Electrophysiologic Effects of Regional Hyperkalemia in the Canine Heart[1] (36860)

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The effects of systemic hyperkalemia on the electrophysiologic properties of the heart and their electrocardiographic effects have been studied extensively (1, 2). However, the observations that ventricular tachyarrhythmias can be produced by intracoronary infusion of potassium (3, 4), as well as the hypothesis that the development of arrhythmia in myocardial infarction may be related to altered distribution of extracellular K^+ following its release from ischemic cells (5), suggested that regional hyperkalemia might modify excitability of the heart selectively. Although the similarities produced in surface electrograms by acute ischemia and application of K^+ salts have long been appreciated (6), no studies of the electrophysiologic consequences of the resulting injury currents (7) or regional hyperkalemia have been reported.

In the experiments to be described, we have assessed changes in excitability and refractoriness which occurred during defined periods of regional hyperkalemia produced by intracoronary infusions of K^+ at rates which did not depress ventricular contractile force (7) and which were designed to simulate electrocardiographically acute myocardial ischemia in an area of the dog heart supplied by the anterior descending branch of the left coronary artery.

Methods. Conditioned mongrel dogs weighing 18–24 kg were anesthetized with pentobarbital sodium (30 mg/kg iv). Arterial blood pressure was measured by means of a Statham transducer. The animals were ventilated through endotracheal tubes using a Harvard respiration pump. Through a midline sternotomy, the stellate ganglia were excised bilaterally to permit atrial pacing at rates of 90–140 per min using bipolar electrodes connected through an isolation transformer to a Grass S-8 stimulator. A pericardial cradle was formed and a 27-gauge needle, bonded to a small polyethylene catheter, was inserted into the midportion of the anterior descending branch of the left coronary artery (Fig. 1). Using a variable-rate infusion pump, an infusion of 0.95% saline (0.1–0.2 ml/sec) was experimentally interchanged with an iso-osmotic saline solution containing KCl in a concentration of 40 mEq/liter.

Unipolar electrograms were recorded from two epicardial ventricular sites using cotton-wicked stainless-steel electrodes and direct-coupled amplifiers on a Sanborn Poly-viso recorder at paper speeds of 25–100 mm/sec. One recording position was 1–2 cm distal to the point of infusion (experimental area; Re, Fig. 1) while the second was located on the postero-lateral surface of the left ventricle (control area; Rc, Fig. 1), well outside the area of distribution of the catheterized artery. The indifferent electrode was a stainless steel pin inserted into the chest wall equidistant from the recording electrodes. Bipolar stimulating electrodes were stainless steel hooks (interelectrodal distance 8–10 mm) positioned adjacent to each recording site and connected to the second output of the stimulator, which could deliver a constant current D.C. pulse of variable intensity to either ventricular site at any desired interval after the basic atrial pacing stimulus. The stimuli were

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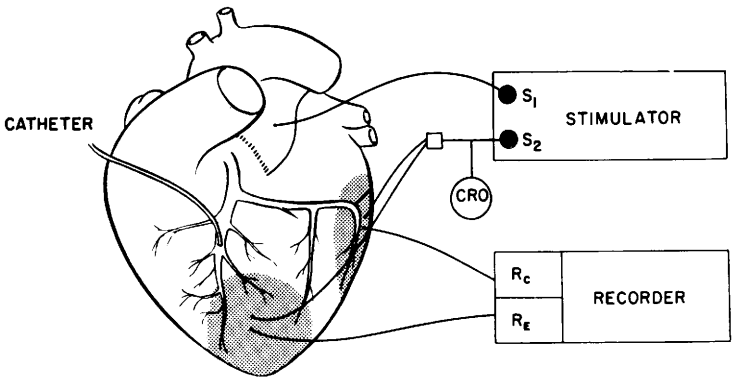

FIG. 1. Schematic representation of the experimental preparation. The catheter was inserted into the left anterior descending coronary artery above the terminal bifurcation. The stippled area at the apex represents the experimental (e) area. S_1 represents the atrial pacing electrode system. S_2 represents the constant-current variable strength stimulus, which could be delivered to either ventricular site. CRO represents the current monitoring oscilloscope. R_c and R_e identify the direct-coupled epicardial electrograms recorded from the control and experimental ventricular sites, respectively.

displayed and quantitated using the voltage-drop technique with a Tektronix #564 oscilloscope (8).

Diastolic threshold (DT) was defined at each test site as the stimulus of minimal strength (mA) of 2.5 msec duration which resulted in a propagated ventricular response when delivered in late diastole. In eight experiments, strength–interval curves were constructed for each test site by progressively increasing the strength of the test stimulus (S_2) necessary to produce a propagated response as the delay between the basic atrial paced ventricular response (R_1) and S_2 was decreased in 10 msec steps. As a measurement of refractoriness in other experiments, we identified the functional refractory period (FRP) defined as the shortest R_1–S_2 interval at which a stimulus of twice DT strength elicited a propagated response (9). The time interval between the paced ventricular response (R_1) and a premature test stimulus (S_2) has been designated the R_1–S_2 interval, where R_1 is the initial deflection of the QRS complex in the appropriate epicardial electrogram and is identical to the initial deflection used to measure the corresponding Q–T interval.

K^+ was substituted for the control solution at rates which delivered 0.05–1.0 μEq K^+/kg/sec for 30 sec periods. In each experiment K^+ was infused at rates which resulted in reproducible and reversible degrees of systolic and diastolic injury patterns in the experimental site electrogram (see Results) and which were known from previous observations not to depress ventricular contractile force or increase systemic arterial K^+ concentrations (7). At the conclusion of each experiment a solution of methylene blue was injected into the coronary catheter to delineate visually the area of infusion and the absence of any flow into the control site.

Results. Qualitative effects of K^+ on D.C. electrograms. Infusion of K^+ into the coronary catheter resulted in specific, reproducible and reversible changes in electrograms recorded from the experimental area (Fig. 2). Diastolic baseline (T–P) depression was observed to begin within 1–3 sec (2B) and progressed gradually and smoothly to its maximum (2D). The control epicardial T waves, which were usually negative, promptly reversed their polarity and changed their configuration, while the S–T segment gradually became elevated. These changes were accompanied by progressive shortening of the Q–T interval (2B, C, D). The magnitude and extent of these changes were variable and were definitely related to the rate of K^+ infusion. In every experiment, however, an infusion rate could be experimentally determined which reproducibly resulted in essentially fused monophasic electrograms, accom-

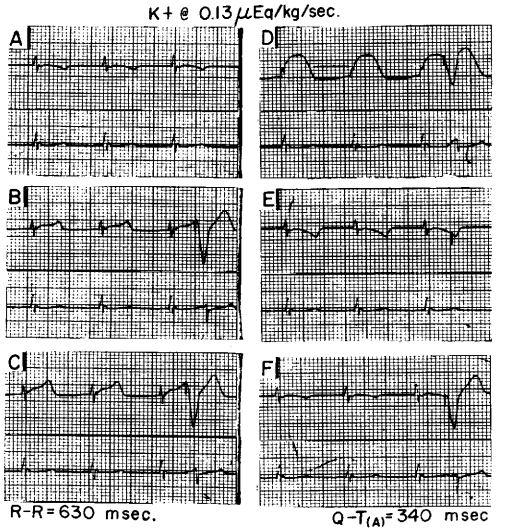

FIG. 2. Effect of K^+ infusion on epicardial electrograms recorded using direct-coupled amplification. The upper tracing of each set (A–F) was recorded from the experimental area (R_e); the lower from the non-perfused control area (R_c). A was recorded during the control period (note that with this amplification system the induced P waves were not identified; however, evidence of atrial P waves were always confirmed in Lead II). B, C, and D were obtained at 5, 10 and 25 seconds during infusion of K^+ at the rate of 0.13 μEq K^+/kg/sec in a 24 kg dog. The control diastolic baseline is shown in D between the second and third complexes. E was recorded 20 sec after termination of a 30 sec K^+ infusion when the Q–T in the R_e was prolonged to 380 msec. F was recorded 2 min after the K^+ infusion was ended. The R–R interval was 630 msec and the control Q–T (A) was 340 msec. The last response in tracings B through F was a FRP determination. The FRP'S were 260, 250, 240, 330 (not shown, but a blocked stimulus artifact appears at 290) and 290 msec, identical to control (A) which was not photographed. Paper speed = 25 mm/sec.

panied by a maximally shortened Q–T interval (2D). When the K^+ was stopped and saline substituted at the same infusion rate, the ECG changes gradually reverted toward control configuration. During this "washout period" when the T–P depression had disappeared and the S–T segment had become isoelectric, the T wave was noted transiently to be more deeply inverted than during the control period, with a prolonged Q–T interval (2E). The T wave regained its original configuration and the Q–T interval returned to control values within 2–5 min after stopping K^+ in all experiments (2F). The extent of the Q–T prolongation and T wave inversion after K^+ seemed to be related to the maximum duration and extent of the K^+ induced shortening of the Q–T interval.

Electrograms recorded from the posterolateral control ventricular site showed no consistent or significant changes during K^+ infusion (Fig. 2), although minor degrees of reciprocal S–T segment depression occasionally were noted when marked S–T segment elevation was noted at the experimental site. The S–T and T changes in Lead II were extremely variable and this record was used only for timing purposes and more detailed analysis of arrhythmias.

Effects of K^+ infusion on strength-interval curves and refractoriness. Strength–interval curves were constructed from data obtained from eight dogs for the control (non-perfused) ventricular site and for the experimental (K^+ perfused) site in the presence and absence of K^+; the effects were qualitatively the same in every animal. The data from a typical experiment are illustrated (Fig. 3), in which the points on the curves were obtained during the last 10 sec of several 30 sec K^+ infusions when the electrograms were stable and showed maximal ECG changes for that infusion rate. Infusion of K^+ at any of the rates studied did not produce any change in DT or refractoriness in the control ventricular site. The strength–interval curve obtained from the experimental site in the absence of K^+ was not different from the control non-perfused area in any experiment.

In marked contrast, infusion of K^+ shifted the strength–interval curve in the experimental area to the left, the extent of which was related to the rate of K^+ infusion (Fig. 3). When K^+ was infused at rates of 0.1 μEq/kg/sec or greater, the absolute refractory period was always shifted 30–60 msec closer to the initial ventricular depolarization deflection of the atrially paced beat, *i.e.*, leftward. The maximum leftward shift of the strength–interval curves was observed when fused monophasic electrograms were

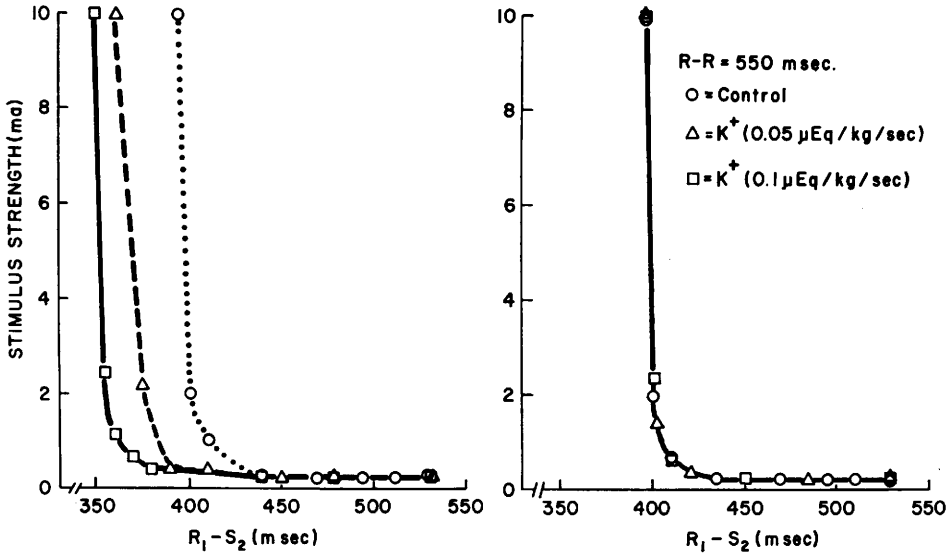

FIG. 3. Strength–interval curves constructed from the control area (right panel) and experimental area (left panel) during saline (–O–) and K^+ infusion at rates of 0.05 (–△–) and 0.1 (–□–) μEq/kg/sec in a 20 kg dog. R_1, beginning of paced ventricular response; S_2, test stimulus.

produced (Fig. 2D). Whenever premature stimuli were introduced into an area perfused by K^+, all propagated responses were invariably conducted into the control area, since there was always sufficient delay in conduction out of the hyperkalemic area to permit recovery and subsequent excitation in the control area. Thus, unidirectional block out of the region of hyperkalemia was not observed in these experiments.

Figure 3 does not demonstrate any change in DT at the time of maximum shift in the refractory period at the experimental site. However, four experiments were designed specifically to determine whether any variation in DT occurred during the course of K^+ infusion. DT in the experimental area during saline infusion ranged from 0.2–0.45 mA. During the initial period of K^+ infusion when the epicardial electrograms were changing rapidly, small but reproducible decreases in DT (0.1–0.15 mA) could always be documented. However, as the diastolic baseline depression stabilized and maximal S–T segment elevation developed, DT gradually returned toward control values and not infrequently exceeded the control values by 0.2–0.6 mA. The increased DT tended to persist for variable periods into the washout period, especially when Q–T prolongation was prominent, but invariably returned to control values when the electrograms had returned to control configuration and duration.

The FRP in the experimental area was similarly shortened 10–60 msec by the infusion of K^+ and precisely paralleled the shortening of the Q–T interval in every test; thus, the extent of the FRP shift was related to the rate of K^+ infusion. The changes in FRP in a typical experiment are also illustrated in Fig. 2. After termination of the K^+ infusion, the FRP was prolonged 10–80 msec for 2–5 min, paralleling the duration and extent of the prolongation of the Q–T interval. Although measurement of FRP during K^+ washout was influenced by the concomitant but slight increase in DT, our studies showed clearly that during recovery from a period of K^+ induced shortening of the refractory period, the occurrence of a prolonged Q–T interval and FRP can usually be observed, a finding similar to that well-documented after acute experimental ischemia (10).

Discussion. These studies were designed to explore the consequences of the production of a discrete area of hyperkalemia on the

electrophysiologic properties of the intact heart without the production of systemic hyperkalemia. The amounts and rates of the K^+ infusion were selected in order to simulate the electrocardiographic changes of acute ischemia and thus to determine whether creation of "K^+ boundaries" simulated the electrophysiologic changes associated with acute myocardial ischemia.

Utilizing the advantages of direct-coupled amplification of epicardial electrograms, K^+ infusions consistently and reversibly produced: (1) diastolic T–P depression; (2) change in polarity and configuration of the T wave accompanied by S–T segment elevation; and (3) shortening of the Q–T interval. The current flowing during diastole (depression of baseline below control) probably represented current flow from normally repolarized muscle to areas depolarized or hypopolarized by the increase of extracellular K^+, with a vector directed away from the less positive recording surface electrode (1). The change in configuration of the T wave and shortening of the Q–T interval probably were related to the more rapid and synchronous repolarization of myocardial cells exposed to increased extracellular K^+. Early repolarization and a more negative plateau potential may also be an explanation for the S–T segment elevation, which creates a differential of potential between the perfused and control sites and a flow of current from the former to the latter. The electrocardiographic changes were similar to those of experimental ischemia-induced injury currents (11) and probably reflected the known interactions of the effects of increased extracellular K^+ on ventricular muscle action potentials via its alteration of both transmembrane K^+ concentration and the membrane conductance for K^+ ion. Our study suggests that the effects of altered distribution of extracellular K^+ could account for the resultant electrocardiographic patterns of systolic and diastolic injury currents which occur in acute ischemia.

The prolongation of the Q–T interval and the occurrence of deeply inverted T waves during the "washout period" were similar to those reported to follow recovery from experimental ischemia (12, 13). Bing *et al.* (13) pointed out that repetitive ventricular arrhythmias often occurred spontaneously during this reccovery period. In our studies, it was frequently possible to induce ventricular fibrillation with a single stimulus of threshold strength during this transient period as well.

The biphasic change in DT observed in this study was similar to that reported during the development of systemic hyperkalemia by Han *et al.* (1). When the myocardium was hypopolarized by K^+, the resting potential in the area was closer to threshold potential and diastolic excitability was increased. However, as the degree or extent of hyperkalemia increased and monophasic potentials were recorded, the threshold potential itself might have decreased (14) or larger numbers of cells might have become non-excitable and influenced this measurement. Our results did not permit discrimination between these two possibilities.

The leftward shift of the strength–interval curves and functional refractory periods demonstrated that localized hyperkalemia, in the absence of significant intraventricular conduction delay (evidenced by the absence of prolongation of the QRS complex) effectively shortened the refractory period and hastened repolarization. These data were similar to the shortened FRP's and leftward displacement of strength–interval curves observed in experimental ischemia (10, 12) and further suggested that K^+ may well be a pathophysiologic factor in the repolarization abnormalities associated with acute ischemia. Other data also suggest that the K^+ induced changes in refractoriness may be associated with alterations in vulnerability to ventricular fibrillation.

The total amount of K^+ infused in any one test was less than the amount of intracellular K^+ contained in one gram of normal cardiac muscle. Thus, the amount of K^+ released from ischemic cells which is necessary to induce maximum evidence of both components of the total injury current need not be great and may explain the evanescent nature of the injury currents in acute myocardial infarction (9).

Summary. KCl (40 mEq/liter) infused

into the anterior descending branch of the left coronary artery of anesthetized dogs resulted in reproducible and reversible electrophysiologic evidence of systolic and diastolic injury currents accompanied by shortening of the Q–T interval in appropriate epicardial electrograms recorded by means of direct-coupled amplification. K^+ infusion shortened the absolute and functional refractory periods in the experimental area, accompanied by a biphasic change in DT. Regional hyperkalemia produced both the electrocardiographic and electrophysiologic characteristics of acute myocardial ischemia and the results suggested that the altered distribution of extraellular K^+ resulting from its release by ischemic myocardial cells could contribute importantly to the complex of "excitatory factors" related to the development of arrhythmias during acute myocardial infarction.

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