1968

Myocardial Water and Electrolyte Changes in Ventricular Fibrillation with Cardiac Massage Followed by Electrical Defibrillation

Alan D. Kaplan
Loyola University Chicago

MYOCARDIAL WATER AND ELECTROLYTE CHANGES IN VENTRICULAR FIBRILLATION WITH CARDIAC MASSAGE FOLLOWED BY ELECTRICAL DEFIBRILLATION

by

Alan D. Kaplan

A Thesis Submitted to the Faculty of the Graduate School of Loyola University in Partial Fulfillment of the Requirements for the Degree of Master of Science

June

1968

ACKNOWLEDGMENTS

I wish to express my most sincere gratitude to Dr. Vincent V. Glaviano, my advisor, for his many hours of help and discussion which made this study possible. His encouragement and enthusiasm were instrumental in helping me through the more problematic areas of the project. Special mention must be made of Dr. Walter C. Randall, Chairman, Department of Physiology, for inspiring me to participate in the combined Medical Doctor-Masters of Science program, and for his thoughful and constructive criticism of the thesis. I should also like to thank Dr. John R. Tobin for his participation on the thesis committee and his helpful suggestions in preparing the final thesis.

Finally, I wish to express my appreciation for the financial support granted by the Division of General Medical Sciences of the National Institutes of Health.

BIOGRAPHY

Alan D. Kaplan was born on May 31, 1943, in Chicago, Illinois.

He was graduated from grade school in 1957 and from Evanston Township High School in 1961. He attended Loyola University in Chicago, Illinois, for three years of study in the field of premedical arts and sciences.

Mr. Kaplan was accepted as a medical student at Loyola University, Stritch School of Medicine, in September, 1965. During the summer of that year he entered the National Institutes of Health combined Medical Student-Master of Science Program in the Department of Physiology, under the supervision of Dr. Vincent V. Glaviano.

In April, 1968, he presented a paper on electrolytes in the canine myocardium following electrical defibrillation, at the Student American Medical Association - University of Texas Research Forum, in Galveston, Texas.

List of Publications:

1. A.D. Kaplan and V.V. Glaviano, Myocardial Electrolyte Changes Before and During Ventricular Fibrillation and Following Electrical Defibrillation, Texas Reports of Biology and Medicine, Summer, 1968.

TABLE OF CONTENTS

LIST OF TABLES

Tables Page

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Clinically it is observed that patients having ventricular fibrillation and who are subsequently defibrillated electrically, frequently revert to this arrhythmia within a few minutes following defibrillation. The material presented in this thesis is intended to draw attention to the unexplored area of electrolyte and water metabolism of the heart in the period immediately following the correction of ventricular fibrillation by electrical counter-shock. More specifically, the investigation was conducted with a three-fold purpose:

1) To determine if delivery of a powerful depolarizing current to the myocardium results in an alteration of myocardial electrolytes and water content.

2) To investigate the possibility that electrical defibrillation may in itself induce a change in cardiac muscle electrolytes which causes the heart to become more susceptible to re-fibrillation.

3) To evaluate the effects of cardiac massage on myocardial electrolytes during ventricular fibrillation.

CHAPTER II

REVIEW OF THE LITERATURE

A. VENTRICULAR FIBRILLATION. The electrical induction of a cardiac arrhythmia that leads to the demise of the animal within three to five minutes was first noted by Ludwig and Hoffa in 1849. Twenty-five years later, Vulpian gave this arrhythmia the name of "Movement Fibrillaire". Although this phenomena was frequently reported in laboratory animals, little definitive work was done in the area until 1940, when Wiggers described the fibrillation threshold, and the course of fibrillation in the canine heart (10). Wiggers described ventricular fibrillation as an incoordinate type of muscular contraction that despite a high metabolic rate rendered the heart incapable of doing work. Through the use of cinematographic and electrocardiographic techniques he observed that the incoordinated beat first involves comparatively large sections of myocardium, which progressively multiply and decrease in size. Four general stages were described:

First, the "undulatory stage", lasting 1 to 2 seconds where there are 3 to 6 undulating contractions, having the characteristics of premature systoles. According to Wiggers, only the first beat is actually a premature

ventricular contraction, the other 2-6 being caused by reentry of the first beat.

The second stage lasts 15 to 40 seconds and is termed the "convulsive uncoordination". It is characterized by more frequent waves of contraction which sweep over smaller sections of the ventricles.

The third stage was designated as "tremulous incoordination". It consisted of increasing fragmentation of the ventricular surface, resulting from smaller and smaller independently contracting areas. During this phase the electrical activity observed on the electrocardiogram was noted to increase. The final stage, "atonic fibrillation", was theorized to result from the increasing anoxia leading to a depression of contractile force, slow conduction and eventually regional blocks with complete failure of contractility (39,40).

More recently, work has been directed toward exploring the electrolyte and metabolic changes in oxygen, glucose, and pyruvates during ventricular fibrillation. Based on coronary sinus catheterization studies, Bing, Pedersen and Siegel (1956) showed that the fibrillating heart loses potassium while it takes up sodium (28). Gregg et al in 1954 also noted similar changes, although he was primarily concerned with myocardial oxygen uptake (11). Both groups of investigators noted an increase in lactic acid with decreased utilization of pyruvate and glucose. Bing et al accounted for these changes on the basis of a "disruption" of the co-carboxylase system, the results would then involve dephosphorylation secondary to the anerobic state. He pointed out that the enzyme, diphospho-thiamine is indispensable

for the oxidative decarboxylation of pyruvate (12,28).

Gregg also studied the effects of ventricular fibrillation on myocardial ATP production. He noted a decrease in the coronary sinus level of ATP. On the other hand, when he perfused the heart and thus maintained myocardial oxygenation, he was able to prevent the loss of potassium, increased production of lactic acid, decreased utilization of glucose, pyruvate and ATP. He found this would hold true, even if fibrillation and perfusion were maintained for periods up to forty minutes. In hearts that were not perfused for thirty minutes, he found that reinstitution of coronary artery perfusion resulted in restoration of rapid fibrillatory movements, although he did not report successful defibrillation in these preparations (11). This apparent improvement in the type of fibrillation (from stage IV to stage II fibrillation as described by Wiggers), was suggested to be due to re-synthesis of high energy phosphate. Senning (1952) and Jwoenelle (1945) in a clinical report along these same lines wrote that ventricular fibrillation was not damaging to the heart per se, provided there was adequate myocardial oxygenation (18,32). Bing, et al in 1959, considered ventricular fibrillation as it effected the transmembrane electrical potentials. They found that during early fibrillation of the ventricles, electrical activity was only slightly irregular with little change in amplitude. As the period of fibrillation was lengthened, an increasing degree of irregularity was present with the occurrence of action potentials of small amplitude (15,16,17).

While those investigators considered so far utilized electrical stimulation to initiate ventricular fibrillation, numerous other studies were conducted in altering the ion concentration of myocardial muscle as the

etiologic agent. It is interesting to consider this approach since ventricular fibrillation induced by electrical means appears to result in abberations of the same ionic constituents (35). It is generally accepted that there is a much greater concentration of potassium within the cardiac muscle cell than there is outside the cell, this being the basis of the potential difference existing across the membrane. Burn (1957) considered the effects of decreasing potassium outside the cell. He postulated that decreasing potassium extracellularly, to approximately 1/4 its normal concentration, would lead to a breakdown of the insulating properties of the membrane to maintain a difference of potassium on both sides of the membrane, eventuating in ventricular fibrillation. However, since ventricular fibrillation will not occur when extracellular potassium is decreased in the face of a concomitant decrease in calcium, it should then be considered that ventricular fibrillation may be related to the Ca^{++}/K^{+} ratio, rather than uniquely to the potassium drop (3).

Hodgkin and Keynes (1954) first introduced the concept that the sodium pump is depressed by low extracellular potassium (14). Burn (1957) pointed out that although this work was done on the nerve from the Sepia, it may also be important in the canine myocardium, i.e. the role of decreased extracellular potassium in the genesis of ventricular fibrillation may involve its action on the intracellular sodium pump (3).

B. DEFIBRILLATION. Until 1933, ventricular fibrillation was considered to be a condition which would almost without exception result in the demise of the patient. In that year Hooker et al (42), developing the work of Prevost and Battelli (1900), demonstrated that a dog's ventricles could successfully be defibrillated and a coordinated heart beat restored

through the application of a 60-cycle alternating current shock of 1 ampere for 0.1-5 seconds.

In 1934 Ferris described the same procedure in close-chest animals, using higher currents (9).

Six years later Carl Wiggers published several papers on the methods of electrical defibrillation (39,42,43). He pointed out that if a period of time elapsed between the onset of fibrillation and the attempt to electrically defibrillate the heart, the difficulty encountered in recovery of the heart was due to incapacity of the myocardium to resume vigorous beating and not the technique of defibrillation. This led to the discovery that survival was enhanced by oxygenation, and he thereafter advocated the use of cardiac massage to maintain oxygen delivery to the heart and periphery.

With regard to actual defibrillation, Wiggers found that serial defibrillation was more efficacious than a single shock. He explained that three to seven brief shocks led to progressive merging of smaller fibrillating areas into larger areas which were contracting out of phase with each other. Then, a final shock stopped all electrical activity and allowed the pacemaker to initiate a coordinated beat (42).

Further work was done by Yarbough (1964) on alternating versus direct current countershocks, and between 1960 and 1965 numerous papers were published on the physical damage resulting from AC and DC shocks. In general, the contention of all these authors was that electrical defibrillation could be achieved with either AC or DC currents, but that the latter caused less of a tissue burn (19,22,24,36,45).

The major alterations noted after defibrillation by Turner and Towers (1964) involved Serum Glutamic Oxalacetic Transaminase elevation and T-wave inversion (37). Although the most popular method for defibrillation is currently with an electrical discharge, in the past, chemical defibrillation was also frequently attempted.

Wiggers (1940) utilized potassium salts on a number of fibrillating dog hearts and came to the conclusion that they do not modify the stages of the fibrillatory process, but that they merely hasten it; the end result being asystole. This asystole results from a rapid depression of conduction of the heart.

Calcium was frequently employed following defibrillation with potassium, in an attempt to reactivate the heart. Wiggers pointed out that when calcium was used, it frequently would generate many pacemakers, in addition to causing hypercalcemia (41).

Procaine (43) was advocated as an adjunct to both chemical and electrical defibrillation, but it was felt by most investigators that its action may be too depressing to be used routinely with either type of defibrillation (43).

In 1965, Hechrein published a paper on the effects of defibrillation on electrolyte levels in the myocardium. He achieved fibrillation with Aconitine and defibrillation with Ajemalin, a reserpine-like compound. His findings revealed that intracellular potassium decreased approximately 15%during fibrillation, and following defibrillation potassium was then restored to normal levels. Intracellular sodium was found to decrease very slightly during fibrillation and then fell markedly during defibrillation. He did not observe a significant alteration in water content during the entire procedure (13).

CHAPTER II

MATERIALS AND METHODS

A. ANESTHESIA AND SURGERY. Twenty-five male mongrel dogs, weighing approximately 14 Kg were utilized in this study. All of these animals had been stabilized as to diet and hydration for a period of one week prior to their use. The dogs were divided into three groups consisting of Group I, 8 control dogs, Group II, 8 dogs with ventricular fibrillation, and Group III, 9 dogs with successful defibrillation. The following surgical procedures were performed on all animals: The trachea was cannulated from a midline neck incision, and the left common carotid artery was isolated (26). A No. 8 United States Catheter and Instruments x-ray catheter was inserted in this vessel and passed through the aortic valve into the left ventricle for monitoring left intraventricular pressure. The left femoral artery was isolated and catheterized with a 7-inch PE 190 Intramedic polyethylene catheter for blood pressure recording. A catheter was also placed in the right femoral vein for injection of heparin (sodium salt). A left lateral thoracotomy involving ribs 2 through 7 was performed and the ribs retracted. The pericardium was incised and a pericardial cradle was constructed to give maximum exposure of the heart.

The left intraventricular catheter and the blood pressure catheter were connected to Sanborn No. 267AC pressure transducers. The standard bipolar limb leads for electrocardiographic monitoring were also connected (8). A Sanborn No. 4560 polygraph was used for continuous recording, while visual monitoring was accomplished on a Sonborn No. 760 oscilloscope. Following the above procedure, Heparin (5 mg/Kg) was administered and the animal was allowed to stabilize for twenty minutes. As the procedures followed from this point on were somewhat different, they are described separately below.

Group I -- a 10cc sample of homogeneous venous blood was taken from the right ventricle by direct puncture. Approximately two grams of cardiac muscle were excised from the lateral border of the left ventricle. The surface blood was rinsed away with triple distilled water and the tissue was blotted and trimmed of fat. The sample was then divided, half being frozen in liquid N_2 for electrolyte analysis and the remainder was dried and extracted with ether for water and fat content.

Group II -- twenty minutes following the administration of Heparin, the heart was fibrillated with a 4-volt, 80-cycle per second sine wave pulse, applied to the apex of the heart for 2-3 seconds. Fibrillation was allowed to proceed for a total period of 30 seconds, during which time cardiac massage was performed to maintain coronary and systemic circulation. After an initial 25 seconds of fibrillation and massage a blood sample was taken from the right ventricle and during the remaining 5 seconds of fibrillation a sample of cardiac muscle was taken from the left ventricle.

Group III -- the same procedure was followed as in Group II, except

that blood and tissue samples were not taken after 30 seconds of fibrillation. Instead, electrical defibrillation was achieved with a Burdick DC/150 defibrillator, having an output of 10 watt-seconds (22). Following the restoration of the heart beat, as varified by the electrocardiogram the preparation was allowed to recover for 90 seconds, and at this time blood and tissue samples were obtained.

B. CHEMICAL DETERMINATIONS. Samples of plasma and left ventricular myocardium during control, fibrillation, and defibrillation were analyzed in all dogs for K+, Na+ and Cl-. The other half of tissue not placed in liquid N_2 was subjected to determinations of water and fat content.

The frozen sample was carefully weighed and then homogenized for three minutes in a Potter-Elvejhem tissue grinder containing 5 ml of 0.5 N HNO_3. The homogenate was then transferred to a centrifuge tube, and a final dilution of 1:15 was achieved after three rinses of the tissue grinder with 0.5 N HNO_3. The diluted tissue homogenate was then centrifuged for 10 minutes at 1200 g for supernatant fractionation. Aliquots of the supernatant were then taken for the separate determinations of Na+, K+ and Cl- as described in the following schema:

Cl-	K+	Na+
1 ml supernatant titrated directly for chloride determination	1 ml supernatant +2.5 ml of 30 mEq/ 100 ml. lithium sulfate diluted to 25 ml with triple distilled water for potassium determination	3 ml supernatant + 2.5 ml of 30 mEq/ 100 ml lithium sulfate diluted to 25 ml with triple distilled water for sodium determination

Sodium and potassium determinations were made on a Process and Instruments (Model 1B) flame photometer, using Lithium as an internal standard. The use of the internal standard results in greater stability, and as such increases the precision of the measurements. Lithium is introduced so as to always yield the same concentration in every solution being analyzed. The light output from the propane flame of the photometer is received by two optical systems simultaneously. One system is provided with a lithium filter and the other with either a potassium or sodium filter depending on the ion being studied. The two beams are allowed to fall on two separate barrier layer photocells (the Li+ cell and the Na+ - K+ cell). The output of the Li+ cell is then balanced against the output of the Na+(K+) cell using the galvanometer as a null point meter. Thus, any factors causing fluctuation in flame intensity of photocell output other than that due to the concentration of Na+, K+, or Li+ in the flame will affect both photocells equally. Since the parameter being measured is the ratio of the outputs, rather than the direct cell output, these fluctuations tend to balance out. This instrument has a reproducibility of 1.0%, and is linear over the range 0 to 100 microequivalents per 100 cc of solution.

Chloride was measured on a Buchler-Cotlove electrical titrator based on the method of Carr (1951) in which silver ions are liberated from a silver electrode at a known rate, to combine with the chloride ion in the solution. Through comparison with a series of standards and blanks, the Cl- concentration in a test sample can be determined (4).

Electrolyte analysis of plasma samples for Na+, K+ and Cl- were also carried out as indicated on the following page:

Cl-	K+	Na+
0.1 ml plasma titrated directly for chlofide determination	1 ml plasma + 2.5 ml of 30 mEq/100 ml lithium sulfate diluted to 25 ml with triple distilled water for potassium determination	0.1 ml plasma + 2.5 ml of 30 mEq/100 ml lithium sulfate diluted to 25 ml with triple distilled water for sodium determination

Water and fat content of left ventricular myocardium was determined by using the following procedure. The second half of the previously described sample was placed in a clean dry weighing bottle, of known weight. The weighing bottle and sample were then weighed. The sample was then dried to constant weight at 100° C for 48 hours and water content was equated to the weight loss between the wet and dried samples. Percentage fat-free dry weight was measured by reweighing the dried sample after double extraction with diethyl ether according to the method of Lowry and Hastings (1942[23]).

C. MATHEMATICAL ANALYSIS OF DATA. In order that the results of tissue analysis be unaffected by variables which were not being considered in the problem, a stable reference base was required which excluded water, fat, and collagen contents of the tissue. Since cardiac muscle is practically devoid of collagen and since heart muscle was removed acutely and therefore no opportunity for increase in collagen content to occur (as in the chronically injured heart), the "collagen-free" factor was not included as part of the analysis. Thus, as a stable reference, tissue values were described as mEq/100 gm fat-free dry tissue (*FFDT*).

Water distribution was calculated on the assumption that chloride is a marker of the extracellular space. This is supported by the contention

that sodium is largely restricted to the extracellular compartment. As a result, potassium and chloride are distributed between intracellular and interstitial water in such a manner that intracellular chloride concentration closely approximates the concentration of potassium in interstitial water (Robertson and Peyser, 1951[30]). The constancy of the chloride space of the heart during fibrillation with cardiac massage and defibrillation was demonstrated on one dog in which chloride levels in the arterial circulation and coronary sinus blood were measured and found not to change significantly.

Distribution of ions within the extracellular phase, i.e. between plasma water and interstitial water, was based on a Gibbs-Donnan equilibrium. A Donnan factor for monovalent ions of 0.98 for the myocardium was used on the basis of the findings of Drinker et al (1940) based on a protein concentration of 4% in cardiac lymph (5,28).

From the previously stated assumptions, the following relationships are generally accepted for cardiac muscle: (5,11,13,28)

$$[K]_E = (K)_p \times 0.98 \qquad (1)$$

$$[Na]_E = (Na)_p \times 0.98 \qquad (2)$$

$$[Cl]_E = (Cl)_p \times 0.98 \qquad (3)$$

$$(H_2O)_E = \frac{1000\ (Cl)_T - [K]_E\ (H_2O)_T}{[Cl]_E - [K]_E} \qquad (4)$$

$$(H_2O) = (H_2O)_T - (H_2O)_T \qquad (5)$$

$$(K)_I \text{ or } (Na)_I = (K)_T - \frac{(K)_E \times (H_2O)_E}{1000} \qquad (6)$$

$$[K]_I \text{ or } [Na]_I = \frac{1000\ (K)_1 \text{ or } (Na)_1}{(H_2O)I} \qquad (7)$$

CHAPTER III

EXPERIMENTAL RESULTS

A. TOTAL TISSUE CONCENTRATION OF POTASSIUM, SODIUM AND CHLORIDE.

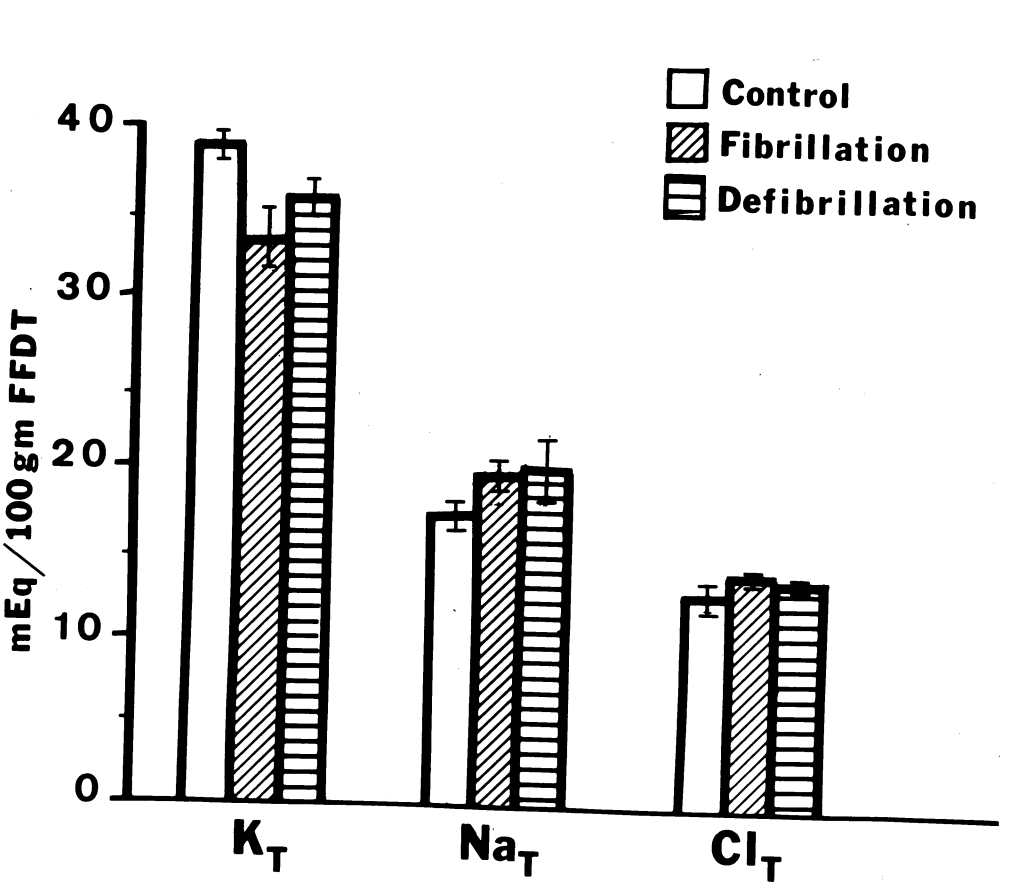
Calculations of intrecellular and extracellular volumes involved the assumption that extracellular K+ closely approximated the concentration of Cl- in the intracellular compartment. As such, these quantities differ by approximately 10% from results reported by Lowry and Hastings (1942). These authors calculated intracellular and extracellular water on the basis of Cl- being restricted purely to the extracellular compartment.

The myocardial concentration of electrolytes in the control dogs are in agreement with those reported by other investigators using fat-free dry myocardium as the reference base (Manery, 1954[25]; Benson et al, 1956[2]; Colman and Glaviano, 1954[5]).

Figure 1 compares the changes observed during control, at the end of 30 seconds of ventricular fibrillation and 90 seconds after defibrillation. During ventricular fibrillation the level of cardiac muscle K+ was observed to drop from an average control level of 39.04 $\pm$.42 mEq/100 gm. FFDT to an average level of 33.42 $\pm$ 1.98 mEq/100 gm FFDT. This was a change of 14.4%

FIGURE 1

Total Tissue Electrolyte Concentrations of Canine Myocardium During Control, Ventricular Fibrillation and Following Electrical Defibrillation



and was significant to a P < 0.02. Ninety seconds after electrical defibrillation potassium was observed to rise to 36.43 ± 1.08 mEq/100 gm FFDT which is still significantly lower than control (P<0.05). The tabulated results are presented in Table I.

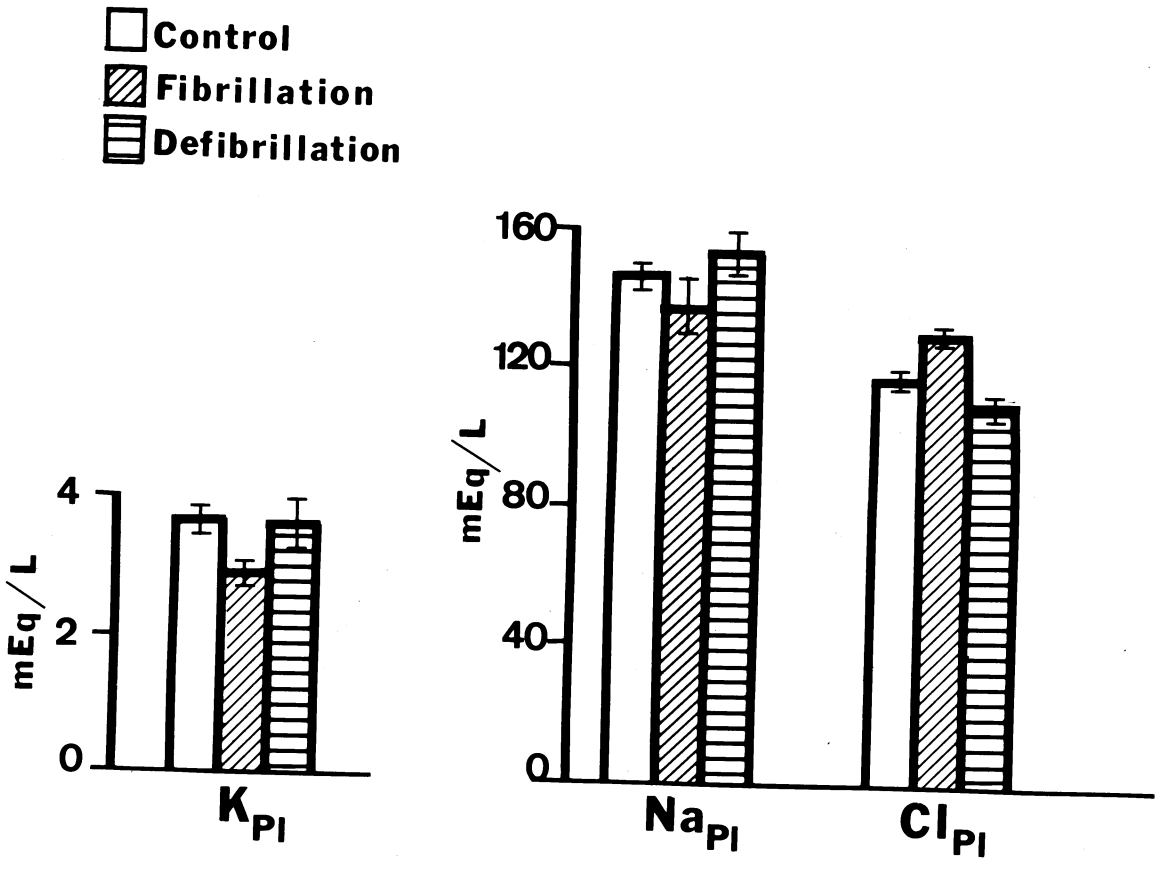
Cardiac muscle sodium was observed to rise during fibrillation from an average control of 17.48 ± 1.06 mEq/100 gm FFDT, a change of approximately 10%. In the post defibrillatory period, sodium was not observed to return toward normal, but continued to rise to 20.97 ± 2.10 mEq/100 gm FFDT, a 20% increase over control. Tabulated results appear in Table II.

Tabulated results for total tissue chloride are given in table III. From the data, chloride was observed to rise slightly from a mean control level of 12.69 ± 0.69 mEq./100 gm. FFDT to 14.02 ± 0.76 mEq./100gm FFDT after 30 seconds of ventricular fibrillation. Following electrical defibrillation, the Cl^- total tissue level decreased to 13.88 ± 0.55 mEq./100 gm FFDT. Although it appeared that the changes observed might be related to the procedure being studied, statistical significance was not obtained with this data, between the control, fibrillation and defibrillation groups of animals.

B. PLASMA CONCENTRATIONS OF POTASSIUM, SODIUM AND CHLORIDE. Plasma ion levels are given in figure 2, and represent analysis of homogenous venous blood present in the right ventricle. Since the blood from the coronary sinus represents only a small contribution to the total volume present in the right ventricle, the changes observed in the right ventricular plasma ion concentration are not expected to vary with the changes observed in total myocardial electrolytes. Potassium ion was found to average 3.67 ±00.11 mEq./L plasma water during control. Ater 30 seconds of fibrillation a decrease to

FIGURE 2

Plasma Electrolyte Concentrations in Control Dogs, Fibrillated Dogs and in Dogs Following Electrical Defibrillation



2.93 ± 0.25 mEq./L was observed, while 90 seconds after electrical defibrillation photometric analysis showed a rise to 3.58 ± 0.40 mEq./L plasma water.

Plasma sodium ranged from an average control of 148.19 ± 3.63 mEq./L plasma water to 139.30 ± 7.71 mEq./L following fibrillation. This level was observed to rise in the post-defibrillation periodto a mean of 152.94 ± 5.05 mEq./L plasma water.

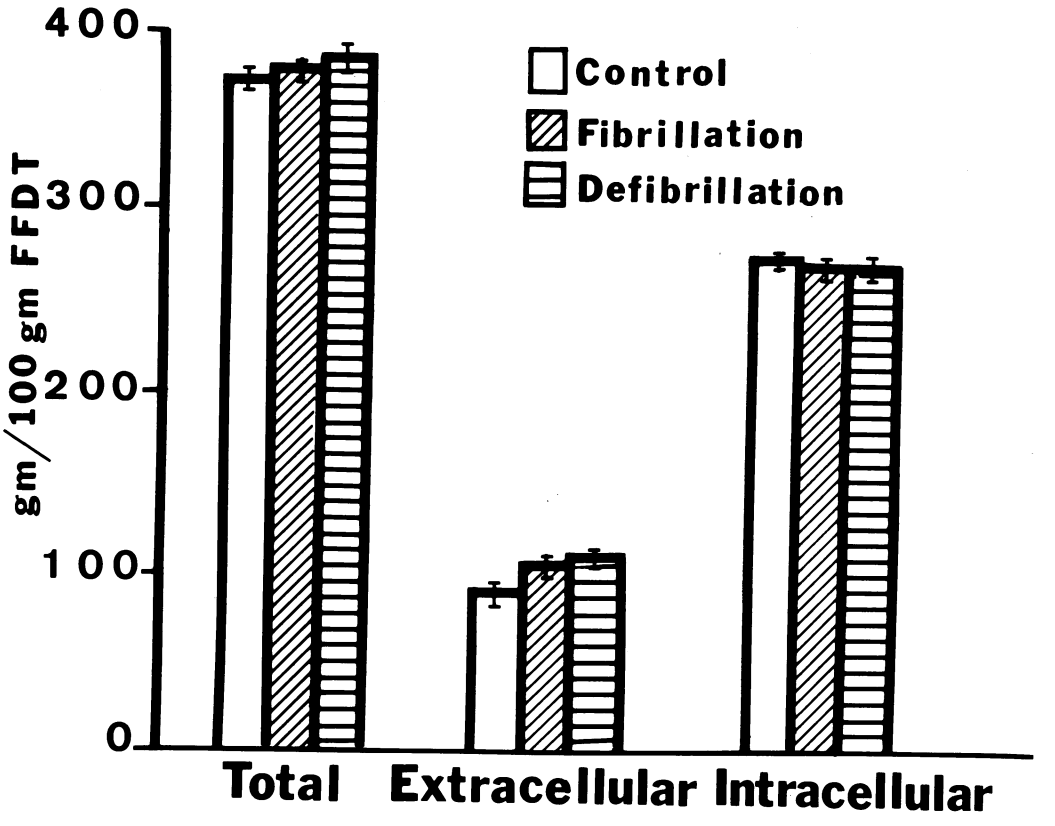
Chloride analysis revealed an increase from a control mean of 117.49 ± 1.11 mEq./L to 121.79 ± 2.09 mEq/L during fibrillation and then a fall to a mean of 115.54 ± 2.48 mEq./L 90 seconds after defibrillation.

Statistical analysis of the data on all three plasma ions (K^+, Na^+ and Cl^-) failed to demonstrate statistically significant changes between fibrillation and defibrillation (P values 0.10- 0.90). Tabulated data appear in tables I, II and III.

C. TOTAL TISSUE AND COMPARTMENTAL WATER OF THE MYOCARDIUM. Values for total tissue water and the division into extra and intracellular water agree closely with those reported by other investigators (Manery, 1954[22]; Benson et al, 1956[2]; Colman and Claviano, 1964[5]). Throughout the experimental procedure, no significant change was observed (P>0.40 - 0.50) in any of the compartments (Figure 3). Control levels averaged 373.16 ± 5.34, 275.61 ± 4.59 and 97.55 ± 5.63 gm/100 gm. FFDT for total tissue water, intracellular water and extracellular water respectively. During fibrillation total tissue water, was 378.61 ± 4.69 gm/100 gm FFDT while intracellular water was 272.54 ± 4.29 gm./100 gm. FFDT, Extracellular averaged in this state water 106.06 ± 5.18 gm./100 gm. FFDT. Following defibrillation water distribution was as follows;

FIGURE 3

Total Tissue and Compartmental Water in Control Dogs, Fibrillated Dogs and Dogs Following Electrical Defibrillation



total tissue 382.07 ± 6.64 gm./100 gm. FFDT, intracellular water 272.27 ± 6.06 gm./100 gm. FFDT and extracellular water 109.80 ± 5.07 gm./100 gm. FFDT. Tabulated data appear in Table IV.

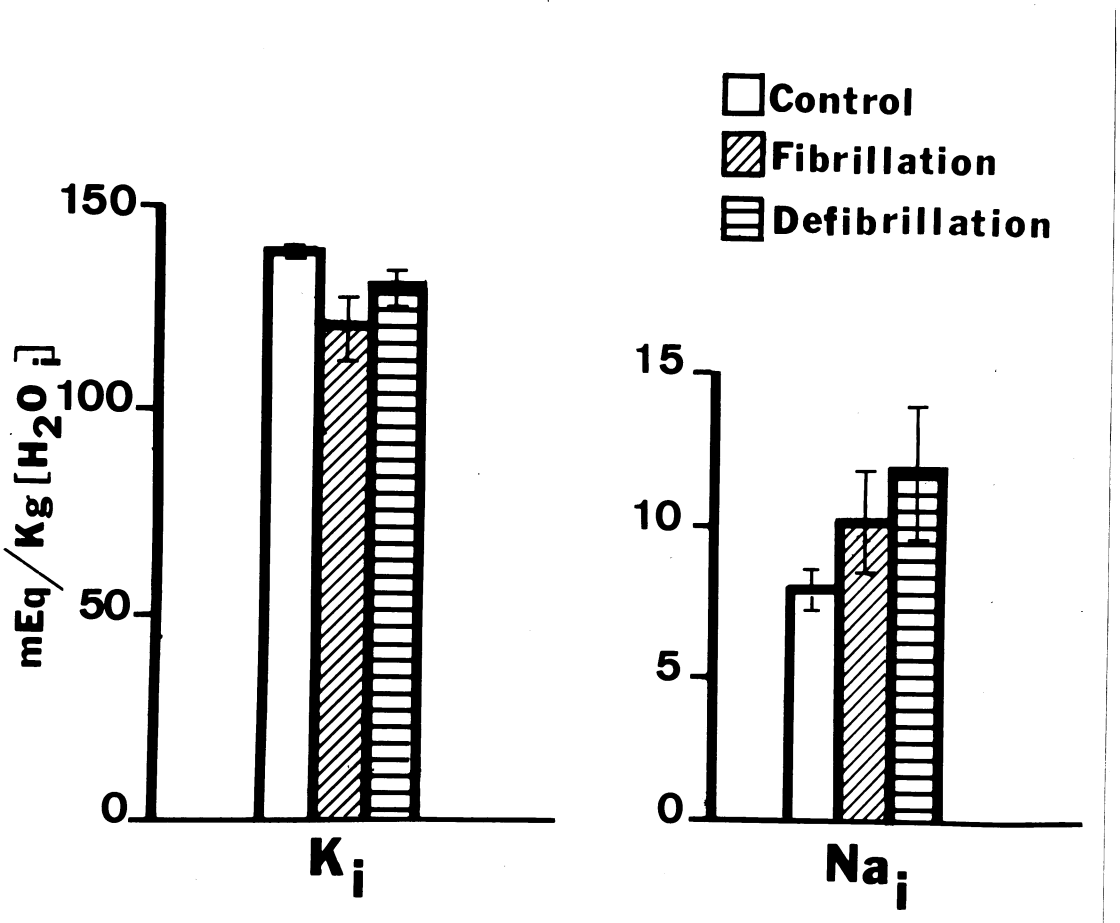
D. DERIVED CONCENTRATIONS OF INTERSTITIAL AND INTRACELLULAR ELECTROLYTES. As described earlier (page 13), the ion distribution in the interstitial phase of the extracellular compartment was determined with a Gibbs-Donnan factor. No significant change was noted during any of the procedures. This was expected since these values were derived directly from the plasma concentration, which also did not show a significant change in electrolytes.

Intracellular electrolytes varied in the same direction as the total tissue values. Figure 4 relates the changes observed in intracellular K^+ and Na^+ during the three periods being studied. Intracellular K^+ decreased from a control of 140.51 ± 1.67 mEq/Kg intracellular H_2O to 121.49 ± 7.04 mEq/Kg intracellular H_2O, a significant change ($P<0.02$). Following electrical defibrillation the concentration of this ion within the cell returned to 132.59 ± 2.83 mEq/Kg intracellular H_2O. A value significantly below that of control ($P<0.05$).

Sodium was observed to rise intracellularly during the fibrillatory period, from a control of 7.895 ± 0.531 mEq/Kg intracellular H_2O to 10.196 ± 1.39 mEq/Kg intracellular H_2O. Following electrical defibrillation the concentration continued to increase, achieving a level of 13.123 ± 2.04 mEq/Kg intracellular H_2O 90 seconds post defibrillation. This was a change of approximately 66% over control and was significant to a $P<0.05$.

FIGURE 4

Intracellular Electrolyte Concentrations of Canine Myocardium During Control, Ventricular Fibrillation and Following Electrical Defibrillation



E. CARDIODYNAMICS. Measurements of cardiac function recorded as the left intraventricular pressure, femoral blood pressure and the electrocardiogram were intended to document the occurrence and progression of ventricular fibrillation, the adequacy of heart massage, and the restoration of cardiac function following electrical defibrillation (Figure 5).

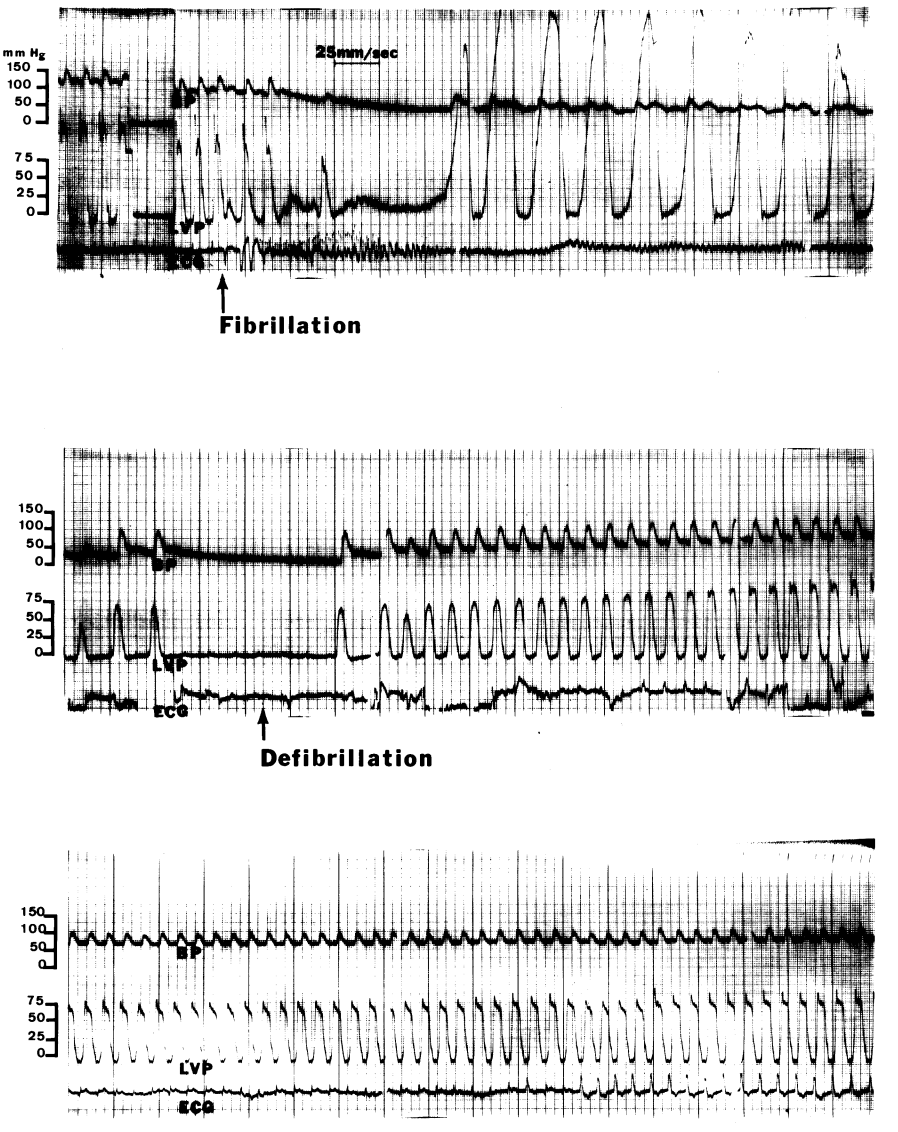
In the top record at the point marked "fibrillation" the typical electrocardiographic pattern as described by Wiggers (1940) was noted. There was a premature beat, followed by a short run of tachycardia, which evolved into a bizzare pattern (40). Also it was observed that with the onset of fibrillation in the electrocardiographic tracing, the left intraventricular pressure and femoral blood pressure immediately fell. Further along on that record the maintenance of systemic circulation was seen, evidenced by the elevated left intraventricular pressure and the femoral blood pressure.

The middle record corresponded to the period immediately following electrical defibrillation, during which a rising femoral blood pressure and increasing left intraventricular pressure were observed.

The bottom record taken one minute after defibrillation revealed a regular electrocardiogram and a continuing rise in the left intraventricular pressure and femoral blood pressure.

FIGURE 5

Cardiodynamic Recordings of a Dog During Control, Ventricular Fibrillation And Following Electrical Defibrillation



Bp = Femoral Blood Pressure LVP = Left Intraventricular Pressure

ECG = Electrocardiogram

TABLE I

POTASSIUM CONCENTRATIONS IN PLASMA AND CARDIAC MUSCLE DURING CONTROL (GROUP I), FIBRILLATION (GROUP II), FOLLOWING ELECTRICAL DEFIBRILLATION (GROUP III)

Group I					Group II				
Exp. No.	$(K^+)_T$	$[K^+]_I$	$[K^+]_E$	$[K^+]_P$	Exp. No.	$(K^+)_T$	$[K^+]_I$	$[K^+]_E$	$[K^+]_P$
301	38.039	141.84	2.5406	2.5925	201	36.679	125.75	3.6605	3.7353
302	40.136	138.64	3.3574	3.4260	202	33.394	115.08	3.5051	3.5767
303	39.723	148.98	4.1999	4.2857	203	22.271	81.43	1.6496	1.6833
304	37.185	139.89	3.8623	3.9412	204	28.145	110.98	2.1181	2.1614
305	40.687	144.25	4.0353	4.1177	205	34.198	127.51	3.0558	3.1182
306	38.756	134.64	3.6894	3.7647	206	36.552	132.52	3.2185	3.2842
307	38.238	140.87	3.4025	3.4720	207	39.545	147.02	2.7195	2.7750
308	39.593	134.97	3.6750	3.7500	208	36.544	136.61	3.0264	3.0882
Mean	39.044	140.51	3.5953	3.6687		33.416	121.49	2.8691	2.9277
S.E.	0.420	1.67	0.1817	0.1855		1.984	7.044	0.2422	0.2471

Group III				
Exp. No.	$(K^+)_T$	$[K^+]_I$	$[K^+]_E$	$[K^+]_P$
101	38.852	139.52	4.3056	4.3935
102	37.751	132.84	3.4843	3.5555
103	37.048	139.63	3.6206	3.6945
104	34.329	138.61	3.9471	4.0277
105	34.745	136.56	3.5933	3.6667
106	30.444	117.56	0.5717	0.5834
107	41.463	138.40	4.7133	4.8095
108	34.637	119.87	3.2665	3.3332
109	38.651	130.35	4.0833	4.1667
Mean	36.431	132.59	3.5095	3.5811
S.E.	1.083	2.83	0.3963	0.4044

$(K^+)_T$ = mEq. Potassium/100gm fat-free dry muscle

$[K^+]_I$ = mEq. Potassium/Kg cell water

$[K^+]_E$ = mEq. Potassium/Kg interstitial water

$[K^+]_P$ = mEq. Potassium/L plasma

TABLE II

SODIUM CONCENTRATIONS IN PLASMA AND CARDIAC MUSCLE DURING CONTROL (GROUP I), FIBRILLATION (GROUP II), FOLLOWING ELECTRICAL DEFIBRILLATION (GROUP III)

Exp. No.	Group I $(Na^+)_T$	Na^+_I	Na^+_E	Na^+_P	Exp. No.	Group II $(Na^+)_T$	Na^+_I	Na^+_E	Na^+_P
301	15.259	7.683	122.01	124.50	201	19.036	9.999	139.92	147.78
302	19.714	6.690	148.25	151.25	202	25.251	13.984	152.76	155.88
303	--	--	144.99	147.95	203	14.505	--	114.44	116.77
304	18.438	6.207	153.13	156.25	204	17.993	--	134.24	136.48
305	18.519	7.616	153.74	156.88	205	18.194	5.674	172.94	176.47
306	15.908	7.486	143.32	146.24	206	20.101	14.254	115.66	118.02
307	17.013	9.995	149.70	152.75	207	18.673	7.636	152.38	115.49
308	18.871	9.589	146.73	149.72	208	19.667	9.629	144.63	147.58
Mean	17.478	7.895	145.23	148.19		19.177	10.196	140.87	139.30
S.E.	0.6278	0.531	3.55	3.63		1.056	1.392	6.93	7.71

Group III

Exp. No.	$(Na^+)_T$	Na^+_I	Na^+_E	Na^+_P
101	10.270	--	147.00	150.00
102	22.922	8.340	157.58	160.80
103	15.961	5.512	157.58	160.80
104	27.204	16.369	150.03	153.09
105	23.042	11.366	156.08	159.26
106	13.387	--	--	--
107	27.756	15.731	166.06	169.45
108	25.613	21.698	119.40	121.84
109	22.569	12.848	145.31	148.28
Mean	20.969	13.123	149.88	152.94
S.E.	2.089	2.040	4.95	5.05

$(Na^+)_T$ = mEq. Sodium/100gm fat-free dry muscle

Na^+_I = mEq. Sodium/Kg cell water

Na^+_E = mEq. Sodium/Kg interstitial water

Na^+_P = mEq. Sodium/L plasma

TABLE III

CHLORIDE CONCENTRATIONS IN PLASMA AND CARDIAC MUSCLE DURING CONTROL (GROUP I), FIBRILLATION (GROUP II), FOLLOWING ELECTRICAL DEFIBRILLATION (GROUP III)

Group I				Group II			
Exp. No.	$(Cl^-)_T$	$[Cl^-]_E$	$[Cl^-]_P$	Exp. No.	$(Cl^-)_T$	$[Cl^-]_E$	$[Cl^-]_P$
301	13.941	122.51	120.06	201	12.343	119.46	117.07
302	14.054	122.18	119.74	202	14.954	123.63	121.16
303	16.173	120.18	117.78	203	15.631	127.52	124.97
304	12.761	118.54	116.17	204	18.281	134.61	131.92
305	11.787	114.87	112.57	205	12.219	121.59	119.16
306	10.984	124.94	122.44	206	13.441	120.33	117.92
307	10.115	118.45	116.08	207	12.958	130.32	127.72
308	11.712	117.46	115.11	208	12.326	116.79	114.45
Mean	12.690	119.89	117.49		14.019	124.28	121.79
S.E.	0.6926	1.13	1.11		0.756	2.13	2.09

Group III

Exp. No.	$(Cl^-)_T$	$[Cl^-]_E$	$[Cl^-]_P$
~~101~~	14.218	129.31	126.72
102	13.852	111.29	109.06
103	10.674	113.72	111.45
104	16.705	111.29	109.06
105	13.583	114.21	111.93
106	13.426	121.50	119.07
107	15.373	125.85	123.33
108	13.162	110.57	108.36
109	13.964	123.38	120.91
Mean	13.884	117.90	115.54
S.E.	0.545		2.48

$(Cl^+)_T$ = mEq. Chloride/100gm fat-free dry muscle

$[Cl^+]_E$ = mEq. Chloride/Kg interstitial water

$[Cl^+]_P$ = mEq. Sodium/L plasma

TABLE IV

WATER CONTENT OF PLASMA AND CARDIAC MUSCLE DURING CONTROL (GROUP I), FIBRILLATION (GROUP II), FOLLOWING ELECTRICAL DEFIBRILLATION (GROUP III)

Group I

Exp. No.	$(H_2O)_T$	$(H_2O)_I$	$(H_2O)_E$
301	374.51	266.24	108.27
302	394.03	286.89	107.14
303	388.48	263.10	125.38
304	367.15	263.07	99.080
305	372.26	279.46	92.794
306	365.16	285.68	79.478
307	347.22	269.57	77.651
308	381.50	290.89	90.609
Mean	373.16	275.61	97.550
S.E.	5.34	4.59	5.634

Group II

Exp. No.	$(H_2O)_T$	$(H_2O)_I$	$(H_2O)_E$
201	383.70	288.93	94.766
202	399.58	286.75	112.83
203	390.18	271.11	119.07
204	382.96	251.10	131.86
205	364.03	276.98	87.048
206	379.54	273.01	106.53
207	362.94	267.17	95.767
208	365.95	265.27	100.68
Mean	378.61	272.54	106.068
S.E.	4.69	4.29	5.184

Group III

Exp. No.	$(H_2O)_T$	$(H_2O)_I$	$(H_2O)_E$
101	378.14	275.29	102.85
102	396.83	281.16	115.85
103	346.05	263.19	82.863
104	387.53	246.16	141.37
105	362.52	251.50	111.02
106	367.73	258.44	109.29
107	406.89	295.81	111.08
108	396.49	285.90	110.59
109	396.49	293.01	103.48
Mean	382.07	272.27	109.801
S.E.	6.64	6.06	5.067

$(H_2O)_T$ = gm water /100 gm fat-free dry muscle

$(H_2O)_I$ = gm intracellular water /100 gm fat free dry muscle

$(H_2O)_E$ = gm interstitial water /100 gm fat-free dry muscle

CHAPTER IV

DISCUSSION

Before attempting to answer the three questions proposed in the introduction, it is necessary to create a unified schema of the alterations which occur during ventricular fibrillation. Recalling the observations of Wiggers (1940) on the progression of fibrillation in the canine heart, he reported that cardiac activity which might result in adequate perfusion (oxygenation) of the myocardium is lost within the first two to three seconds of fibrillation (40). This is due to the breakup of simultaneous contraction of the entire musculature of the heart into very small areas. Confirmation of the early loss of perfusion can be observed in the upper trace of figure 5, where left intraventricular and femoral blood pressure are noted to decline within two seconds after the onset of fibrillation.

Following the loss of local tissue oxygenation there occurs a period of progressive failure in contraction, until the individual units no longer are active. Wiggers (1940) stated that this was due to the anoxic condition of the heart (40). Gregg and Bing, who studied the venous efflux of

blood from the fibrillating heart (Chapter I) identified the decreased utilization of pyruvate as characteristic of the response of anoxia (11,28). Finally, Bing pointed out that with decreased tissue oxygenation there is deactivation of the co-carboxylase system, which leads to dephosphorylation of pyruvate (28). If the metabolism of pyruvate is markedly lowered, this would result in a decrease in the production of high energy compounds such as ATP. Since ATP is regarded as essential fuel for the mechanisms of electrolyte transport located in the cardiac cell, it would be expected that alterations of the electrolyte concentrations maintained on either side of the membrane by these pumps, will rapidly occur. Indeed, early in the course of fibrillation arterio-venous electrolyte studies (1954)[11], Bing (1965)[28] and Kaplan (unpublished) reveal that the heart loses potassium and gains sodium. Confirmatory evidence is also available from the findings presented in Chapter III, that during the first 30 seconds of ventricular fibrillation both the total tissue and the intracellular concentrations of K^+ are substantially decreased. These same studies also reveal rising levels of total tissue and intracellular sodium.

The effect of this alteration in electrolyte balance across the membrane will be to lower the transmembrane potential (Nerst equation $E_m = \frac{RT}{F} \text{ in } \frac{[K^+]_I}{[K^+]_E}$).[31] This increases the susceptibility to generate ectopic foci. The cyclic nature of the system just described will be interrupted in one of two ways. If untreated, potassium will continue to exit while sodium will build up within the cell, until the membrane becomes so completely depolarized that re-polarization is unable to occur. This would correspond to

the end of Wiggers fourth stage of fibrillation. On the other hand, the cyclic process may be interrupted by defibrillation and the patient may recover.

It appears that electrical defibrillation would most likely interrupt the system described above at the point of generation of the ectopic foci by the re-entry currents. By achieving depolarization of the entire heart at one time, all circus movements are cancelled and the pacemaker is allowed to generate the next coordinated beat.

From studies on prolonged periods of ventricular fibrillation with coronary perfusion (11, 18,32,33), it appears that the alterations in cardiac function only advance to the stage of conduction defect characterized by circus currents. No alteration in metabolism occurs. Thus when electrical defibrillation is attempted in these hearts, the additional problem of an electrolyte imbalance may not be present.

When cardiac massage is used to maintain myocardial oxygenation the changes resulting from fibrillation lie somewhere between the severe electrolyte imbalance seen in the anoxic heart and the minor changes observed in the perfused heart. When electrical defibrillation is attempted and achieved in this type of preparation, K^+ ion is observed to rise toward normal in both the total tissue measurements and in the intracellular compartment. Sodium on the other hand does not revert toward its pre-fibrillatory level, but continues to rise. At 90 seconds post defibrillation an increase of 66% over control is observed.

Hechrein, (1963), has demonstrated that when Ajmaline was used to achieve defibrillation, the intracellular sodium decreased[13]. This leads to speculation that a differential effect is produced on the pumps regulating

sodium and potassium when electrical defibrillation is employed. The sodium pump has been shown to be energy dependent (dinitrophenol studies), while a conclusive study has not been completed in the case of the potassium pump.[6,7] Thus an unknown effect of the strong electrical discharge may well be related to a disruption of the sodium transport system.

The effects of this altered ionic state of the cardiac cell in the early post defibrillatory period are almost identical with those observed in the late stages of anoxic fibrillation. The low intracellular potassium and high intracellular sodium would result in a lowering of the membrane potential ie. hypopolarization, making the cell quite susceptible to production of a spike potential, with obvious consequences.

In all phases of the experimental procedure, water distribution studies were performed. From the findings that there were nosignificant changes either in total tissue water or in compartmental water, it can be assumed that the preparations involved in the study were not in failure.[44] Thus it may be concluded that changes observed in chemical and hemodynamic findings represent changes due to fibrillation and electrical defibrillation.

Clinically this study indicates that the patient who is not undergoing coronary perfusion, whether in surgery, hospital bed or emergency room, and who has been electrically defibrillated for correction of ventricular fibrillation is particularly susceptible to refibrillation in the early postdefibrillatory period. As the evidence presented points to the electrolyte imbalance as a possible major contributor to the genesis of refibrillation, consideration of agents which would rapidly correct this electrolyte imbalance would be worthile. Although sodium and calcium ions most probably

are involved in this problem, the low intracellular potassium suggests itself to therapeutic regimen since polarizing solutions have already been demonstrated to rapidly elevate intracellular potassium. [21,27]

CHAPTER V

SUMMARY

Determinations of total tissue, plasma, interstitial and intracellular sodium, potassium, chloride and water were performed on control dogs in ventricular fibrillation and following electrical defibrillation. The following significant changes were found:

a) Decreases in total tissue potassium were observed during ventricular fibrillation. Ninety seconds after electrical defibrillation these levels were observed to have returned toward normal but were still significantly below normal.

b) Elevations in total tissue and intracellular sodium were observed during ventricular fibrillation. Ninety seconds after electrical defibrillation levels of sodium continued to rise.

c) Water content of left ventricular muscle remained constant. Statistical changes were not observed in water distibution between fluid compartments.

The decrease in myocardial intracellular potassium, and elevation of intracellular sodium during ventricular fibrillation may have been due to failure of the membrane regulatory systems, secondary to local tissue anoxia.

The failure of sodium to return toward control levels following electrical defibrillation is felt to be related to an unknown effect of the powerful electrical depolarizing current on the sodium pump and its related energy system.

The observed alterations in myocardial electrolytes in the early post-defibrillatory period caused hypopolarization of the membrane, which can result in an increased susceptibility of the heart to re-fibrillation.

BIBLIOGRAPHY

1. Alden, H. L. and E. B. Roessler. Introduction to probablity and statistics, 3d Ed. San Francisco: W. H. Freeman & Co., 129, 1964.

2. Benson, E., E. F. Freier, B. E. Hallaway and M. J. Johnson. Distribution of fluid and electrolytes and concentration of actomycin and other proteins in the myocardium of dogs with chronic congestive heart failure. Am. J. of Physiol., 187: 483, 1956.

3. Burn, J. and F. R. S. Harold. Ion movement and cardiac fibrillation. Proc. Royal Soc. of Med., 50: 725, 1957.

4. Carr, C. W. The amperometric titration of plasma chloride and urine chloride. Arch. Biochem. and Biophys., 34: 299, 1951.

5. Coleman, Bernell and V. V. Glaviano. Electrolyte and water distribution in the heart in irreversible hemorrhagic shock. Am. J. of Physiol., 207: 352, 1964.

6. Dawson, Hugh. A textbook of general physiology. Boston: Little Brown & Co., 862, 1964.

7. Eccles, John C. The physiology of synapses. Berlin: Spinzer-Verlarz, 182, 1964.

8. Einthoven, W. Ann. Phys., 12: 1059-1071, 1903.

9. Ferris, L. P., B. G. King, W. P. Spence and B. H. Williams. The effect of electric shock on the heart. Electrical Engineering, May, 1936.

10. Friedberg, Charles K. Diseases of the heart, 3d Ed. Philadelphia: W. B. Saunders Co., 572, 1966.

11. Gregg, D. E., M. H. Paul, E. O. Theilen, J. B. Marsh and G. G. Costen. Cardiac Metabolism in experimental ventricular fibrillation. Circ. Res. 2, #6, 573, 1954.

12. Harper, Harold A. Review of physiological chemistry. 187, 1964.

13. Hocheim. H. Myocardial electrolyte metabolism in ventricle fibrillation and defibrillation by Ajamalin. Med. Welt., 12: 577, 1965.

14. Hodgkin and Keyes. From burns' paper of 1957. 1954.

15. Hoffman, B. F. and Paul F. Cranfield. Electrophysiology of the heart. New York: 80 and 94, 1960.

16. Hoffman, B. F. and E. E. Suckling. Cellular potentials of intact mammalian hearts. Am. J. of Physiol., 170: 357, 1952.

17. Hogancamp, Charles E., M. Karidst, W. H. Danforth, and R. J. Bing. Transmembrane electrical potentials in ventricular tachycardia and fibrillation. Am. H. J., 57: 214, 1959.

18. Juvenelle, A. A., J. Lind and C. Wegolius. A new method of extracorporeal circulation. Am Heart J. 47: 692, 1954.

19. Kouwenhoven, W. B. The effects of electricity on the human body. Bull. Hopkins Hosp., 115: 425, 1964.

20. Kouwenhoven, W. B. Treatment of ventricular fibrillation using a capacitor discharge. J. Appl. Physiol., 7: 253, 1954.

21. Kunlin, J., S. Richard and A. C. Benitte. Essaies favorables de reanimation cardique apres embolie gazeuse coronarienne experimentale. Comptes Rendus Des Seances De La Societe De Biologie, 152: 1687, 1958.

22. Leeds, ... Production of fibrillation and defibrillation in dogs by means of accurately measured shocks across exposed hearts. Am. J. Physiol., 165: 179, 1951.

23. Lowry, O. H. and A. B. Hastings. Histochemical changes associated with aging: I. Methods and calculations. J. Biol. Chem., 143:

24. Maclean, L. D. Ventricular defibrillation, an experimental investigation of voltage requirements and effect of electrode size. J. AMA, 175: 471, 1961

25. Manery, J. F. Water and electrolyte metabolism. Physiol. Rev., 34: 334, 1954.

26. Miller, Malcolm. Anatomy of the dog. W. B. Saunder Co., 267 and 291, 1964.

27. Pallares, Sodi. The polarizing treatment of acute myocardial infarction: possibility of its use in other cardiovascular conditions. Dis. Chest, 43: 424, 1963.

28. Pedersen, A., A. Siegel and R. J. Bing. Cardiac metabolism in experimental ventricular fibrillation. Am. H. J., 52: 695, 1956.

29. Robertson, William Van B. and F. W. Dunajue. Water and electrolyte distribution in cardiac muscle. Am. J. of Physiol., 177: 292,

30. Robertson, William Van B. and Peyser .... Changes in water and electrolytes of cardiac muscle following epinephrine. Am. J. of Physiol., 166: 277, 1951.

31. Ruch, T. and J. Fulton. Medical physiology and biophysics, 18th Ed. Saunders Co., 616, 1960.

32. Senning, A. Ventricular fibrillation during extracorporeal circulation, Acta Chirurgrien Scan. Suppl. 171: 1, 1952.

33. Senning, A. Extracorporeal circulation combined with hypotension. Acta Chirurgrien Scan., 107: 516, 1954.

34. Sugimata, Tsunacki, M. B. Schaal, and .... Wallace. Factors determining vulnerability to ventricular fibrillation induced by 60 cps alternating current. Cir. Res., 21: 601, 1967.

35. Sumykin, G. L., ... Samson,and L. Gulliam. Ventricular fibrillation precipitated by imbalance and hypoxia. Am. H. J., 52: 619, 1956.

36. Tecleschi, C. G. and C. W. White, Jr. A morphologic study of canine hearts subjected to fibrillation, electrical defibrillation and manual compression. Cir., 9: 916, 1954.

37. Turner,... and ...Towers, Myocardial damage from therapeutic electric shock. Lancet, 1: 1396, 1964.

38. Watamabe, Yashio, L. S. Dreifus,and V. P. Satinsky. Mechanisms of ventricular fibrillation. Mechanisms and Therapy of Cardiac Arrhythmias, New York: Grune & Stratton, ed. by L. Dreifus and

39. Wegria, Rene and Carl Wiggers. Factors determining the production of ventricular fibrillation by direct currents. Am. J. of Physiol. 131: 104, 1940.

40. Wiggers, Carl J. The mechanism and nature of ventricular fibrillation. Am. H. J., 20: 399, 1940.

41. Wiggers, Carl J. Studies of ventricular fibrillation caused by electric shock (Inhib. by K+ and revival with calcium). Am. H. J., 5: 351, 1930.

42. Wiggers, Carl J. The physiologic basis for cardiac resuscitation from ventricular fibrillation-method for serial defibrillation. Am. H. J., 20: 413.

43. Wiggers, Carl J. and Rene Wegria. Quantitative measurement of the fibrillation threshold of the mammalian ventricles with observations on the effects of procaine. Am. J. of Physiol., 131: 296, 1940

44. Yankopoulos, N. A., J. O. Davis, E. Catlove and M. Trapasso. Mechanism of myocardial edema in dogs with chronic congestive heart failure. Am. J. of Physiol., 199: 603, 1960.

45. Yarbough, R. A comparison of the effects of A. C. and D. C. counter shock on ventricular function in thoracotomized dogs. Am. J. Card., 14: 504, 1964.

APPROVAL SHEET

The thesis submitted by Alan D. Kaplan has been read and approved by three members of the faculty of the Graduate School

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

May 27, 1968
Date

Vincent H. Clarke
Signature of Advisor