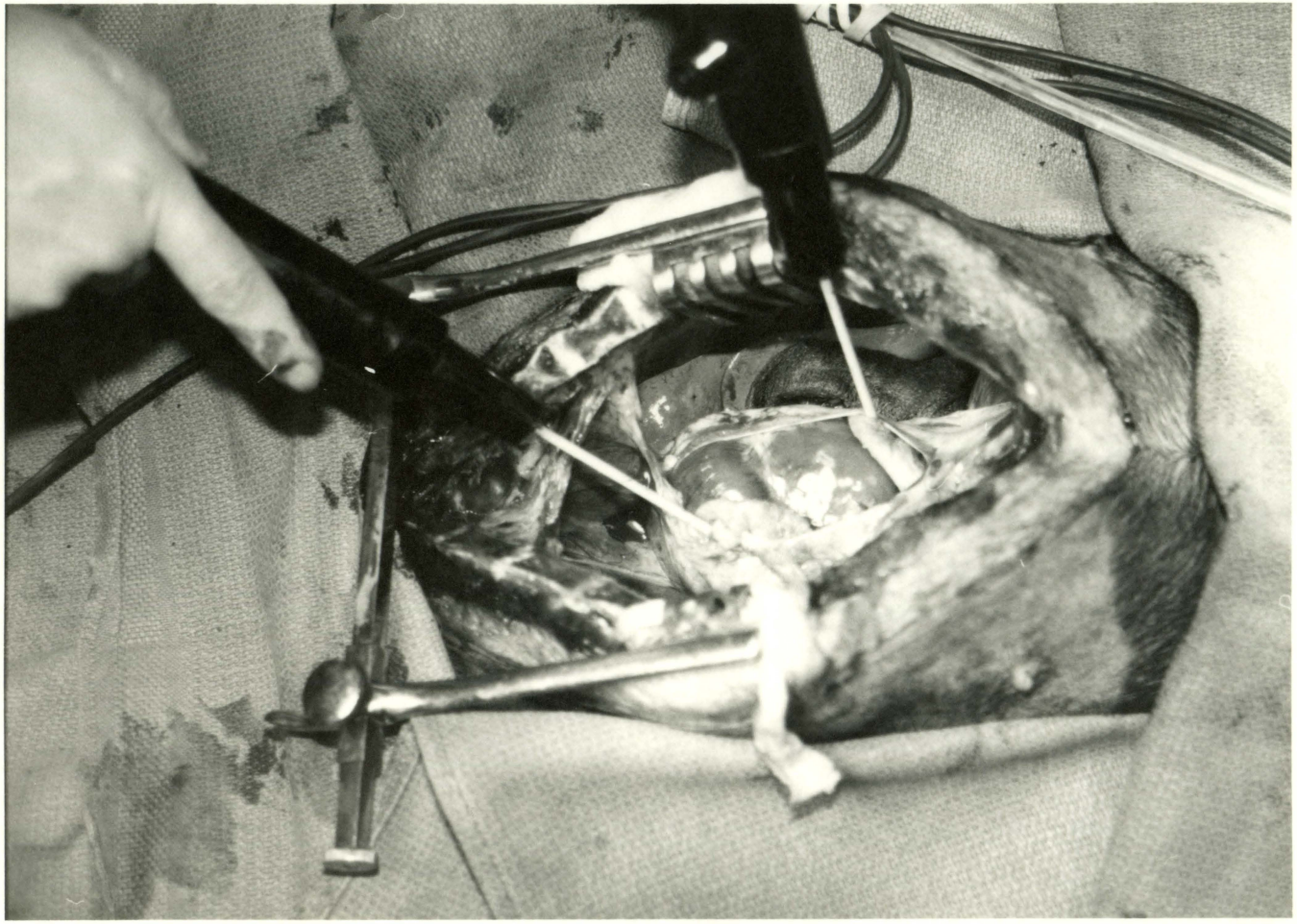

Figure 10b. Direct defibrillation with hand-held paddles

If the animal was not successfully defibrillated, a higher voltage transchest defibrillation pulse was administered immediately. If this backup pulse was unsuccessful in defibrillating the dog, a third, much higher voltage, pulse was delivered. If necessary, additional transchest defibrillation pulses were given using an American Optical Model 10645 DC Defibrillation unit. These defibrillation pulses were delivered using the chest paddles supplied with the defibrillation unit.

After defibrillating the animal, the EKG and pressure were closely monitored for arrhythmias or insufficient pressure. A ten minute rest was taken between each defibrillation episode to allow time for myocardial reperfusion. At the end of the rest period, most animals had recovered to the point where their arterial pressure and heart rate had returned to pre-fibrillation levels. In those animals that had not recovered to a near normal state, a longer rest period was permitted.

After a successful defibrillation, the process was repeated at a new defibrillation voltage level. If the initial voltage setting had been successful, the next shock was set for a value 10% lower than the first. If the first shock had not worked, the voltage was set 10% higher. This determination of defibrillation values continued until the peak current of an unsuccessful defibrillation attempt was within 10% of the peak current of the last successful defibrillation. The latter was then considered the defibrillation threshold (DFT).

After establishing DFT, the arterial pressure catheter was removed, the femoral artery tied off and the incision closed with 2-0 chromic gut

(Ethicon) and the skin closure made with 3-0 prolene. The stimulating catheter was removed, the jugular vein incision sutured with 6-0 prolene, a subcutaneous closure was made with 2-0 chromic gut and the incision closed with 3-0 prolene. The EKG and chest electrodes were removed and the animal removed from anesthesia and watched until conscious, then returned to its cage.

The animals were observed daily for any signs of infection and given proper medical attention if needed. For 6 weeks, eight animals were given daily oral doses of 200 mg. amiodarone hydrochloride, either as the injectable preparation (Cordarone, from Labaz Laboratories) or as a powder (Sanofi Recherches, Montpellier, France) in a gelatin tablet. The control animals received no medication. Weekly blood samples were taken from the animals on amiodarone. The plasma was frozen for future amiodarone concentration assay.

Follow-up Procedure

After six weeks on the study, each of the dog's transchest defibrillation threshold was determined in a follow-up procedure. In addition, direct heart defibrillation thresholds were determined.

Each animal was prepared for surgery in a manner similar to the initial protocol, with only a few alterations. Prior to anesthetizing with Surital, a 10 cc blood sample was taken from the dogs on amiodarone for analysis. For all animals, since the follow-up procedure was terminal, the surgical sites were not scrubbed, nor was an aseptic

method used during surgery. In addition to shaving the sides of the chest for defibrillation electrodes, the hair over the sternum was shaved.

A pressure catheter was inserted into the right femoral artery (since the left one had been tied off in the initial procedure). The stimulating catheter was inserted in the right jugular vein just caudal to the insertion site from the initial surgery. In animals that had totally occluded right jugulars, the left jugular was used.

The transchest defibrillation thresholds were determined as described for the initial procedure. Following the determination of transchest threshold, a blood sample was taken, and the stimulating electrode was pulled out of the right ventricle.

The sternum was then split open to expose the heart. The animal was kept on positive pressure ventilation by a Bird Mark 14 Positive phase ventilator. An approximately 3" long longitudinal slit in the pericardial sac was made, permitting one to remove the heart from the sac while defibrillating and place it back within the sac during the 10 minute rests between shocks.

Fibrillation was induced by touching the ventricular epicardium with a pair of stimulating electrodes connected to the Grass stimulator. Fibrillation was verified both visually and by a drop in arterial pressure. After a 15-20 second fibrillation period, the hand-held defibrillation paddles were placed on the right and left ventricular free walls, close to the base, and the heart was defibrillated (see

Figure 10a). To enhance the electrical contact between the heart and the defibrillation electrodes, the electrodes were covered with surgical sponges that had been soaked in normal saline. Voltage for the initial defibrillation setting was arbitrarily set for 400 volts. Subsequent voltage settings were 10% higher or lower, depending on the failure or success of the first shock.

After establishing direct defibrillation threshold, a final blood sample was withdrawn, the animal was terminated and the heart removed from the chest cavity. An examination was made for any obvious pulmonary anomalies, the presence of heart worms or any obvious myocardial abnormalities. The atria were trimmed away, and the ventricular mass was measured on a Torsion Balance Co. Model DLM5 balance and recorded. The ventricles of the animals on amiodarone were frozen for future drug concentration assay.

Amiodarone Assays

The concentration of amiodarone in the plasma and right ventricular free wall was determined with high performance liquid chromatography (HPLC) using a technique similar to that described by Plomp et al. (1983).

The HPLC equipment consisted of a Waters Associates Chromatography Pump Model 6000A connected to a Spectra-Physics SP8780 XR Sampler and a Waters uBondpack C-18 column (P/N 27324). The detector in the system was a Waters Lambda-Max Model 480 LC Spectrophotometer. The analog

signal from the detector was fed into a Nelson Analytical 760 Series Interface, and was digitally processed with Nelson Analytical Chromatography Software (Ver. 3.5) on an IBM XT Personal computer. Hard copies of the data were printed on an IBM Personal Computer Graphics Printer.

The mobile phase for the assay consisted of 0.6% ammonium hydroxide (25%) in methanol, and was the same for both tissue and plasma assays. An internal standard solution of L8040 (provided by Sanofi Recherches) in acetonitrile (100 ug./ml.) was made, as well as a standard solution of amiodarone in acetonitrile (100 ug./ml.) and desethyl amiodarone in acetonitrile (100 ug./ml.).

To assay the plasma, 1 ml. of plasma that had been taken from the amiodarone treated dogs just prior to termination was mixed with 0.2 ml. of the internal standard solution and 1.8 ml. of acetonitrile, to make a 3 ml. solution. The solution was vortexed for 5-10 seconds, and allowed to mix for 10 minutes on a rotary mixer. The samples were then centrifuged at maximum speed in a Beckman Model TJ-6 Centrifuge for 10 minutes. The supernatant was transferred to a clean microfilter centrifuge tube (Bioanalytical Systems, West Lafayette, Indiana) containing a 0.45 micron filter. The samples were centrifuged at maximum speed in the TJ-6 for another 10 minutes, and the filtrate then pipetted into clean autosampler vials, capped and inserted into the Spectra-Physics autosampler.

Calibration samples of control plasma were also run at the same

time. To prepare the six calibration samples, 1 ml. of plasma from a dog that had received no amiodarone was placed in each of six vials. Each vial then received 0.2 ml. of the internal standard, L8040 (100 ug./ml.). Different amounts of amiodarone and desethyl amiodarone and acetonitrile were added to each vial to give calibration levels ranging from 0.33 to 3.0 ug. of amiodarone and desethyl amiodarone per milliliter of solution. The vials were then vortexed, centrifuged, and filtered as above.

HPLC was run on each sample. The mobile phase had a flow rate of 1.4 ml./min., and 20 microliter injections were made for each sample. The complete operating parameters for the data acquisition are listed in Appendix D. Data from the HPLC were recorded on a floppy disk.

For plasma samples with low levels of amiodarone that could not be detected with this procedure, a method of concentrating the solutions was developed. Aliquots of the previously prepared 3 ml. solution were measured into vials and evaporated in a Savant Speed Vac Concentrator for 3 hours. The dried precipitate was reconstituted with 0.25 ml. of the mobile phase. This solution was placed in a clean microfilter tube (0.45 micron filter) and centrifuged for 5 minutes. The filtrate was pipetted into a clean autosampler tube. Aliquots from each of the four calibration solutions were likewise concentrated.

To assay the tissue samples, approximately 0.2 grams of myocardial tissue was dissected from each right ventricular free wall near the apex of the heart from each dog. The tissue was minced, patted dry between

two pieces of clean filter paper and weighed on a Mettler analytical balance, and the mass recorded. The tissue was then placed in a glass tissue homogenizer with 1.0 ml. of 50% ethanol in water. After approximately 5 minutes of homogenization with a Con-Torque Tissue Grinder Assembly, the homogenate was poured into a vial, 0.2 ml. of internal standard (L8040) solution added, and 1.8 ml. of acetonitrile added. The solution was vortexed 15 seconds, mixed for 10 minutes, and centrifuged for 10 minutes. The supernatant was pipetted into a plastic microfilter tube, a 0.45 micron filter inserted, and the tube was centrifuged for 10 minutes. The filtrate was then pipetted into clean autosampler vials, capped and inserted into the Spectra-Physics autosampler.

Calibration samples were also made for the tissue assay using tissue harvested from a dog that had received no amiodarone. Sufficient amiodarone and desethyl amiodarone were added to give four calibration levels ranging form 0 to 10.0 ug./ml.

Statistics

The means and standard deviations of all the threshold data were calculated, as well as the body weight normalized and ventricular weight normalized thresholds. Comparisons between the control and amiodarone treated animals were made using a one-tailed Student's T-test. Significant changes were defined as $p < .05$. Slight differences were defined as $p < .10$.

All plots show population means with a bar indicating the standard deviation (standard error). Correlation coefficients are denoted by "r", and are the linear correlation coefficient of the plotted data. Equations shown on plots assume "x" to be the abscissa and "y" the ordinate.

CALCULATIONS

Several threshold parameters were calculated from the voltage and current waveform data, including tilt, leading and trailing edge impedances, and pulse energy. A typical waveform is labelled below (see Figure 11).

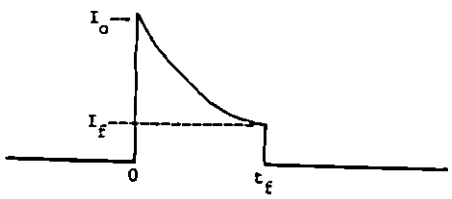

Figure 11. Typical defibrillation current waveform

By definition, tilt is the decrease in current expressed as a fraction of the level of current at the beginning of the pulse, or:

$$T = (I_o - I_f) / I_o$$

where I_o is the leading edge current (amps), I_f is the trailing edge current (amps) and T is the tilt of the waveform. Tilt can be expressed as a percentage by multiplying the fractional value by 100.

The leading and trailing edge impedances were calculated using Ohm's Law:

$$Z_o = V_o / I_o \quad \text{and} \quad Z_f = V_f / I_f$$

where Z_o, Z_f are leading and trailing impedances (ohms), respectively;

V_o, V_f are leading and trailing voltages (volts), respectively; and I_o, I_f are leading and trailing currents (amps), respectively. Note that the impedance value is only resistive. This can be verified by noting the lack of phase shift between the current and voltage waveforms.

Using the preceding definition of tilt, one can express the average current of a pulse by:

$$I_{av} = (T\ I_o) \ /\ \ln\ (1/1-T)$$

where I_{av} is the average current in the pulse. The derivation of this equation appears in Appendix A.

The energy of each pulse can be calculated from the current and voltage waveforms:

$$U = I_o\ V_o\ t_f\ (2T - T^2) \ /\ 2\ \ln(1/1-T)$$

where U is the energy in joules, t_f is the duration of the pulse in seconds. The derivation of this equation appears in Appendix B.

RESULTS

Initial Transchest Defibrillation Thresholds

All the initial surgeries were successful, and transchest threshold values were obtained for each animal in the study. The follow-up surgery, however, did not proceed as smoothly, and several animals died during the open chest procedure. Dogs 5712, 5772, and 6031 died before the direct defibrillation thresholds could be determined. In each case, the heart had been successfully defibrillated, but either went into asystole, or it developed bradycardia with insufficient pressure to maintain the animal. In each case, the animal had a condition which may have contributed to the death of the animal. Dog 5712 had what appeared to be right ventricular hypertrophy. Dog 5772 had adult heart worms in the right ventricle, and dog 6031 had a recently fractured sternum, as evidenced by its limping gait at the beginning of the study and subsequent visual inspection of the sternum during the open chest procedure. Two additional dogs were placed on the study to bring the direct defibrillation control population back to the originally planned eight. Subsequently, one of the replacement animals died during the direct defibrillation procedure.

The data from the initial series of procedures were grouped together with the data from the replacement studies. Dog 5782 was used to develop the surgical technique for opening the chest, and the direct defibrillation thresholds from the animal were added to the control data

group. Because of this, the control and study group have different populations.

For the purpose of comparison, the defibrillation data have been separated into six distinct groups: initial transchest thresholds (controls), initial transchest thresholds (amiodarone), follow-up transchest thresholds (controls), follow-up transchest thresholds (amiodarone), direct defibrillation thresholds (controls), and direct defibrillation thresholds (amiodarone). Data from each individual experiment, including total number of shocks (both primary and backup) needed to determine DFT, voltages and currents, are listed in Appendix C. Summaries of the group results and significant differences in population means are presented in this section. Significant differences in means were evaluated using a Student's one-tailed T-test at a 0.05 level of significance.

A summary of the initial defibrillation thresholds for the control animals is listed in Tables 1, which compares the body weight normalized threshold values of voltage, current and energy. As one would expect, since none of the amiodarone dogs had yet received any amiodarone, there is no significant difference between the control group and the amiodarone group for the initial transchest procedure.

It is interesting, however, to note the rather broad spread of data for each parameter. One way to characterize this spread is through the use of the coefficient of variability (C. V.), which is defined as the standard deviation of a parameter divided by its mean. For example, the

C. V. for the body weight normalized energy was 42% and 33% for the control and amiodarone group, respectively. This represents a very broad, and imprecise measurement. The mean current was 25% and 20% for the control and amiodarone group, respectively. The body weight normalized mean current is the comparative parameter preferred by several investigators. However, the spread of data for the body weight normalized peak voltage was slightly less (C. V.'s = 22% and 16% for the controls and amiodarone group, respectively). Perhaps the normalized peak current would be a more precise measure of defibrillation threshold than the mean current value.

Table 1. Initial transchest defibrillation, body weight normalized values (controls vs. amiodarone)

	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (A/Kg)	Mean Current (A/Kg)	Energy (J/Kg)
Controls:					
N =	10	10	10	10	10
Average =	47	32	.68	.46	1.11
St. Dev. =	11	7	.16	.11	.46
Amiodarone:					
N =	8	8	8	8	8
Average =	42	29	.63	.43	.88
St. Dev. =	7	5	.13	.09	.29

Follow-up Transchest Defibrillation Thresholds

The summary of the follow-up transchest defibrillation thresholds are reported in Tables 2A and 2B. Table 2A lists the body weight

normalized values, and Table 2B summarizes the heart weight normalized values. It would appear that the amiodarone treated animals required slightly ($p < .10$) lower normalized mean peak currents and lower body weight normalized energy, but the difference is not enough to be significant.

Table 2A. Follow-up summary of transchest defibrillation thresholds, body weight normalized values (controls vs. amiodarone)

	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (A/Kg)	Mean Current (A/Kg)	Energy (J/Kg)
Controls:					
N =	10	10	10	10	10
Average =	52	36	.84	.57	1.42
St. Dev. =	14	10	.30	.21	.62
Amiodarone:					
N =	8	8	8	8	8
Average =	46	31	.64*	.44*	1.05*
St. Dev. =	9	6	.12	.08	.30

*$p < .10$.

Table 2B. Summary of transchest defibrillation thresholds, heart weight normalized values: follow-up controls vs. follow-up amiodarone

	Ventricle Mass (grams)	Peak Voltage (V/g)	Mean Voltage (V/g)	Peak Current (A/100g)	Mean Current (A/100g)	Energy (J/100g)
Controls:						
N =	10	10	10	10	10	10
Average =	126	7.37	5.04	11.85	8.07	20.14
St. Dev. =	25	2.14	1.52	4.95	3.42	9.89
Amiodarone:						
N =	8	8	8	8	8	8
Average =	124	6.46	4.42	9.12*	6.20*	14.91
St. Dev. =	11	1.11	.74	1.84	1.24	4.28

*$p < .10$.

If one compares the initial control group with the follow-up control group, it becomes apparent that the transchest thresholds for the control animals did not stay constant over the length of the six week study. The body weight normalized peak and mean current increased slightly ($p < .10$) from the initial procedure to the follow-up (see Figure 12). The amiodarone treated group did not show a rise in mean current. Indeed, between the initial and follow-up procedures, there were no noticeable ($p > .10$) changes in any of the normalized defibrillation parameters for the amiodarone treated animals.

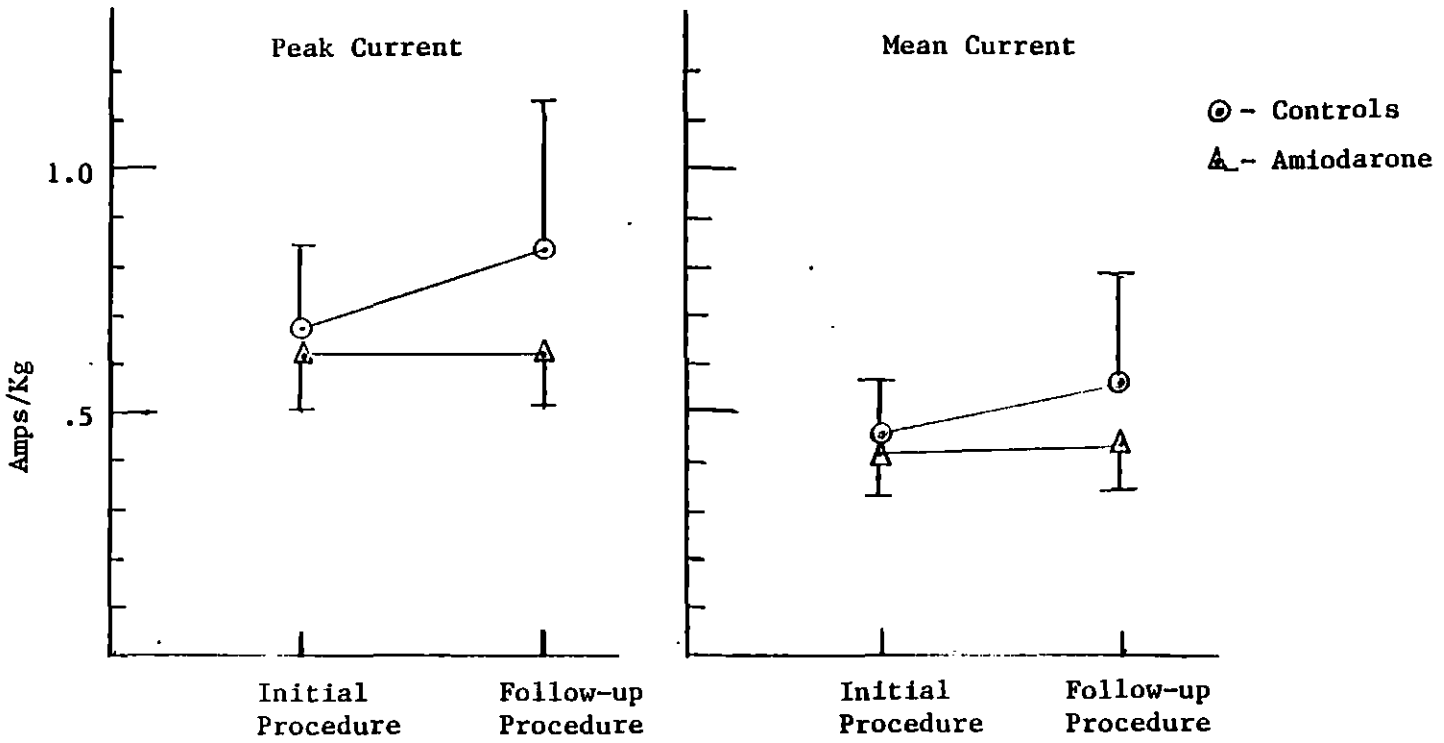

Figure 12. Defibrillation threshold currents (initial vs. follow-up)

Although not in the original protocol, measurements of chest breadth and chest wall thickness for several animals were made. The chest breadth was measured across the chest at the end of expiration. The distance measured was the straight line span between the centers of the chest electrodes. The chest wall thickness was measured on the left side of the chest, at the location of the left chest electrode. A summary of the chest measurement appears in Table 3. Note that there was a significant difference in between the controls and treated group in the chest breadth measurement. The amiodarone dogs tended to have narrower chest breadth measurements.

Table 3. Summary of chest parameters: control vs. amiodarone

	Chest Breadth (cm)	Chest Wall Thickness (cm)
Control:		
N =	7	7
Average =	12	1
St. Dev. =	1	0
Amiodarone:		
N =	8	6
Average =	10*	1
St. Dev. =	1	0

*$p < .05$.

The chest measurements were taken because it was felt that the diameter of the chest and the chest wall thickness may be related to the

transchest threshold. It was presumed that the wider chests and chests with thicker walls would present a greater impedance to the defibrillation pulse. In retrospect, this measurement was unnecessary, since the impedance of all the tissue between the transchest electrodes could be determined from the voltage and current waveforms. From the follow-up threshold data in Appendix C and chest data in Table 3, we observe that the amiodarone dogs had significantly narrower chests ($p < .05$), but slightly higher impedances ($p < .10$). If one plots the chest diameter against the measured chest impedance, it becomes obvious that there is no linear correlation between chest breadth or chest wall thickness and tissue impedance (see Figure 13).

Direct Defibrillation Thresholds

The summary results of the direct defibrillation threshold determination appear in Tables 4A and 4B. Because dogs 5712, 5772 and 6031 died during the direct defibrillation procedure, electrical data from these animals are not included in the tables.

No significant differences were noted for the body weight normalized direct defibrillation thresholds, although the mean and peak currents were slightly ($p < .10$) lower for the amiodarone treated animals.

In Table 4B, the control and amiodarone group are compared on a heart weight normalized basis. Again, there is no significant difference, although the mean current for the amiodarone treated animals

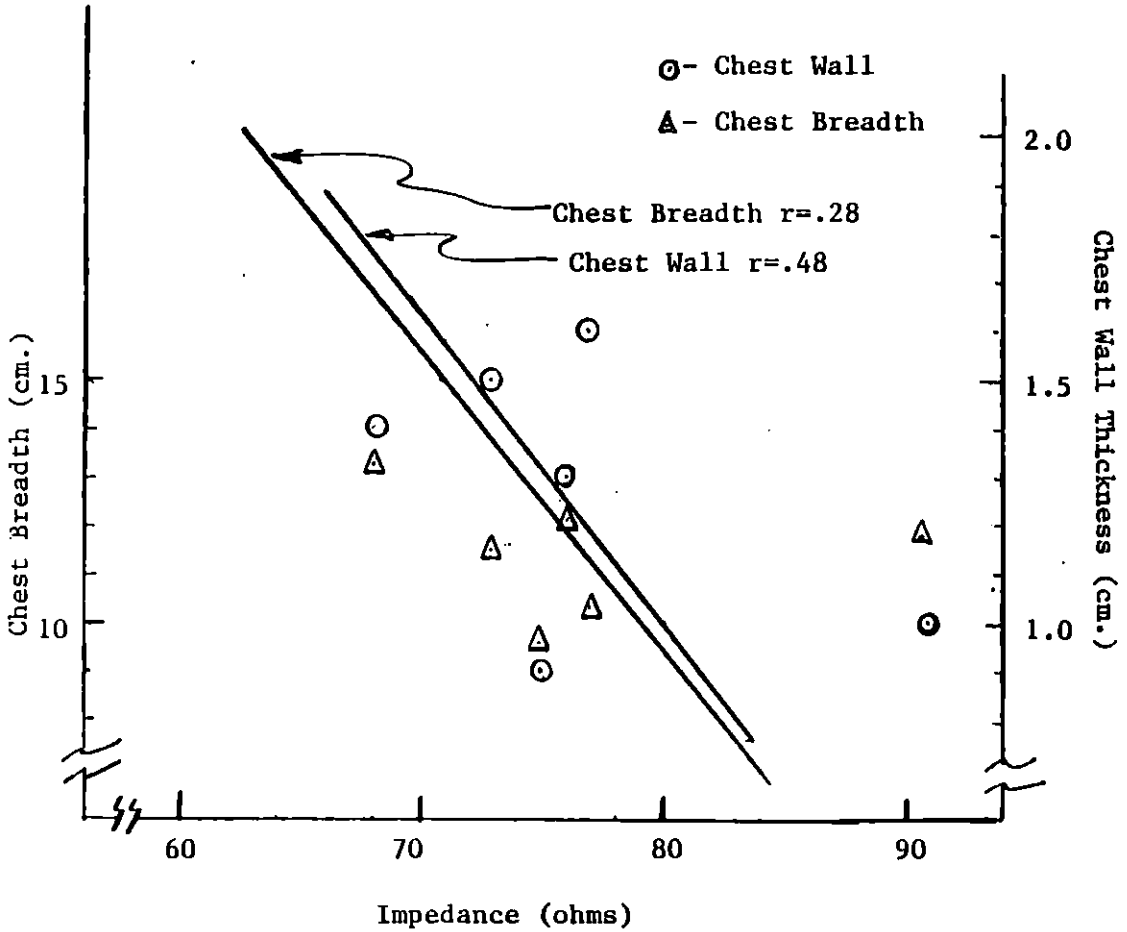

Figure 13. Chest parameters versus electrical impedance

Table 4A. Summary of direct defibrillation thresholds normalized on a body weight basis: control vs. amiodarone

	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (Amp/Kg)	Mean Current (Amp/Kg)	Energy (J/Kg)
Control:					
N =	8	8	8	8	8
Average =	19	13	.25	.16	.18
St. Dev. =	5	3	.05	.03	.07
Amiodarone:					
N =	8	8	8	8	8
Average =	17	11	.21*	.14*	.14
St. Dev. =	4	3	.03	.02	.06

*$\underline{p} < .10$.

Table 4B. Summary of direct defibrillation thresholds normalized on a heart weight basis: controls vs. amiodarone

	Peak Voltage (V/g)	Mean Voltage (V/g)	Peak Current (A/100g)	Mean Current (A/100g)	Energy (J/100g)
Control:					
N =	7	7	7	7	7
Average =	2.70	1.79	3.44	2.30	2.58
St. Dev. =	.67	.46	.62	.44	.87
Amiodarone:					
N =	8	8	8	8	8
Average =	2.37	1.59	2.96	1.97*	2.04
St. Dev. =	.59	.41	.59	.39	.88

*$\underline{p} < .10$.

Concentrations of amiodarone in serum and cardiac tissue are listed in Table 5. Each animal in the amiodarone treated group had detectable serum and tissue concentrations of the drug, although the range of concentrations was rather broad (% C. V. = 56 for serum, 58 for tissue).

Table 5. Amiodarone concentration in plasma and tissue

Dog Number	Plasma Concentration (ug/ml)	Tissue Concentration (ug/ml)
5773	.69	4.4
5797	.56	10.0
5830	.14	2.8
5834	.26	2.6
5835	.17	5.5
5878	.48	11.4
5953	.27	5.6
5954	.26	5.9
N =	8	8
Average =	.34	6.0
St. Dev. =	.19	3.5
% C. V. =	56	58

To determine if a linear correlation exists between amiodarone concentration and defibrillation threshold, the data were plotted in Figure 14. The linear correlation coefficient for the data is 0.58, indicating a low correlation between amiodarone concentration and defibrillation threshold.

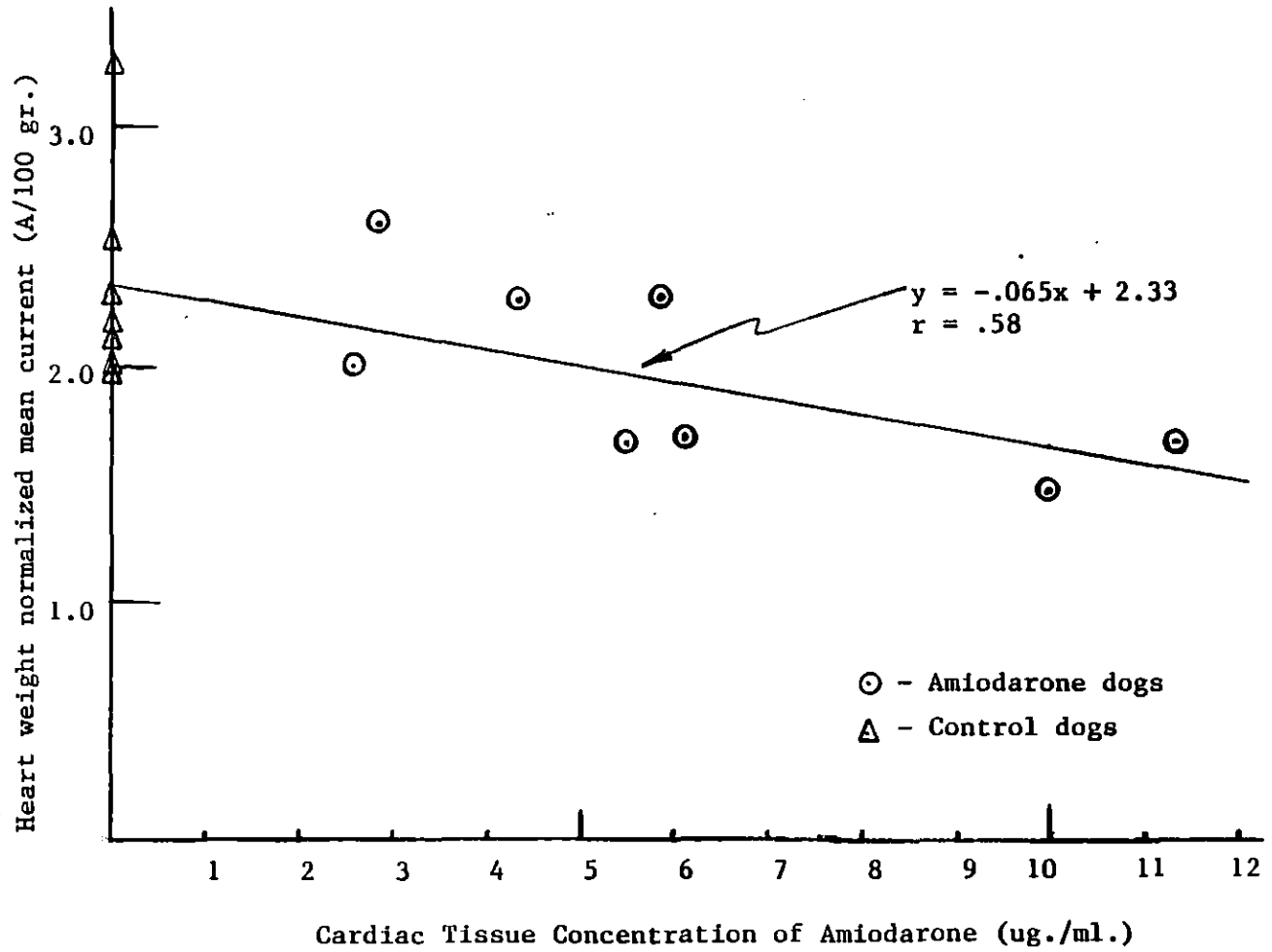

Figure 14. Heart weight normalized mean current versus tissue amiodarone concentration

Blood Gasses

The pO_2, pCO_2, pH and base excess for each initial transchest procedure are listed in Table 10 (controls) and Table 11 (amiodarone). The blood gas data for the follow-up procedure are listed in Table 12 (controls) and Table 13 (amiodarone).

Blood samples for dog 5733 (initial surgery) and dog 5834 (follow-up surgery) were inadvertently not taken.

Because the animals were on Metofane mixed with 100% oxygen, the pO_2 levels were often abnormally high. In addition, the animals tended to acidotic and had elevated pCO_2 values.

In Tables 8 and 9 one will note a substantial decrease in pO_2 between the second and third blood sample. The second blood sample was taken just prior to opening the chest, and the third sample was taken just a before terminating the animal. During the interim, the animal was ventilated with a mechanical respirator. In several animals, the artificial ventilation pressure was too low to fully inflate the dogs lungs. This resulted in a substantial decrease in pO_2.

Table 6. Blood gasses for initial controls

Dog	Sample[a]	pH	pCO_2	pO_2	Base Excess	Date
5712	1	7.29	60.5	356.6	0.4	7/3
	2	7.37	58.2	414.7	5.6	
	3	7.35	60.0	418.5	5.3	
5762	1	7.50	47.9	130.5	11.8	7/10
5774	1	7.26	58.9	359.9	-2.7	7/26
	2	7.28	53.9	373.4	-2.5	
5771	1	7.38	43.2	422.1	-0.1	7/29
	2	7.39	42.9	384.2	0.9	
	3	7.42	40.0	367.8	1.2	
5772	1	7.30	51.7	354.6	-2.3	7/31
	2	7.35	51.5	154.0	1.2	
5780	1	7.25	55	485.8	-3.4	8/5
	2	7.26	49.4	462.4	-4.7	
6031	1	7.28	59.1	367.1	-0.9	11/7
	2	7.25	62.8	293.3	-1.6	
6041	1	7.23	61.8	310.7	-3.9	11/12
	2	7.20	70.2	302.4	-3.4	
5802	1	7.27	63.1	318.7	0.0	9/17
	2	7.17	85.2	333.2	-0.9	
	3	- clotted -				

[a]Sample 1 - taken at start of surgery
Sample 2 - taken just prior to transchest procedure
Sample 3 - taken just after transchest DFT.

Table 7. Blood gasses for initial amiodarone dogs

Dog	Sample[a]	pH	pCO_2	pO_2	Base Excess	Date
5802	1	7.28	57.3	488.7	0.1	8/2
	2	7.30	54.4	494.8	0.0	
	3	7.29	60.1	526.4	1.6	
5830	1	7.33	42.9	253.3	-3.0	8/9
	2	7.31	50.0	321.4	-0.9	
	3	7.34	44.3	300.8	-1.8	
5797	1	7.29	50	370	-2.1	8/14
	2	7.31	50	424	-0.8	
	3	7.33	48	424	-0.9	
5834	1	7.27	48.9	372.4	-4.3	8/16
	2	7.19	62.4	340.0	-4.3	
	3	7.20	62.5	319.8	-3.4	
5835	1	7.34	45	484	-1.6	8/21
	2	7.28	55	504	-1.0	
	3	7.28	55	527	-0.8	
5773	1	7.27	62.2	363.0	-0.5	8/27
	2	7.24	67.3	326.7	-1.4	
	3	7.30	59.0	304.1	0.4	
5954	1	7.19	80.3	439.1	-0.3	10/29
	2	7.12	101.0	445.7	-0.9	
5953	1	7.35	51.9	461	1.5	10/31
	2	7.32	54.2	439.6	0.4	
5878	1	7.27	56.3	374.7	-2.9	11/4
	2	7.29	54.5	384.4	-1.6	

[a]Sample 1 - taken at start of surgery
Sample 2 - taken just prior to transchest procedure
Sample 3 - taken just after transchest DFT.

Table 8. Blood gasses for follow-up control dogs

Dog	Sample[a]	pH	pCO_2	pO_2	Base Excess	Date
5712	1	7.30	48.2	317.3	-2.4	8/12
	2	7.19	60.9	374.9	-4.9	
5733	1	7.25	53.2	364.3	-4.0	8/19
	2	7.24	52.8	402.3	-4.9	
	3	-- clotted sample --				
5762	1	7.34	46.3	468.9	-0.7	8/22
	2	7.46	32.6	216.8	-0.2	
	3	7.44	32.1	84.4	-2.0	
5772	1	7.30	56.5	296.2	-2.5	9/5
	2	7.26	62.9	275.9	-0.8	
5774	1	7.48	97.4	49.3	39.5	9/10
	2	7.36	48.8	52.2	1.5	
5771	1	7.28	51.7	218.9	-3.5	9/12
	2	7.29	54.5	289.4	-1.6	
	3	7.40	38.0	118.3	-2.9	
5782	1	7.31	43	342	-4.4	8/7
	2		-- no sample taken --			
	3	7.44	32	524	-2.1	
5780	1	7.26	72.1	192.8	2.1	10/3
	2	7.23	86.9	339.5	4.6	
	3[b]	7.23	93.6	19.9	9.1	
6031	1	7.28	52.9	407.8	-3.0	11/21
	2	7.18	64.0	378.0	-6.3	
6041	1	7.31	48.4	285.1	-2.6	11/26
	2	7.29	52.9	311.6	2.7	
	3	7.31	48.7	70.4	-2.1	

[a]Sample 1 - taken at start of surgery
Sample 2 - taken just prior to transchest procedure
Sample 3 - taken just after direct DFT.

[b]Venous blood sample.

Table 9. Blood gasses for follow-up amiodarone dogs

Dog	Sample[a]	pH	pCO_2	pO_2	Base Excess	Date
5830	1	7.31	52.5	278.5	-1.3	9/19
	2	7.28	53.4	263.9	-2.8	
	3	7.28	55.5	89.9	-3.6	
5797	1	7.27	62.4	364.8	-0.7	9/24
	2	7.35	45.2	365.4	-1.1	
	3	7.40	41.7	373.8	0.9	
5835	1	7.26	60.7	436.6	-2.0	10/1
	2	7.20	71.0	416.6	-2.6	
5773	1	7.28	48.3	250.5	-4.8	10/8
	2	7.26	49.3	238.1	-5.5	
	3	7.10	79.5	41.9	-6.5	
5954	1	7.25	45.0	392.1	-7.7	12/12
	2	---	no sample	taken ---		
	3	7.18	59.7	86.8	-4.3	
5953	1	7.38	40.9	465	-1.1	12/18
	2	7.32	42.5	468	-4.5	
	3	7.25	48.8	141.3	-6.5	
5878	1	7.19	66.9	349.5	-5.2	12/19
	2	7.25	56.6	375.5	-4.0	
	3	7.08	78.7	47.8	-8.3	

[a]Sample 1 - taken at start of surgery
Sample 2 - taken just prior to transchest procedure
Sample 3 - taken just after direct DFT.

DISCUSSION AND CONCLUSION

The results indicate that amiodarone had no significant effect on either transchest or direct defibrillation thresholds. Several concerns must be addressed before this conclusion can be made with confidence. First, why did the control group's transchest threshold increase from the initial procedure to the follow-up procedure? Second, did the amiodarone treated animals have concentrations of amiodarone high enough to have caused an electrophysiologic effect? And third, were there any metabolic conditions that could have masked the effect of amiodarone?

Temporal Stability of Defibrillation Thresholds

While the control group showed a slight increase in mean current from the initial to the follow-up transchest procedure, it was not statistically significant.

One would expect the control transchest thresholds to not change, or to decrease slightly over time, based on previous investigations. Kerber et al. (1983b), demonstrated that DFT remains constant over several hours in a series of transchest dog defibrillation experiments. Recent work by Ruffy et al. (1986) indicated thresholds in a 7 dog, 5 day study decreased on the second day of the study, then remained constant for the remaining 3 days. They hypothesized that the defibrillations on the first day of the study caused enhanced myocardial sympathetic activity, which resulted in lowered DFT in subsequent

trials. While the Ruffy study did show a decrease in DFT, there is no known data on the long term stability of defibrillation thresholds in dogs (Ruffy et al., 1986).

Therapeutic Levels of Amiodarone

Several investigators have studied the effects of amiodarone without measuring the blood or tissue concentrations. In long term medication, it had been assumed that the patient would be at therapeutic levels if one prescribed the proper dose. However, this is a dubious assumption to make, since amiodarone has been shown to have variable uptake and metabolism rates. Early investigators compensated for this variable uptake by heavily medicating patients with a "loading" dose of 1200 mg./day for adult humans for a week, then cutting the medication back to a "maintenance" dose of 200-400 mg./day. Having done this, it was assumed any electrophysiologic phenomenon noted would be due to the effects of the amiodarone, without actually assaying for the drug.

As HPLC techniques for detecting amiodarone developed, researchers began quantifying their results, and began specifying therapeutic and toxic ranges for amiodarone.

In human studies, the therapeutic range of serum concentration has been reported as 1.0 to 3.5 ug./ml. in humans by Zipes et al. (1984), although the same group found levels as low as 0.6 ug./ml. in their patients. In another study cited by Gilles and Kates (1984), the suggested therapeutic serum concentration range was 0.5 to 3.0 ug.,

although the range of efficacy of amiodarone in controlling arrhythmias was 0.1 to 11.9 ug./ml. in a study of 18 human patients. Latini et al. (1984) found a therapeutic mean of .67 ug./ml. (s. d. = .31, N = 24).

The average serum concentrations found in this current study was .34 ug./ml. (s. d. = .19), which is significantly lower (p = .005) than the levels described by Latini. From examination of the serum levels alone, it would appear that the amiodarone treated dogs were not at therapeutic levels.

However, in evaluating the concentrations of amiodarone, one must differentiate between serum and tissue levels of the drug. Most commonly, amiodarone levels are determined from serum, although it is thought that the myocardial tissue level of amiodarone is more reflective of its therapeutic characteristics (Connolly et al., 1984).

Data on myocardial concentrations of amiodarone are difficult to find, since the tissues biopsies required for living patients are a rather traumatic, and not normally performed in a clinical setting. Magioni et al. (cited by Latini et al. 1984) did report on the concentrations of amiodarone in heart tissue that had been taken during an autopsy. He found a cardiac tissue concentration of 5 ug./ml. in a patient that had been on amiodarone for a long term.

The average tissue concentration found in this study was 6.0 ug./ml. (s. d. = 3.5). This would tend to support the idea that the amiodarone concentration in the animals was at a therapeutic level at the time of the follow-up surgery.

In the results, it was noted that there is a low correlation between the concentration of amiodarone in the tissues and the defibrillation thresholds. A low correlation between amiodarone concentration and other electrophysiologic effects has been noted by other investigators. Connolly et al. (1984) studied the effect of bolus injections of amiodarone on EKG timing intervals in dogs. He found a wide variation in animal response to the amiodarone, which could not be correlated to the measured myocardial or plasma tissue levels of amiodarone.

Based on the facts that the dosing used in this experiment is comparable to that used by other investigators, and the tissue concentrations measured are similar to those few reported by others, it is concluded that there is a high probability that the amiodarone treated dogs were at a therapeutic level.

Influence of Blood Gasses on Defibrillation Thresholds

Several metabolic conditions can influence defibrillation thresholds. Until recently, it was thought that metabolic acidosis would increase defibrillation thresholds (Kerber et al., 1983a). In a later study, however, Kerber et al. (1983b) found that neither metabolic nor respiratory acidosis had an effect on canine DFT. Therefore, although all the animals is this current study showed signs of compensated respiratory acidosis, the acid/base balance should not have had an effect on defibrillation.

The one metabolic abnormality that Kerber found that did influence DFT was hypoxia, which caused a significant ($p < .01$) decrease in DFT. The finding of a hypoxic effect was supported by Lake et al. (1984) in a human prospective study. None of the animals in this study were hypoxic, but most were hyperoxic. There is no known effect of high levels of pO_2 on defibrillation thresholds, although research in the area of hyperbaric oxygen toxicity has indicated two major effects on the cardiovascular system from hyperoxia in man. Paradoxically, both bradycardia and increased heart rate have been attributed to hyperoxia. Schaefer (1982) claims bradycardia is of vagal origin, and increased pulse rate and blood pressure can be due to increased sympathetic activity. Schaefer also noted that potassium ions accumulate in the extracellular fluid in rats that had been exposed to 100% oxygen at four times the normal atmospheric pressure. This increase had been attributed to the inhibition of the sodium-potassium ATPase by the high level of oxidants in the blood.

If an increase in extracellular potassium occurs at normal anesthesia pressures, it could have an effect on defibrillation thresholds. Babbs et al. (1980) demonstrated that transchest defibrillation thresholds would fall during potassium intoxication. If, by breathing 100% oxygen, the animals in this study had increased potassium levels it is possible the defibrillation thresholds were low, and the effect of the amiodarone could have been masked by the altered potassium levels. However, there was no evidence found in the

literature that would indicate that potassium levels are altered by breathing 100% oxygen at normal ventilation pressures. Perhaps in future studies, the potassium levels of plasma could be monitored to verify they remain normal during the procedure.

Conclusion

In studying defibrillation thresholds, it is important to realize the limitations of the investigation. Several environmental conditions can have an effect on the measurement of transchest DFT. The location and contract pressure of the transchest paddles, the conductivity of the electrode paste, body weight, heart weight and cardiac temperature are parameters affecting threshold. It should be noted that the importance of these parameters is not universally accepted by all investigators. For example, the heart weight parameter that Geddes et al. claim is important for predicting defibrillation thresholds, is disputed by Lake et al. (1984) who found this to be important only at low level (< 1 joule) direct defibrillation.

In planning the protocol for this thesis, an attempt was made to use established techniques for evaluating defibrillation thresholds. The surgical approach, placement of transchest and direct defibrillation paddles, the calculation of threshold values, the amiodarone dosing levels and the assay technique for evaluating tissue and plasma concentrations of the drug were modeled after established techniques used by major investigators. As a result, I am confident in concluding

that the results of this study show amiodarone hydrochloride may have slightly depressed thresholds, there is no statistically significant effect on lowering either transchest or direct defibrillation thresholds.

BIBLIOGRAPHY

Babbs, C. F. 1981. Alteration of defibrillation threshold by antiarrhythmic drugs: a theoretical framework. Crit. Care Med. 9:362-363.

Babbs, C. F., G. K. Yim, S. J. Whistler, W. A. Tacker, Jr., and L. A. Geddes. 1979. Elevation of ventricular defibrillation threshold in dogs by antiarrhythmic drugs. Am. Heart J. 98:345-350.

Babbs, C. F., S. J. Whistler, G. K. Yim, W. A. Tacker, Jr., and L. A. Geddes. 1980. Dependence of defibrillation threshold upon extracellular/intracellular K+ concentrations. Electrocardiology 13:73-78.

Beck, C. S., W. H. Pritchard, and H. S. Feil. 1947. Ventricular fibrillation of long duration abolished by electric shock. JAMA 135:985-986.

Bourland, J. D., W. A. Tacker, L. A. Geddes and V. Chafee. 1978. Comparative efficacy of damped sine wave and square wave current for transchest ventricular defibrillation in animals. Med. Instr. 12:42-45.

Canada, A. T., L. J. Lesko, C. I. Haffajee, B. Johnson, and G. K. Asdourian. 1983. Amiodarone for tachyarrhythmias: pharmacology, kinetics and efficacy. Drug Intell. Clin. Pharm. 17:100-104.

Connolly, J. S., R. Latini, and R.E. Kates. 1984. Pharmacodynamics of intravenous amiodarone in the dog. J. Cardiovasc. Pharm. 6:531-535.

Cranefield, P. F. 1973. Ventricular fibrillation. N. Engl. J. Med. 289:732.

Davies, M. J., R. H. Anderson, and A. E. Becker. 1983. The conduction system of the heart. London: Butterworth and Co.

Deeb, G. M., R. L. Hardesty, B. P Griffith, M. E. Thompson, M. S. Heilman, and R. L. Myerowitz. 1983. The effects of cardiovascular drugs on the defibrillation threshold and the pathological effects on the heart using an automatic defibrillator. Ann. Thorac. Surg. 35:361-366.

Ewy, G. A., D. Taren, J. Bangert, S. McClung, and D. A. Hellman. 1980. Comparison of myocardial damage from defibrillator discharges at various dosages. Med. Instrum. 14:9-12.

Fogoros, R. N. 1984. Amiodarone-induced refractoriness to cardioversion. Ann. Int. Med. 100:699-700.

Garrey, W. E. 1914. The nature of fibrillary contraction of the heart. Its relation to mass and form. Am. J. Physiol. 33:297.

Geddes, L. A. 1984. A short history of the electrical stimulation of excitable tissue. Physiologist 27(1 Suppl.):S1-S47.

Geddes, L. A., and L. E. Baker. 1967. The specific resistance of biological material--A compendium of data for the biomedical engineer and physiologist. Med. & Biol. Engng. 5:271-293.

Geddes, L. A. and C. P. da Costa. 1973. The specific resistance of canine blood at body temperature. IEEE Trans. Biomed. Eng. 20:51-53.

Geddes, L. A., and R. Hamlin. 1983. The first human heart defibrillation. Am. J. Cardiol. 52:403-405.

Geddes, L. A. and H. Kidder. 1976. Specific resistance of blood at body temperature II. Med. Biol. Eng. 14:180-185.

Geddes, L. A., and W. A. Tacker, Jr. 1983. Ventricular fibrillation and defibrillation. Austral. Phys. Eng. Sci. in Med. Jan. 1983:9-19.

Geddes, L. A., W. A. Tacker, Jr., J. McFarlane, and J. Bourland. 1970. Strength-duration curves for ventricular defibrillation in dogs. Circ. Res. 27:551-560.

Geddes, L. A., P. Cabler, A. G. Moore, J. Rosborough, and W. A. Tacker, Jr. 1973a. Threshold 60-Hz current required for ventricular fibrillation in subjects of various body weights. IEEE Trans. Biomed. Eng. 20:465-468.

Geddes, L. A., W. A. Tacker, Jr., and J. McFarlane. 1973b. Ventricular defibrillation with single and twin pulses of half-sinusoidal current. J. Appl. Physiol. 34:8-11.

Geddes, L. A., W. A. Tacker, J. Rosborough, A. G. Moore, P. Cabler, M. Bailey, J. D. McCrady, and D. Witzel. 1974. The electrical dose for ventricular defibrillation with electrodes applied directly to the heart. J. Thorac. Cardiovasc. Surg. 68:593-602.

Geddes, L. A., S. S. Grubbs, P. G. Wilcox, and W. A. Tacker. 1977. The thoracic windows for electrical defibrillation current. Am. Heart J. 94:67-72.

Geddes, L. A., J. D. Bourland, and W. A. Tacker. 1980. Energy and current requirements for ventricular defibrillation using trapezoidal waves. Am. J. Physiol. 237:H231-H236.

Geuze, R. H. 1983. Two methods for homogeneous field defibrillation and stimulation. Med. & Biol. Eng. & Comput. 21:518-520.

Gillis, A. M., and R. E. Kates. 1984. Clinical pharmacokinetics of the newer antiarrhythmic agents. Clin. Pharmacokinet. 9:375-403.

Gold, J. H., J. C. Schuder, and H. Stoeckle. 1980. Ventricular defibrillation with myocardial electrodes in the dog, calf, pony, and pig. Med. Instrum. 14:19-22.

Gullett, J. R., W. W. Havens, W. A. Tacker, L. A. Geddes, and H. E. Hoff. 1968. Optimum duration of 60-Hz current for direct ventricular defibrillation in the dog. Cardiovasc. Res. Cent. Bull. 6:117-123.

Gutgesell, H. P., W. A. Tacker, L. A. J. S. Geddes Davis, J. T. Lie, and D. G. McNamara. 1976. Energy dose for ventricular defibrillation of children. Pediatrics 58:898-901.

Hamlin, R. L., and C. R. Smith. 1977. Electrophysiology of the heart. Pages 70-80 in M. J. Swenson, ed. Dukes' Physiology of Domestic Animals. Cornell University Press, London. 914 pp.

Harris, L., C. R. K. Hind, W. J. McKenna, C. Savage, S. J. Krikler, G. C. A. Storey, and D. W. Holt. 1983. Renal elimination of amiodarone and its desethyl metabolite. Postgrad. Med. J. 59:440-442.

Harrison, D. C., editor. 1972. Management of acute myocardial infarction. Medcom Press, New York.

Hoffmann de Visme, G., and A. Furness. 1983. Electrical waveforms for cardiac defibrillation which dissipate least heat in the cardiac circuit. Med. & Biol. Eng. & Comput. 21:259-263.

Hooker, D. R. 1930. Chemical factors in ventricular fibrillation. Am. J. Physiol. 92:639.

James, T. N., L. Sherf, R. C. Schlant, and M. E. Silverman. 1982. Anatomy of the heart. Pages 22-74 in J. W. Hurst, R. B. Logue, C. E. Rackley, R. C. Schlant, E. H. Sonnenblick, A. G. Wallace and N. K. Wenger, eds. The heart. McGraw-Hill Book Company, New York.

Kerber, R. E., J. Carter, S. Klein, J. Grayzel, and J. Kennedy. 1980. Open chest defibrillation during cardiac surgery: energy and current requirements. Am. J. Cardiol. 46:393-396.

Kerber, R. E., S. R. Jensen, J. A. Gascho, J. Grayzel, R. Hoyt, and J. Kennedy. 1983a. Determinants of Defibrillation: Prospective Analysis of 183 patients. Am. J. Cardiol. 52:739-745.

Kerber, R. E., N. G. Pandian, R. Hoyt, S. R. Jensen, S. Koyanagi, J. Grayzel, and R. Kieso. 1983b. Effect of ischemia, hypertropy, hypoxia, acidosis, and alkalosis on canine defibrillation. Am. J. Physiol. 13:H825-H831.

Kerber, R. E., D. McPherson, F. Charbonnier, R. Kieso, and P. Hite. 1985. Automated impedance-based energy adjustment for defibrillation: experimental studies. Circulation 71:136-140.

Koo, C. C., J. D. Allen, and J. F. Pantridge. 1984. Lack of effect of bretylium tosylate on electrical ventricular defibrillation in a controlled study. Cardiovasc. Res. 18:762-767.

Lake, C. L., T. D. Sellers, S. P. Nolan, I. K. Crosby, H. A. Wellons, and R. S. Crampton. 1984. Energy dose and other variables possibly affecting ventricular defibrillation during cardiac surgery. Anesth. Analg. 63:743-51.

Landymore, R., A. Marble, G. MacKinnon, R. Leadon, and M. Gardner. 1984. Effects of oral amiodarone on leftg ventricular function in dogs: clinical implications for patients with life-threatening ventricular tachycardia. Ann. Thorac. Surg. 37:141-146.

Latini, R., G. Tognoni, and R. E. Kates. 1984. Clinical pharmacokinetics of amiodarone. Clin. Pharmacokinet. 9:136-156.

Lewis, T. 1920. Observations upon flutter and fibrillation. Heart 7:127.

McComb, J. M., K. R. Logan, M. M. Khan, J. S. Geddes, and A. A. Adgey, A. A. J. 1980. Amiodarone-induced ventricular fibrillation. Eur. J. Cardiol. 11:381-385.

McFarlane, J., W. Milnor, L. A. Geddes, J. Bourland, and T. W. Coulter. 1969. Ventricular defibrillation in the dog using single half-wave sinusoidal current pulses of various durations. Cardiovasc. Res. Cent. Bull. 7:151-157.

McGovern, B., H. Garan, and J. N. Ruskin. 1984. Serious adverse effects of amiodarone. Clin. Cardiol. 7:131-137.

Meulendyk, J. 1984. Anesthetic considerations with amiodarone: report of a case. JOAO 83:585/83-588/86.

Mirowski, M., P. R. Reid, M. M. Mower, L. Watkins, E. V. Platia, L. S. C. Griffith, and J. M. Janteguy. 1984. Clinical experience with the implantable cardioverter-defibrillator. Ann. N. Y. Acad. Sci. 427:297-306.

Niebauer, M. J., C. F. Babbs, L. A. Geddes, and J. D. Bourland. 1983a. Efficacy and safety of defibrillation with rectangular waves of 2- to 20-milliseconds duration. Crit. Care Med. 11:95-98.

Niebauer, M. J., C. F. Babbs, L. A. Geddes, J. C. Carter, and J. D. Bourland. 1983b. Functional cardiac depression caused by defibrillator shocks. Jpn. Heart J. 25:773-781.

Niebauer, M. J., C. F. Babbs, L. A. Geddes, and J. D. Bourland. 1984. The efficacy and safety of defibrillation with 10-millisecond trapezoidal waves of different tilts. Med. Instrum. 18:119-121.

Plomp, T. A., M. Engels, E. O.Robles de Medina, and R. A. A. Maes. 1983. Simultaneous determination of amiodarone and its major metabolite desethylamiodarone in plasma, urine and tissues by high-performance liquid chromatography. J. Chromatogr. 273:379-392.

Prevost, J. L., and F. Battelli. 1899. On some effects of electric discharges on the hearts of mammals. Comptes Rendus Acad. Sci. 129:1267-8.

Ralston, S. H., W. D. Voorhees, L. Showen, P. Schmitz, C. Kougias, and W. A. Tacker. 1985. Venous and arterial blood gases during and after cardiopulmonary resuscitation in dogs. Am. J. Emerg. Med. 3:132-136.

Riva, E., M. Gerna, P. Neyroz, R. Urso, I. Bartosek, and A. Guaitani. 1982. Pharmacokinetics of amiodarone in rats. J. Cardiovasc. Pharm. 4:270-275.

Rosenbaum, M. B., P. A. Chiale, M. S. Halpern, G. J. Nau, J. Przybylski, R. J. Levi, J. O. Lazzari, and M. V. Elizari. 1976. Clinical efficacy of amiodarone as an antiarrhythmic agent. Am. J. Cardiol. 38:934-43.

Rubin, L., and P. Hudson. 1985. Epicardial versus parietal pericardial defibrillation. Am. J. Emerg. Med. 3:160-164.

Ruffy, R., K. Schechtman, and E.Monje. 1985. Beta-adrenergic modulation of direct defibrillation energy in anesthetized dog heart. Am. J. Physiol.: Heart & Circ. Physiol. 17:H674-H677.

Ruffy, R. R., K. Schechtman, E. Monje, and J. Sandza. 1986. Adrenergically mediated variations in the energy required to defibrillate the heart: observations in closed-chest, nonanesthetized dogs. Circulation 73:374-380.

Schaefer, K. E. 1982. Hyperbaria--O_2 toxicity. Pages 291-304 in Loeppky, J. A. and M. L. Riedesel, eds. Oxygen transport to human tissues. Elsevier Science Publishers, Amsterdam.

Scherf, D., and R. Teranova. 1949. Mechanism of auricular flutter and fibrillation. Am. J. Cardiol. 159:137.

Schuder, J. C., G. A. Rahmoeller, H. Stoeckle. 1966. Transthoracic ventricular defibrillation with triangular and trapezoidal waveforms. Circ. Res. 19:689-94.

Singh, B. N. 1983. Amiodarone: Historical development and pharmacologic profile. Am. Heart J. 106:788-797.

Singh, B. N., K. Nademanee, M. A. Josephson, N. Ikeda, N. Venkatesh, and R. Kannan. 1984. The electrophysiology and pharmacology of verapamil, flecainide, and amiodarone: correlations with clinical effects and antiarrhythmic actions. Ann. N. Y. Acad. Sci. 432:210-35.

Sloskey, G. E. 1983. Amiodarone: A unique antiarrhythmic agent. Clin. Pharm. 2:330-40.

Tacker, W. A., Jr., and L. A. Geddes. 1980. Electrical defibrillation. CRC Press, Inc., Boca Raton, FL. 192 pp.

Tacker, W. A., Jr., L. A. Geddes J. McFarlane, W. Milnor, J. Gullett, W. Havens, E. Green, and J. Moore. 1969. Optimum current duration for capacitor-discharge defibrillation of canine ventricles. J. Appl. Physiol. 27:480-483.

Tacker, W. A., Jr., G. A. Guin, L. A. Geddes J. D. Bourland, F. L. Korompai, and P. A. Rubio. 1978. The electrical dose for direct ventricular defibrillation in man. J. Thorac. Cardiovasc. Surg. 75:224-26.

Tacker, W. A., Jr., M. J. Niebauer, C. F. Babbs, W. J. Combs, B. M. Hahn, M. A. Barker, J. F. Seipel, J. D. Bourland, and L. A. Geddes. 1980. The effect of newer antiarrhythmic drugs on defibrillation threshold. Crit. Care Med. 8:177-180.

Thakor, N. V., 1984. From Holter monitors to automatic defibrillators: developments in ambulatory arrhythmia monitoring. IEEE Trans. Biomed. Eng. BME-31:770-778.

Vander, A. J., J. H. Sherman, and D. S. Luciano. 1975. Human physiology. McGraw-Hill, Inc., New York.

Van Vleet, J. F., W. A. Tacker, Jr., L. A. Geddes, V. J. Ferrans. 1976. Acute cardiac damage in dogs given multiple transthoracic shocks with a trapezoidal wave-form defibrillator. Am. J. Vet. Res. 38:617-26.

Varma, M. P. S., J. S. Geddes, J. F. Pantridge. 1981. D. C. conversion in patients on amiodarone. Eur. J. Cardiol. 12:271-274.

Waleffe, A., P. Bruninx, and H. E. Kulbertus. 1978. Effects of amiodarone studied by programmed electrical stimulation of the heart in patients with paroxysmal re-entrant supraventricular tachycardia. J. Electrocardiology 11:253-260.

Wellens, H. J. J., P. Brugada, H. Abdollah, and W. R. Dassen. 1984. A comparison of the electrophysiologic effects of intravenous and oral amiodarone in the same patient. Circulation 69:120-124.

Wessale, J. L., J. D. Bourland, W. A. Tacker, and L. A. Geddes. 1980. Bipolar catheter defibrillation in dogs using trapezoidal waveforms of various tilts. J. Electrocardiology 13:359-366.

Wiggers, C. J., and R. Wegria. 1940. Ventricular fibrillation due to single, localized induction and condenser shocks applied during the vulnerable phase of ventricular systole. Am. J. Physiol. 128:500

Winkle, R. A., E. B. Stinson, S. M. Bach, D. S. Echt, P. Oyer, and K. Armstrong. 1984. Measurement of cardioversion/defibrillation thresholds in man by a truncated exponential waveform and an apical patch-superior vena caval spring electrode configuration. Circulation 69:766-771.

Zipes, D. P., E. N. Prystowsky, and J. J. Heger. 1984. Amiodarone: Electrophysiologic actions, pharmacokinetics and clinical effects. J. Am. Coll. Cardiol. 3:1059-71.

ACKNOWLEDGEMENTS

The author would like to thank all those who have contributed to this work, and without whose help, this research could not have been completed. Several individuals' assistance proved to be invaluable. I would particularly like to thank Dr. Pam McAllister for all the assistance she lent during the coursed of this research. Without her expertise in the areas of surgery and animal care, I would not have been able to progress as readily as I did. I would also like to thank Dr. Frederick Hembrough, Dr. Donald Dyer and Dr. David Carlson for their assistance in their respective areas. Finally, I thank my wife for her patience, enthusiasm and love.

APPENDIX A: CALCULATION OF AVERAGE CURRENT

The current from a charged capacitor flowing through a resistive element can be described mathematically as

$$i(t) = I_o \exp(-t/\tau) \quad (1)$$

where $i(t)$ is the time dependent current, I_o is the initial current, t is the time and τ is the time constant (RC time constant) of the circuit. The average current during a pulse can be described as i_{av}:

$$I_{av} = (1/\Delta t) \int i \, dt \quad (2)$$

Substituting equation (1) into (2), and evaluating the integral from $t = 0$ to $t = t_f$, where t_f is the end of the defibrillation pulse, we find

$$I_{av} = (-\tau/t_f) (I_o \exp (- t_f/\tau) - I_o) \quad (3)$$

Since $i(t_f) = I_o \exp (-t_f/\tau) = I_f$, then

$$I_{av} = (-\tau/t_f) (I_f - I_o) \quad (4)$$

Now, note that $I_f = I_o \exp (-t_f/\tau)$. Taking the natural log of both sides and rearranging,

$$(-\tau/t_f) = -1/(\ln I_o - \ln I_f) \quad (5)$$

Substituting into equation (4) and rearranging,

$$I_{av} = (I_o - I_f) / (\ln I_o - \ln I_f) \quad (6)$$

The tilt (T) of a current pulse has been defined as

$$T = (I_o - I_f) / I_o$$

Rearranging,

$$1 / (1 - T) = I_o / I_f$$

By taking the natural log of both sides, we can substitute into equation

(6) to get

$$I_{av} = (I_o - I_f) / \ln (1/(1-T))$$

and since $I_o T = I_o - I_f$, then

$$I_{av} = TI_o / \ln (1/(1-T))$$

APPENDIX B: CALCULATION OF PULSE ENERGY

For a capacitive discharge into a resistive load, current and voltage vary as follows:

$$i(t) = I_o \exp(-t/\tau) \quad \text{and} \quad v(t) = V_o \exp(-t/\tau)$$

where $i(t)$, $v(t)$ are the time dependent current and voltage, respectively; I_o and V_o are the initial current and voltage, respectively; and τ is the RC circuit time constant. The energy within a single pulse can be calculated by the integral

$$U = \int v\, i\, dt$$

evaluated from $t = 0$ (start of the pulse) to $t = t_f$ (end of the pulse). Or,

$$U = \int I_o V_o (\exp(-t/\tau))^2 dt$$

Evaluating the integral,

$$U = I_o V_o \quad (1 - \exp(-2t_f/\tau)) \qquad (1)$$

From Appendix A, we know

$$\tau = t_f / \ln(1/1-T)$$

so equation (1) becomes

$$U = (I_o V_o t_f (1 - \exp(-2t_f/\tau)) / 2 \ln(1/1-T) \qquad (2)$$

Since the tilt (T) of the defibrillation pulse is defined as

$$T = (I_o - I_f) / I_o$$

Then,

$$2T - T^2 = (I_o^2 - I_f^2) / I_o^2$$

and since

$$I_f = I_o \exp(-t_f/\tau)$$

Then,

$$(2T - T^2) = (I_o^2 - I_o^2 \exp(-2t_f/\tau)) / I_o^2$$

or,

$$(2T - T^2) = 1 - \exp(-2t_f/\tau)$$

Substituting into equation (2), we conclude

$$U = (I_o V_o t_f (2T - T^2)) / (2 \ln(1/1-T))$$

APPENDIX C: THRESHOLD DATA FROM INDIVIDUAL DOGS

Tables 10A-C list the initial transchest defibrillation values for the controls. Tables 11A-C list the initial transchest defibrillation values for the amiodarone treated animals. Tables 12A-D list the follow-up transchest thresholds for the controls. Tables 13A-D list the follow-up transchest thresholds for the amiodarone treated animals. Tables 14A-E list the direct defibrillation thresholds and the chest measurements for the controls. Tables 15A-E list the direct defibrillation thresholds and chest measurements for the amiodarone treated animals.

Table 10A. Initial transchest defibrillation thresholds (controls)

Dog Number	M/F	Wt. (Kg)	Total Shocks	Leading Voltage (Volts)	Trailing Voltage (Volts)	Leading Current (Amps)	Trailing Current (Amps)
5712	M	18	11	1180	520	19.00	8.50
5733	M	12	6	780	340	10.20	4.40
5762	F	13	7	680	280	7.80	3.20
5774	M	20	10	800	360	10.40	4.40
5771	F	22	3	880	380	12.60	5.40
5772	M	15	5	800	340	9.40	4.20
5802	F	17	6	640	280	11.20	4.80
5780	F	20	12	680	300	11.20	4.80
6031	F	19	8	820	360	12.40	5.60
6041	F	16	10	760	320	12.80	5.60
N =		10	10	10	10	10	10
Average =		17	8	802	348	11.70	5.09
St. Dev. =		3	3	152	69	3.00	1.40
% C. V. =		18	37	19	20	26	28

Table 10B. Initial transchest defibrillation thresholds (controls)

Dog Number	Pulse Width (msec)	Tilt (%)	Leading Edge Impedance (Ohms)	Trailing Edge Impedance (Ohms)	Pulse Energy (Joules)
5712	3.70	55	62	61	41
5733	4.50	57	76	77	17
5762	5.00	59	87	88	12
5774	4.40	58	77	82	17
5771	4.00	57	70	70	21
5772	4.50	55	85	81	17
5802	3.40	57	57	58	12
5780	3.80	57	61	63	14
6031	3.80	55	66	64	19
6041	3.70	56	59	57	18
N =	10	10	10	10	10
Average =	4.08	57	70	70	19
St. Dev. =	.50	1	11	11	8
% C. V. =	12	2	15	16	44

Table 10C. Initial transchest defibrillation thresholds normalized on a body weight basis (controls)

Dog Number	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (Amp/Kg)	Mean Current (Amp/Kg)	Pulse Energy (J/Kg)
5712	64.90	44.30	1.05	.72	2.27
5733	63.56	43.18	.83	.56	1.41
5762	51.59	34.20	.59	.39	.94
5774	40.00	27.55	.52	.35	.87
5771	39.51	26.73	.57	.38	.96
5772	51.76	34.79	.61	.42	1.09
5802	38.05	25.89	.67	.45	.70
5780	33.24	22.70	.55	.37	.68
6031	44.00	29.98	.67	.46	1.04
6041	47.77	31.97	.80	.55	1.11
N =	10	10	10	10	10
Average =	47.44	32.13	.68	.46	1.11
St. Dev. =	10.65	7.18	.16	.11	.46
% C. V. =	22	22	24	25	42

Table 11A. Initial transchest defibrillation thresholds (amiodarone treated dogs)

Dog number	M/F	Wt. (Kg)	Total shocks	Leading Voltage (Volts)	Trailing Voltage (Volts)	Leading Current (Amps)	Trailing Current (Amps)
5830	M	17	10	552	248	9.60	4.20
5797	F	18	9	640	280	8.80	4.00
5834	M	20	13	920	400	16.00	7.00
5835	M	15	11	512	216	7.80	3.40
5773	F	18	7	780	340	11.60	5.00
5954	F	15	4	760	340	12.60	5.60
5953	F	15	4	700	300	9.20	4.20
5878	F	17	4	760	340	9.60	4.40
N =		8	8	8	8	8	8
Average =		17	8	703	308	10.65	4.73
St. Dev. =		2	3	132	59	2.65	1.13
% C. V. =		12	38	19	19	25	24

Table 11B. Initial transchest defibrillation thresholds (amiodarone treated dogs)

Dog Number	Pulse width (msec)	Tilt (%)	Leading Edge Impedance (Ohms)	Trailing Edge Impedance (Ohms)	Pulse Energy (Joules)
5830	3.40	56	58	59	9
5797	4.10	55	73	70	12
5834	3.60	56	58	57	26
5835	3.90	56	66	64	8
5773	3.90	57	67	68	17
5954	3.60	56	60	61	17
5953	4.40	54	76	71	14
5878	4.40	54	79	77	16
N =	8	8	8	8	8
Average =	3.91	56	67	66	15
St. Dev. =	.37	1	8	7	6
% C. V. =	10	2	12	11	39

Table 11C. Initial transchest defibrillation thresholds normalized on a body weight basis (amiodarone treated dogs)

Dog Number	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (Amp/Kg)	Mean Current (Amp/Kg)	Energy (J/Kg)
5830	32.82	22.59	.57	.39	.52
5797	36.10	24.57	.50	.34	.66
5834	44.98	30.52	.78	.53	1.27
5835	34.13	22.86	.52	.35	.51
5773	44.00	29.89	.65	.44	.96
5954	52.25	35.90	.87	.59	1.17
5953	46.67	31.47	.61	.43	.95
5878	45.19	31.05	.57	.40	.97
N =	8	8	8	8	8
Average =	42.02	28.61	.63	.43	.88
St. Dev. =	6.87	4.75	.13	.09	.29
% C. V. =	16	17	20	20	33

Table 12A. Follow-up transchest defibrillation thresholds (controls)

Dog Number	M/F	Wt. (Kg)	Total Shocks	Leading Voltage (Volts)	Trailing Voltage (Volts)	Leading Current (Amps)	Trailing Current (Amps)
5712	M	20	18	1160	540	24.00	10.50
5733	M	12	17	1060	480	17.50	8.00
5762	F	14	4	660	280	8.80	3.80
5774	M	19	6	840	380	10.40	4.60
5771	F	22	7	840	360	11.80	5.00
5772	M	15	9	920	400	15.40	6.80
5802	F	17	8	660	280	10.40	4.40
5780	F	22	14	1120	500	15.50	7.00
6031	F	18	9	940	420	15.50	6.50
6041	F	16	11	800	340	13.80	6.00
N =		10	10	10	10	10	10
Average =		18	10	900	398	14.31	6.26
St. Dev. =		3	5	175	89	4.42	2.00
% C. V. =		19	45	19	22	31	32

Table 12B. Follow-up transchest defibrillation thresholds (controls)

Dog Number	Pulse Width (msec)	Tilt (%)	Leading Edge Impedance (Ohms)	Trailing Edge Impedance (Ohms)	Pulse Energy (Joule)
5712	3.00	56	48	51	41
5733	3.60	54	61	60	34
5762	4.40	57	75	74	12
5774	4.60	56	81	83	20
5771	4.20	58	71	72	20
5772	3.50	56	60	59	24
5802	3.90	58	63	64	13
5780	4.30	55	72	71	37
6031	3.60	58	61	65	25
6041	3.50	57	58	57	19
N =	10	10	10	10	10
Average =	3.86	56	65	65	24
St. Dev. =	.50	1	10	9	10
% C. V. =	13	2	15	14	40

Table 12C. Follow-up body weight normalized transchest values (controls)

Dog Number	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (Amp/Kg)	Mean Current (Amp/Kg)	Pulse Energy (J/Kg)
5712	58.00	40.54	1.20	.82	2.04
5733	86.37	59.65	1.43	.99	2.75
5762	48.40	32.50	.65	.44	.91
5774	44.00	30.38	.54	.37	1.04
5771	37.71	25.43	.53	.36	.89
5772	59.53	40.40	1.00	.68	1.58
5802	38.21	25.66	.60	.40	.74
5780	50.29	34.52	.70	.48	1.68
6031	51.70	35.50	.85	.57	1.37
6041	50.29	33.79	.87	.59	1.18
N =	10	10	10	10	10
Average =	52.45	35.84	.84	.57	1.42
St. Dev. =	13.94	9.83	.30	.21	.62
% C. V. =	27	27	36	36	44

Table 12D. Follow-up heart weight normalized transchest values (controls)

Dog Number	Ventricle Mass (Grams)	Peak Voltage (V/g)	Mean Voltage (V/g)	Peak Current (A/100g)	Mean Current (A/100g)	Pulse Energy (J/100g)
5712	108	10.71	7.49	22.16	15.08	37.71
5733	92	11.56	7.98	19.08	13.24	36.80
5762	90	7.31	4.91	9.75	6.59	13.71
5774	154	5.44	3.76	6.74	4.61	12.84
5771	160	5.25	3.54	7.38	4.95	12.43
5772	130	7.06	4.79	11.81	8.07	18.72
5802	113	5.82	3.91	9.17	6.15	11.27
5780	150	7.49	5.14	10.37	7.15	25.00
6031	134	7.00	4.81	11.54	7.71	18.52
6041	131	6.11	4.10	10.53	7.15	14.36
N =	10	10	10	10	10	10
Average =	126	7.37	5.04	11.85	8.07	20.14
St. Dev. =	25	2.14	1.52	4.95	3.42	9.89
% C. V. =	20	29	30	42	42	49

Table 13A. Follow-up transchest defibrillation thresholds (amiodarone treated dogs)

Dog Number	M/F	Wt. (Kg)	Total Shocks	Leading Voltage (Volts)	Trailing Voltage (Volts)	Leading Current (Amps)	Trailing Current (Amps)
5830	M	19	6	740	340	12.00	5.20
5797	F	18	12	560	260	7.40	3.20
5834	M	22	10	940	420	14.20	6.00
5835	M	15	10	760	340	11.60	5.00
5773	F	20	8	940	420	13.60	6.00
5954	F	15	11	780	340	11.00	5.00
5953	F	15	9	880	380	10.40	4.60
5878	F	18	4	760	320	9.60	4.20
N =		8	8	8	8	8	8
Average =		18	9	795	353	11.23	4.90
St. Dev. =		3	3	125	53	2.18	.93
% C. V. =		14	30	16	15	19	19

Table 13B. Follow-up transchest defibrillation thresholds (amiodarone treated dogs)

Dog Number	Pulse Width (msec)	Tilt (%)	Leading Edge Impedance (Ohms)	Trailing Edge Impedance (Ohms)	Pulse Energy (Joule)
5830	3.70	57	62	65	16
5797	4.50	57	76	81	9
5834	3.90	58	66	70	25
5835	3.80	57	66	68	16
5773	4.10	56	69	70	26
5954	4.00	55	71	68	17
5953	4.80	56	85	83	22
5878	4.60	56	79	76	16
N =	8	8	8	8	8
Average =	4.18	56	72	73	18
St. Dev. =	.41	1	8	6	5
% C. V. =	10	2	11	9	30

Table 13C. Follow-up body weight normalized transchest defibrillation values (amiodarone treated dogs)

Dog Number	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (Amp/Kg)	Mean Current (Amp/Kg)	Pulse Energy (J/Kg)
5830	38.76	26.94	.63	.43	.84
5797	31.59	22.06	.42	.28	.51
5834	43.08	29.58	.65	.44	1.14
5835	50.67	34.81	.77	.52	1.08
5773	48.09	33.02	.70	.48	1.32
5954	50.47	34.29	.71	.49	1.12
5953	60.50	40.93	.72	.49	1.49
5878	41.80	27.98	.53	.36	.90
N =	8	8	8	8	8
Average =	45.62	31.20	.64	.44	1.05
St. Dev. =	8.79	5.80	.12	.08	.30
% C. V. =	19	19	18	18	29

Table 13D. Follow-up heart weight normalized transchest defibrillation values (amiodarone treated dogs)

Dog Number	Ventricle Mass (Grams)	Peak Voltage (V/g)	Mean Voltage (V/g)	Peak Current (A/100g)	Mean Current (A/100g)	Pulse Energy (J/100g)
5830	112	6.62	4.60	10.73	7.27	14.27
5797	133	4.22	2.94	5.57	3.77	6.81
5834	138	6.81	4.68	10.29	6.90	17.99
5835	112	6.82	4.68	10.40	7.03	14.53
5773	130	7.24	4.97	10.48	7.16	19.87
5954	124	6.30	4.28	8.89	6.15	13.95
5953	111	7.91	5.35	9.35	6.39	19.48
5878	133	5.73	3.84	7.24	4.93	12.38
N =	8	8	8	8	8	8
Average =	124	6.46	4.42	9.12	6.20	14.91
St. Dev. =	11	1.11	.74	1.84	1.24	4.28
% C. V. =	9	17	17	20	20	29

Table 14A. Direct defibrillation thresholds (controls)

Dog Number	M/F	Wt. (Kg)	Total Shocks	Leading Voltage (Volts)	Trailing Voltage (Volts)	Leading Current (Amps)	Trailing Current (Amps)
5733	M	12	10	376	160	4.40	1.90
5762	F	14	8	272	112	3.00	1.20
5774	M	19	17	392	160	5.10	2.20
5771	F	22	5	352	144	4.80	2.00
5802	F	17	14	256	104	3.40	1.40
5780	F	22	4	352	144	5.20	2.20
5782	M	19	12	328	136	4.40	1.80
6041	F	18	7	320	128	4.20	1.70
N	=	8	8	8	8	8	8
Average	=	18	10	331	136	4.31	1.80
St. Dev.	=	3	4	48	21	.78	.36
% C. V.	=	19	44	14	15	18	20

Table 14B. Direct defibrillation thresholds (controls)

Dog Number	Pulse Width (msec)	Tilt (%)	Leading Edge Impedance (Ohms)	Trailing Edge Impedance (Ohms)	Pulse Energy (Joules)
5733	5.00	57	85	84	3.96
5762	5.30	60	91	93	2.10
5774	4.60	57	77	73	4.37
5771	4.50	58	73	72	3.52
5802	4.60	59	75	74	1.87
5780	4.20	58	68	65	3.52
5782	4.50	59	75	76	3.04
6041	4.80	60	76	75	3.06
N =	8	8	8	8	8
Average =	4.69	58	78	77	3.18
St. Dev. =	.34	1	7	9	0.86
% C. V. =	7	2	9	11	29

Table 14C. Direct defibrillation, body weight normalized values (controls)

Dog Number	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (Amp/Kg)	Mean Current (Amp/Kg)	Pulse Energy (J/Kg)
5733	30.64	20.60	.36	.24	.33
5762	19.95	13.22	.22	.14	.15
5774	20.53	13.56	.27	.18	.23
5771	15.80	10.45	.22	.14	.16
5802	14.82	9.77	.20	.13	.11
5780	15.80	10.45	.23	.16	.16
5782	17.60	11.70	.24	.16	.16
6041	18.05	11.82	.24	.16	.17
N =	8	8	8	8	8
Average =	19.15	12.70	.25	.16	.18
St. Dev. =	5.06	3.46	.05	.03	.07
% C. V. =	26	27	20	21	37

Table 14D. Direct defibrillation thresholds, heart weight normalized values (controls)

Dog Number	Ventricle Mass (Grams)	Peak Voltage (V/gr.)	Mean Voltage (V/gr.)	Peak Current (A/100g)	Mean Current (A/100g)	Pulse Energy (J/100g)
5712[a]	108					
5733	92	4.10	2.76	4.80	3.25	4.37
5762	90	3.01	2.00	3.32	2.18	2.20
5774	154	2.54	1.68	3.31	2.24	2.88
5771	160	2.20	1.45	3.00	2.00	2.24
5772[a]	130					
5802	113	2.26	1.49	3.00	1.99	1.65
5780	150	2.35	1.56	3.48	2.33	2.45
6031[a]	134					
6041	131	2.44	1.60	3.21	2.11	2.28
N =	10	7	7	7	7	7
Average =	127	2.70	1.79	3.44	2.30	2.58
St. Dev. =	25	.67	.46	.62	.44	.87
% C. V. =	20	25	26	18	19	34

[a]Died during open chest surgery, no direct threshold.

Table 14E. Chest parameters (controls)

Dog Number	Chest Breadth (cm)	Chest Wall Thickness (cm)
5762	11.50	1.00
5774	10.60	1.60
5771	11.60	1.50
5802	9.50	.90
5780	13.40	1.40
6031	11.60	1.20
6041	12.10	1.30
N =	7	7
Average =	11.47	1.27
St. Dev. =	1.21	.26
% C. V. =	11	20

Table 15A. Direct defibrillation thresholds (amiodarone treated dogs)

Dog Number	M/F	Wt. (Kg)	Total Shocks	Leading Voltage (Volts)	Trailing Voltage (Volts)	Leading Current (Amps)	Trailing Current (Amps)
5830	M	19	7	360	152	4.40	1.80
5797	F	18	13	212	84	3.00	1.20
5834	M	22	6	360	152	4.20	1.70
5835	M	15	8	232	96	2.80	1.20
5773	F	20	9	360	152	4.50	1.80
5954	F	15	3	360	160	4.20	1.80
5953	F	15	7	232	96	2.90	1.20
5878	F	18	9	224	96	3.30	1.40
N =		8	8	8	8	8	8
Average =		18	8	293	124	3.66	1.51
St. Dev. =		3	3	72	33	.73	.29
% C. V. =		14	37	25	27	20	19

Table 15B. Direct defibrillation thresholds (amiodarone treated dogs)

Dog Number	Pulse Width (msec)	Tilt (%)	Leading Edge Impedance (Ohms)	Trailing Edge Impedance (Ohms)	Pulse Energy (Joules)
5830	4.90	59	82	84	3.61
5797	4.70	60	71	70	1.44
5834	5.20	60	86	89	3.74
5835	5.00	57	83	80	1.50
5773	4.80	60	80	84	3.60
5954	4.70	57	86	89	3.30
5953	4.80	59	80	80	1.50
5878	4.30	58	68	69	1.44
N =	8	8	8	8	8
Average =	4.80	59	79	81	2.52
St. Dev. =	.26	1	7	8	1.13
% C. V. =	5	2	8	10	44

Table 15C. Direct defibrillation values, normalized by body weight (amiodarone treated dogs)

Dog Number	Peak Voltage (V/Kg)	Mean Voltage (V/Kg)	Peak Current (Amp/Kg)	Mean Current (Amp/Kg)	Pulse Energy (J/Kg)
5830	18.86	12.64	.23	.15	.19
5797	11.96	7.80	.17	.11	.08
5834	16.50	11.06	.19	.13	.17
5835	15.47	10.28	.19	.13	.10
5773	18.42	12.34	.23	.15	.18
5954	23.29	15.96	.27	.18	.22
5953	15.95	10.60	.20	.13	.10
5878	12.32	8.31	.18	.12	.08
N =	8	8	8	8	8
Average =	16.60	11.12	.21	.14	.14
St. Dev. =	3.68	2.59	.03	.02	.06
% C. V. =	22	23	16	17	39

Table 15D. Direct defibrillation, heart weight normalized values (amiodarone treated dogs)

Dog Number	Ventricle Mass (Grams)	Peak Voltage (V/gr.)	Mean Voltage (V/gr.)	Peak Current (A/100g)	Mean Current (A/100g)	Pulse Energy (J/100g)
5830	112	3.22	2.16	3.94	2.60	3.23
5797	133	1.60	1.04	2.26	1.48	1.03
5834	138	2.61	1.75	3.04	2.00	2.63
5835	112	2.08	1.38	2.51	1.69	1.40
5773	130	2.77	1.86	3.47	2.27	2.75
5954	124	2.91	1.99	3.39	2.29	2.77
5953	111	2.09	1.39	2.61	1.73	1.36
5878	133	1.69	1.14	2.49	1.67	1.15
N =	8	8	8	8	8	8
Average =	124	2.37	1.59	2.96	1.97	2.04
St. Dev. =	11	.59	.41	.59	.39	.88
% C. V. =	9	25	26	20	20	43

Table 15E. Chest parameters (amiodarone treated dogs)

Dog Number	Chest Breadth (cm)	Chest Wall Thickness (cm)
5830	11.00	1.20
5797	8.90	-[a]
5834	12.10	1.90
5835	9.40	1.60
5773	11.00	-[a]
5954	9.10	1.30
5953	9.70	1.10
5878	11.40	1.80
N =	8	6
Average =	10.33	1.48
St. Dev. =	1.19	.33
% C. V. =	12	22

[a]No measurement taken.

APPENDIX D: METHOD USED FOR HPLC

Method file name: B:M9DLY
Default Sample Name: Heart Tissue
Operator: JEG Date: 02-07-1986

ACQUISITION PARAMETERS

SINGLE OR DUAL CHANNEL (1 OR 2)	1.00
RUN TIME (minutes)	9.00
END TIME FOR PLOTS (default=RUN TIME)	9.00
SOLVENT DELAY TIME (minutes)	0.00
PEAK DETECTION THRESHOLD (microv/sec)	0.05
MINIMUM PEAK WIDTH (seconds)	10.00
TIME FOR ONE SAMPLE (seconds)	1.00
NUMBER OF REAL TIME CRT PAGES TO PLOT (0 TO 99)	1.00
REAL TIME PLOT FULL SCALE FOR CH.0 (millivolts)	100.00
REAL TIME FULL SCALE FOR CH.1 (millivolts)	200.00
HARD COPY REAL TIME PLOT	NO
AUTO ZERO REAL TIME PLOT	NO
RECORD AREA TABLES ON DISK	YES
RECORD RAW DATA	YES
NUMBER OF CRT PAGES FOR REPLOT (1 TO 99)	1.00
VERTICAL SCALE FACTOR FOR REPLOT (units of largest peak)	1.00
OFFSET FOR THE REPLOT (millivolts)	0.00
PUT NAMES ON REPLOT?	NO
PRINT AREA PERCENT REPORT	YES
PRINT EXTERNAL STANDARD REPORT	NO
PRINT INTERNAL STANDARD REPORT	NO
FINAL REPORT AREA REJECT (microvolt-sec)	0.00
LINK TO USER PROGRAM	NO
FORCE DROP LINE INTEGRATION	YES
FORCE COMMON BASE LINE	YES
FULL SCALE RANGE FOR A.D.C. (3=1VOLT, 1=2VOLT, 0=10VOLT)	3.00
AREA REJECT FOR REFERENCE PEAKS?	1000.00
% RET TIME WINDOW FOR REFERENCE PEAKS	0.00
RET TIME WINDOW IN SECONDS FOR REF.PEAKS	0.00
AREA OR PEAK HEIGHT QUANTITATION (0 OR 1)	0.00
PRINT GROUP REPORT	NO
NUMBER OF CALIBRATION LEVELS (1 TO 6)	4.00

FIT TYPE FOR MULTILEVEL CALIBRATION (0=PT-TO-PT, 1=LINEAR)	1.00
LIST COMPONENTS NOT FOUND IN SAMPLE?	YES
INCLUDE UNKNOWN PEAKS IN REPORTS?	YES
UPDATE RESPONSE FACTORS WITH REPLACEMENT (0) OR AVERAGE (1)	0.00
DEFAULT DILUTION FACTRO	1.00
DEFAULT SAMPLE AMOUNT	20.00
DEFAULT AMOUNT OF INTERNAL STANDARD	1.00
PRINT GPC MW DISTRIBUTION	0.00
PRINT SIMULATED DISTILLATION REPORT	0.00