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Abstract

The effect of increasing extracellular potassium concentration (K_o) upon electrical ventricular defibrillation threshold was investigated in pentobarbital anesthetized dogs treated with intravenous potassium chloride. Defibrillation threshold fell during potassium intoxication. The percent decrease in defibrillation threshold was linearly related to the logarithm of K_o and to the potassium equilibrium potential, E_K, calculated from measured extracellular and intracellular potassium concentrations of ventricular muscle. In dogs supported by left ventricular bypass in order to maintain the circulation during potassium intoxication, the values of K_o and E_K required for spontaneous, K^+ induced defibrillation (electrical defibrillation threshold = zero) were 16.6 mEq/L and -46 mV compared to the normal values of 3.9 mEq/L and -84 mV. Changes in defibrillation threshold related to changes in E_K may be significant events in digitalis intoxication and in myocardial anoxia during prolonged fibrillation.

Defibrillation of the heart is often discussed as a large scale analog of cardiac pacing. Termination of atrial or ventricular fibrillation by a strong electric shock, applied with paddle electrodes across the chest or directly to the heart, is assumed to be the result of stimulation of a diffuse mass of potentially excitable cells (1, 2). The mechanism of defibrillation is usually stated to be the consequent production of a simultaneously refractory state in the entirety of a critical mass of the fibrillating myocardium (3, 4).

Key words: cardiac muscle, equilibrium potential, potassium, Nernst equation, transmembrane potential.

Introduction

The present report describes a pharmacologic test of this hypothesis. If indeed the process of fibrillation is analogous to electrical excitation of a single resting myocardial cell, then the shock intensity required for defibrillation should decrease if cardiac cells are partially depolarized by pre-treatment with a drug such as potassium chloride. In particular, the shock strength required for defibrillation should be proportional to the difference between the resting membrane potential of non-excited cells in the fibrillating myocardium and the firing or threshold potential of these

cells. Defibrillation should be accomplished with zero electric shock at a transmembrane potential approximately equal to the firing threshold -50-60 mV in typical preparations (5, 6). Indeed, before the existence of electrical defibrillators, chemical defibrillation, developed by Hooker (7), was practiced at surgery by flushing the coronary vascular bed with potassium solution (8).

The ratio of intracellular potassium concentration, K_i, to extracellular potassium concentration, K_o, is a major determinant of the resting transmembrane potential. A first order approximation of the transmembrane potential is given by the Nernst equation for the potassium equilibrium potential,

$$E_K \text{ (in mV)} = -61.5 \log (K_i/K_o).$$

Under physiologic conditions, measured resting transmembrane potentials are slightly less negative than this value due to inward leakage of sodium ions (5, 9). Note that because K_i is normally much greater than K_o (90 – 150 mEq/L vs. 2 - 5 mEq/L) small absolute changes in K_o produced by KCl infusion may cause relatively large changes in E_K and transmembrane potential, without significantly altering intracellular or total body potassium levels. Accordingly, the objectives of the studies here reported were:

1) to investigate changes in the ventricular defibrillation threshold produced by changes in extracellular potassium ion concentration (K_o) in dogs;
2) to hold total body potassium content essentially constant during these studies;
3) to measure the intracellular potassium ion concentration (K_i) of the ventricular myocardium; and
4) to plot defibrillation threshold as a function of $E_K = -61.5 \log (K_i/K_o)$.

If indeed defibrillation is analogous to cardiac pacing, the defibrillation threshold should be a decreasing function of E_K that approaches zero as E_K approaches the cellular firing threshold (-50 to -60 millivolts).

Methods

Animal preparation

Healthy mongrel dogs weighing 7-20 kilograms served as subjects. Anesthesia was induced with intravenous pentobarbital sodium (25-30 mg/kg) and maintained with additional 2 mg/kg boluses as necessary. This anesthetic alone does not alter the defibrillation threshold (10). No other drug except potassium chloride was administered. Esophageal temperature, the ECG, aortic blood pressure, respiratory minute volume, and arterial blood pH, pCO_2, and pO_2 were monitored as described previously (11). One hour before the beginning of defibrillation threshold measurements, the right and left ureters were ligated through a midline laparotomy to prevent rapid excretion of the infused potassium.

Defibrillation threshold was determined three times during the 120 min period before potassium administration, and three times during the 120 min period after potassium administration. Details of the procedure for measuring defibrillation threshold have been reported previously (11, 12). In brief, threshold was determined by repeated trials of fibrillation and transchest defibrillation, each with a damped sinusoidal defibrillator shock of peak current amplitude 10% less than the amplitude of the preceding shock. (The defibrillator had a capacitance of 16 μF, an inductance of 44 mH and an internal-resistance of 7 Ω (13).) A bipolar catheter electrode was placed in the right ventricle via a jugular venous cut-down to initiate ventricular fibrillation with 3 sec bursts of 60 Hz electrical stimuli. The lowest shock intensity able to achieve defibrillation, and differing no more than 10% in amplitude from an intensity that did not defibrillate was defined as threshold.

The hearts of the animals were never permitted to fibrillate more than 30 sec prior to defibrillation and never refibrillated until arterial blood pressure had returned to a stable level. The peak voltage and peak current for each shock were recorded on a storage oscilloscope. Only data from the first shocks applied after the onset of ventricular fibrillation were used in the calculation of threshold. Delivered energy was calculated as previously described (13).

Plasma levels of sodium and potassium in arterial blood were monitored at 10-20 min intervals using an Instrumentation Laboratories Model 443 flame photometer. After the first three pre-drug threshold determinations, intravenous potassium chloride in a dose of 1.0 mEq/kg was given slowly over a period of 5-10 min as the ECG was closely monitored for arrhythmias. Following this injection, a slow infusion of potassium chloride at 0.01 mEq/kg/min was begun using a motor driven syringe. After stable, elevated levels of plasma potassium were attained, three more measurements of the defibrillation threshold were made during the 120 min following the onset of potassium administration. This dosage regimen was selected because it produced in preliminary experiments the greatest stable elevations of serum potassium that could be tolerated during repeated episodes of ventricular fibrillation and defibrillation. With higher levels of potassium intoxication, some animals did not recover from post defibrillation A-V block and hypotension.

Measurement of intracellular potassium concentration by a double perfusion technique

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

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

K_t = overall potassium concentration of myocardial tissue, σ_o = volume fraction of the

extracellular space, and σ_i = volume fraction of the intracellular space = $(1-\sigma_o)$ for heart muscle. The intracellular potassium concentration is calculated as

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

provided σ_o, the volume fraction of the extracellular space, is known. Classically, σ_o is measured as the volume of distribution of an indicator substance which is permeable to capillaries, but which is excluded from cells. ^{24}Na, thiosulfate, and mannitol have been used as indicators for this purpose (14). The method developed for the present studies employs nonisotopic sodium as the indicator substance. This indicator is subtracted rather than added to the extracellular space as the myocardium is perfused with two different isotonic solutions, the first (lactated Ringer's solution) containing physiologic sodium concentration and the second (5% dextrose in water) containing zero sodium concentration. Samples of tissue and perfusate are analyzed for total sodium and potassium content by flame photometry after each perfusion, permitting calculation of σ_o. and K_i.

Procedure

After completion of the defibrillation threshold measurements, the potassium infusion was stopped and median sternotomy and pericardiotomy were performed. The heart was perfused first with lactated Ringer's solution and then with 5% dextrose in water via a cannula placed in the left brachiocephalic artery. All other branches of the aortic arch except the coronary arteries were ligated. Before perfusion, the cavae and descending thoracic aorta were clamped; the atria were cut to promote drainage of blood and perfusate. After perfusion with 500 ml of lactated Ringer's solution, a 1 gram sample of right ventricular muscle nourished by the left anterior descending coronary artery was excised for assay of sodium and potassium content. Then perfusion with 500 ml of dextrose solution was carried out and a 1 gram sample of right ventricular muscle nourished by the right coronary artery was excised for assay of tissue sodium and potassium content. The assay procedure employed overnight digestion of the tissue sample in 10 volumes of 1 molar H_2SO_4 at 80°C. Such digestion for one hour or longer produced maximal recovery of sodium and potassium from the pieces of myocardium. Assay of the supernatant solution for sodium and potassium concentration was accomplished using the flame photometer, calibrated with solutions of 1 molar H_2SO_4 containing known concentrations of Na^+ and K^+ ions. Samples of coronary sinus effluent taken after perfusion with 400 ml of each solution provided a measure of extracellular sodium and potassium concentrations in each case. Perfusion pressure was always 80-120 mmHg.

Calculations

Total tissue sodium concentration, Na_t, is given by the expression

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

where, as before, σ_o = volume fraction of the extracellular space $\sigma_i = 1 - \sigma_o$ = volume fraction of the intracellular space, Na_i = intracellular sodium concentration, and Na_o = extracellular sodium concentration. During the perfusion procedure, σ_o, σ_i, and Na_i are constants. Therefore, σ_o was calculated from measurable quantities as

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

assuming that sodium ions distributed only to the extracellular space and did not cross cell membranes significantly during the period of perfusion. Intracellular potassium concentration was then calculated from total tissue and plasma potassium concentrations as

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

Investigation of higher levels of K_o

The potassium treatment schedule for the first ten animals just described was designed to produce stable elevations of extracellular potassium concentration near the maximal levels tolerated by the animals, without profound hypotension, depression of the sinoatrial or atrioventricular nodes, or intractable tachyarrhythmias. In preliminary experiments such complications did occur with more rapid rates of potassium infusion. Consequently, to elucidate the influence of high concentrations of extracellular potassium upon defibrillation threshold, a second experiment was designed to determine at what concentration of extracellular potassium the ventricles of dogs would spontaneously defibrillate, that is, at what level of K_o defibrillation threshold was zero. These studies were carried out in open-chest dogs in whom cardiac output was maintained by a left ventricular bypass pump. The problem of circulatory collapse produced by very high levels of plasma potassium was thus obviated. No defibrillator was needed for the study. Neither was it necessary to establish a control level of the defibrillation threshold, since zero threshold current is equivalent to zero percent of control in any case.

Nine pentobarbital anesthetized dogs served as subjects in this second experiment. After median sternotomy and pericardiotomy had been performed, surgical hemostasis secured, and heparin (2 mg/kg i.v.) administered, ventricular fibrillation was initiated by 60 Hz stimulation of the right ventricular surface. Each animal was immediately placed on

a La Farge-type left ventricular bypass system. Blood was withdrawn from the left ventricle through a large bore, multiple side-hole cannula inserted through a small stab wound in the cardiac apex. Blood withdrawn from the left ventricle was led through a Travenol roller pump and re-infused into the animal via a large bore, right-angle cannula previously placed in the abdominal aorta. Prior to institution of the bypass, the tubing was filled with warmed (30-40 °C) Ringer's solution. Care was taken to ensure that the left ventricular cannula was not pushed through the aortic valve from the left ventricle, since a short circuit would have been created. To remove venous return, the animal's hindquarters were elevated 30 degrees and up to 1000 ml of additional Ringer's solution infused as necessary to maintain a stable artificial cardiac output.

After the bypass system had been adjusted, potassium chloride was infused via the femoral vein at a rate of 0.2 mEq/kg/min, calculated to raise the extracellular potassium concentration by approximately 1 mEq/L/min. Esophageal temperature, the ECG, arterial blood pressure, and arterial blood pH, pCO_2, and pO_2 were monitored. Two arterial blood samples were taken at the time of spontaneous, chemical defibrillation for analysis of plasma potassium concentration. The first sample was taken at the moment fibrillation appeared to cease, as judged by the ECG and direct visual inspection of the heart. The second sample was taken when defibrillation was confirmed by electrical pacing of the ventricles by single 10 volt, 2 msec stimulus applied to the ventricular surface with hand-held bipolar electrodes. Generation of ventricular ectopic beats in the ECG was taken as confirmation of ventricular defibrillation. The average plasma potassium concentration of the first and second samples was taken as the level required for defibrillation with zero current and energy.

Results

The elevation of plasma potassium concentration produced by the "bolus plus infusion" technique in ten dogs is illustrated in Figure 1. The technique described produced a stable plateau of extracellular potassium concentration for defibrillation studies. The overall mean control potassium level was 3.9 mEq/L and the overall potassium infusion level was 7.5 mEq/L. Calculated levels of intracellular potassium concentration in four of these animals and in four animals which did not receive prior potassium infusions are given in Table 1. The mean value for intracellular potassium was 91 mEq/L and the standard error of the mean was 3.6 mEq/L. Intracellular potassium concentrations of dogs that received potassium treatment were not significantly different from those of dogs that did not ($t = 0.66$, $p = 0.53$).

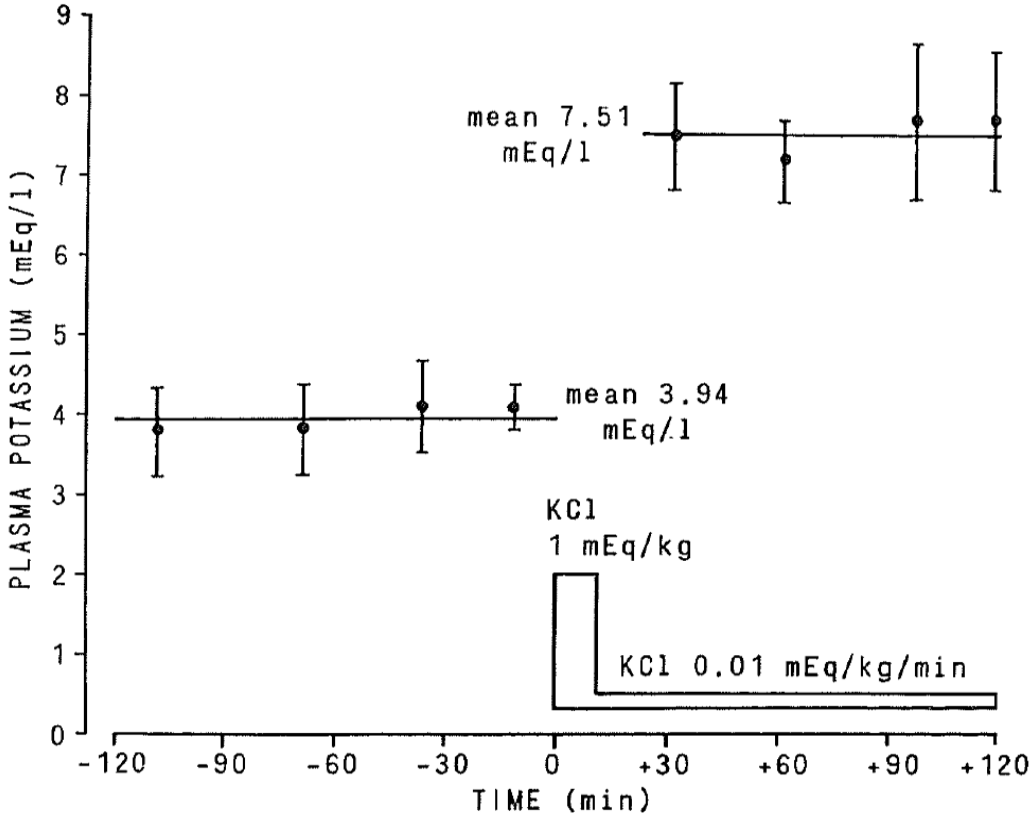

Figure 1. Elevation of plasma potassium in 10 dogs produced by a slow intravenous injection of potassium chloride, 1.0 mEq/kg, followed by a constant infusion of potassium chloride, 0.01 mEq/kg/min. Error bars represent standard deviations.

Table 1. Ionic concentrations in canine ventricular muscle. σ_o = volume fraction of extracellular space; Na_t = tissue sodium concentration; K_t tissue potassium concentration; Na_i, = intracellular sodium concentration; K_i intracellular potassium concentration. Prior KCl = KCl 1.0 mEq/kg i.v. slowly, followed by KCl 0.01 mEq/kg/min for 120 min. Student's t values (two-tailed) test the null hypothesis that tabulated values for dogs 1-4 (no prior KCl) are equal to tabulated values for dogs 5-8 (prior KCl treatment). Prior KCl did not cause significant changes in the tabulated values.

Dog #	Prior KCl	σ_o	Na_1 mEq/L	K, mEq/L	Na_1 mEq/L	Ki, mEq/L
	no	0.27	37	54	16	77
2	no	0.26	45	82	15	109
3	no	0.15	31	71	14	83
4	no	0.20	36	69	11	85
5	yes	0.26	40	75	7	99
6	yes	0.18	29	73	6	88
7	yes	0.17	34	76	17	90
8	yes	0.24	40	74	8	97
Mean		0.22	37	72	12	91
S.D.		0.047	5.2	8.1	4.3	10.2
t		0.66	0.38	-0.95	1.63	-0.66
p		0.53	0.72	0.38	0.15	0.53

Figure 2 summarizes the effects of increased extracellular potassium concentration on ventricular defibrillation threshold. Defibrillation threshold as percent of control is plotted as a function of plasma potassium concentration and of calculated potassium equilibrium potential. The left-hand and middle data points represent mean control and mean post-potassium threshold values. The right-hand data point represents the mean plasma potassium concentration for spontaneous defibrillation with zero current or energy. The upper scale for potassium equilibrium potential was calculated from the Nernst equation using the mean value of intracellular potassium concentration reported in Table 1. As extracellular potassium concentration is increased, ventricular defibrillation threshold dramatically decreased, reaching zero value when K_o was 16.6mEq/L and E_K was -46mV.

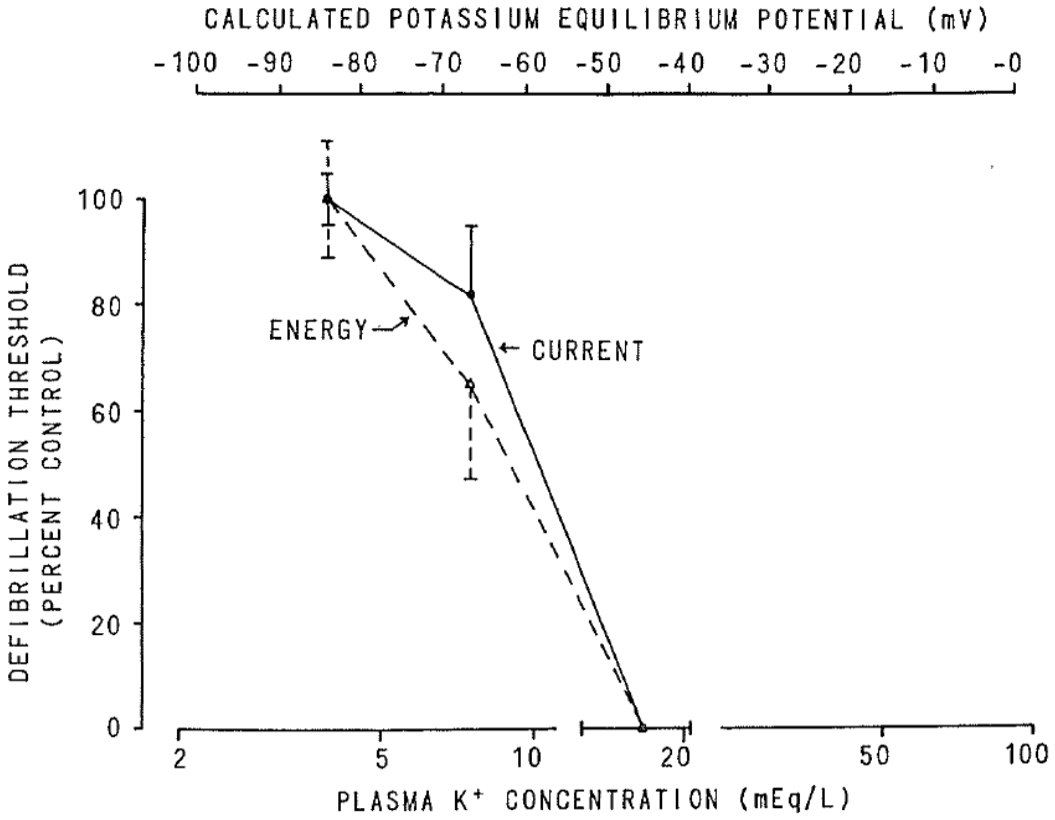

Figure 2. Effect of elevated extracellular potassium concentration on ventricular defibrillation threshold in dogs. Results from both experimental protocols are combined. Error bars represent ±1 standard deviations. The abscissa is broken to delineate standard deviation of potassium concentrations for spontaneous defibrillation (horizontal error bars). Results are similar whether threshold shock strength was measured in terms of energy or current.

Discussion

As the potassium equilibrium potential, E_K, is made less negative by KCl infusion, the gap between the theoretical equilibria for resting membrane potential and cellular firing threshold narrows. It is predicted that this change, in turn, will decrease the defibrillation threshold. As indicated in Figure 2, the decrease in defibrillation threshold is in fact related to the increase in E_K , and defibrillation threshold falls to zero not far from the expected value of cellular firing threshold. The fact that the observed value of E_K at zero defibrillation threshold is somewhat less negative than the typically quoted value of -60 mV for cellular firing threshold of ventricular fibers may be related to the critical mass concept of Zipes (3, 4). According to this concept, depolarization of a large critical mass of ventricular muscle is required for defibrillation, including cells with higher-than-average threshold. Hence, if complete defibrillation is taken as the endpoint, the calculated value of E_K would be associated with the cells in the critical mass with the highest thresholds. In addition, measured plasma levels of K_o in the second experiment were undoubtedly slightly greater than tissue levels, since plasma concentrations were increasing and complete equilibration of plasma and interstitial compartments could not have occurred. With these reservations, the results obtained are very close to those predicted by the hypothesis that defibrillation is a large scale analog of cardiac pacing.

Although potassium concentrations in circulating plasma comparable to those used in the present study are not routinely encountered in the clinic, local tissue elevations in extracellular potassium may be quite significant in certain pathophysiologic states related to defibrillation. For example, Tacker et al. (16) found a dose-related decrease in defibrillation threshold current and energy in dogs following toxic doses of the digitalis glycoside, ouabain. A dose of 50 µg/kg produced an average maximum decrease in threshold energy of 20%, a finding virtually identical to that reported earlier by Lown et al. (17)

These findings are consistent with the effects of potassium reported in this paper and may be explained as an indirect effect of the well-known inhibition of membrane-bound sodium/potassium ATPase by digitalis glycosides. This cellular effect of digitalis preparations causes inhibition of active transport of sodium ions out of and potassium ions into myocardial cells. As a result, there is a net outward leakage of potassium ions (18) which could produce local elevations in extracellular potassium concentration with resultant enhanced excitability and depression of the defibrillation threshold.

These indirect alterations in defibrillation threshold by induced changes in local extracellular potassium concentration may also explain the recent (unpublished) observation in our laboratories that defibrillation threshold decreases following durations of fibrillation and total circulatory arrest lasting more than two minutes.

In addition to depression of defibrillation threshold, we have found in preliminary experiments that the potassium concentration of blood recovered from the coronary vascular bed increases progressively as the duration of fibrillation and cardiac anoxia is lengthened. This shift of potassium from intracellular to extracellular fluid compartments during ischemia has been demonstrated in several animal models (19, 20, 21).

Hence, although elevations of extracellular potassium concentration as great as those reported in the present studies would never be produced for therapeutic reasons, the finding of threshold depression by potassium may be important in understanding both the mechanism of defibrillation and changes in defibrillation threshold during certain pathophysiologic states.

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