The QRS Complex during Myocardial Ischemia

AN EXPERIMENTAL ANALYSIS IN THE PORCINE HEART

ROGER P. HOLLAND and HAROLD BROOKS

From the Experimental Hemodynamics Laboratory, Department of Medicine–Cardiology, The University of Chicago Pritzker School of Medicine, Chicago, Illinois 60637

ABSTRACT Although ST segment deflections have been widely utilized as a means of assessing the degree of underlying ischemic injury, the relationship of QRS complex alterations to the ischemic process is poorly understood. In this study we made a beat-to-beat analysis of the QRS complex in terms of ventricular activation time (CT) and R wave voltage (V) in the acutely ischemic porcine myocardium and analyzed the relationship of these responses to changes in the area of ischemic involvement, altered myocardial energy demands, and plasma $[K^+]_o$ levels.

With the onset of ischemia the QRS complex underwent a specific and reproducible biphasic sequence with an initial decrease in CT and V indicating a transient increase in the conduction velocity of the ischemic tissue. Subsequently both CT and V returned briefly to control and then increased dramatically, now indicating a marked decrease in conduction velocity. The time when CT first began to increase (Tc) was shortened by enlarging the area of ischemia or after an inotropic intervention and was lengthened by decreasing the area of ischemia or with administration of propranolol. Moreover Tc was found to be inversely proportional to plasma $[K^+]_o$ in the range 3.4–8.8 mM, above which the initial decrease in CT and V was no longer present.

We conclude that this biphasic sequence of QRS alterations in early myocardial ischemia is attributable to a progressive leakage of potassium out of the ischemic cells which in turn alters both the time-course and transmural pathway of the activation process through the ischemic tissue. These changes are related to both inotropic state and the area of ischemic involvement.

Dr. Brooks is the recipient of a Research Career Development Award from the National Institutes of Health (HL 70-132-02).

Received for publication 11 April 1975 and in revised form 15 October 1975.

INTRODUCTION

Although ST segment deflections have been widely utilized as a means of assessing the degree of underlying ischemic injury (1, 2) the relationship of QRS complex alterations to the ischemic process is poorly understood. The casual observations of changes in R wave amplitude noticed by some ST segment investigators after coronary artery occlusion in the dog (3-5) as well as the more specific studies of Hamlin et al. (6-8), Scher (9), and Durrer and van der Tweel (10) in the dog and goat suggest that ischemic QRS complex alterations may bear characteristic temporal and/or spatial relationships to the underlying ischemic process.

In the present study we have characterized the temporal sequence of QRS complex alterations during early myocardial ischemia in the intact porcine heart, their modification by changes in the area of ischemic involvement, and altered myocardial energy demands, as well as the important role of potassium in their genesis.

METHODS

Experimental techniques. Experiments were performed in 18 open-chest domestic pigs weighing from 30 to 45 kg. After induction of anesthesia with a small intravenous injection of thiopental, the animals were anesthetized with an intravenous infusion of a warmed solution of alpha chloralose (60 mg/kg). During the study supplementary doses of chloralose were given in order to maintain a relatively uniform state of anesthesia. Respiration was maintained by a volume respirator (Harvard Apparatus Co., Inc., Millis, Mass.), regulated to maintain an arterial pH of 7.45 ± 0.05 throughout the experiment. The pump was connected to a tracheostomy tube and supplemental oxygen was administered to maintain arterial oxygen saturation at 95%. The heart was exposed by a midsternal thoracotomy, a pericardiotomy was performed, and a pericardial cradle was created to support the exposed heart.

The anterior left ventricular free wall supplied by branches of the left anterior descending coronary artery was

selected for study. Epicardial electrical potentials were recorded by a firmly attaching atraumatic electrode (diameter, 1.0 cm) recently designed for this purpose (11). The electrode was positioned over the myocardium supplied by the particular arterial branches selected and fixed to the epicardial surface with a new tissue bonding agent, Eastman 910 (Eastman Chemical Division, Kingsport, Tenn.) (12).

Silk ligatures (00) were placed around the selected artery at various distances from its origin. Reversible occlusion of any of the ligatures was achieved by tightening the silk snares with a polyethylene collar. The duration of the occlusions was limited to 150 s in order that complete electrical recovery of the ischemic tissue could reasonably be assured.

Experimental groups. The following three sets of experiments were performed to elucidate the mechanism underlying the observed ischemic changes in the QRS complex. In the initial experiments (group I), large and small areas of ischemic involvement were compared. Small areas of ischemia were produced by occluding the distal portion of the first or second major left ventricular branch of the anterior descending artery. Large areas of ischemia were produced by an occlusion of the anterior descending artery above the origin of the ventricular branch selected for the small area of ischemia, insuring then that the large area completely enclosed the small area. With occlusion, an area of cyanotic discoloration was identifiable and was drawn to scale on a previously sketched anterolateral view of the porcine heart. The surface area of ischemia so estimated ranged from 2 to 6 cm^2 with a small occlusion and 12–25 cm^2 with the larger occlusion.

In preliminary studies the sequence of QRS alterations was similar in both the dog and the pig. However, since they were more reproducible and pronounced in the latter, this animal was chosen as the experimental model for the study. Furthermore, in previous experiments it has been shown that occlusion of a specific length of the anterior descending artery in pigs produces an ischemic area of relatively uniform size and distribution (13). In addition, the less extensive distribution of collateral vessels in the pig ventricle, as compared to the dog ventricle (14), insured that occlusion of a single coronary artery branch resulted in an electrically identifiable area of ischemic damage.

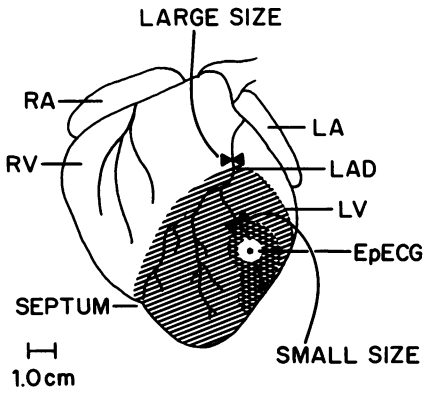

FIGURE 1 Illustration of small and large areas of ischemic involvement and epicardial electrode (EpECG) placement. The area of ischemic involvement was approximated by the cyanotic discoloration of the myocardium after left anterior descending (LAD) coronary artery occlusion.

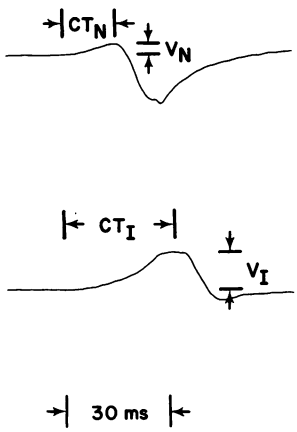

FIGURE 2 Measurements of CT and V before (upper tracing) and during (lower tracing) acute coronary artery occlusion. Control and ischemic measurements are identified by the subscripts "N" and "I," respectively. Both CT and V are measured from the base to the peak of the R wave.

In group II the pattern of ischemic QRS alterations was assessed in relation to pharmacologically induced alterations in myocardial energy demands. Isoproterenol, a beta-adrenergic agonist, at a constant intravenous infusion (0.4 μg/kg per min) and propranolol, a beta-adrenergic antagonist, (intravenous bolus, 1.0 mg/kg) were selected because of their known effects on oxygen consumption in the intact heart. With isoproterenol infusion the heart rate increased an average 64±10 beats/min ($P < 0.005$) and arterial blood pressure decreased by 31±7 mm Hg ($P < 0.025$). After propranolol administration the heart rate decreased an average 21±4 beats/min ($P < 0.005$) without any significant change observed in blood pressure.

In group III the pattern of ischemic QRS alterations was studied at different levels of plasma potassium ($[K^+]_o$).[1] $[K^+]_o$ was increased from control values by a slow intravenous infusion of KCl with an infusion pump. $[K^+]_o$ levels were obtained from carotid arterial samples taken immediately after the beginning of each coronary occlusion and were measured with a flame photometer (Instrumentation Associates, Millis, Mass.).

In groups II and III the epicardial electrode was centrally positioned in the cyanotic area. In group I it was placed in the center of the small area of ischemia and left in place when the larger occlusion was made. The manner of ligature and electrode placement in the group I animals is illustrated in Fig. 1.

Analysis of the QRS complex. All electrical signals were recorded with a Bioelectric Amplifier (no. 8811A, Hewlett-Packard Co., Palo Alto, Calif.) having a low- and high-frequency response of 0.15 Hz and 300 Hz (–3 dB),

[1] *Abbreviations used in this paper:* CPK, phosphokinase creatine; CT, ventricular activation time; E_k, potassium equilibrium potential; GTAF, Gomori-trichrome aldehyde fuchsin; $[K^+]_o$, plasma potassium; Tc, the period of time from the beginning of the occlusion to that point when CT_I/CT_N first exceeded unity; V, R wave voltage; P-M, Purkinje fiber-muscle. The subscripts "I" and "N" indicate measurements before and during coronary occlusion, respectively.

respectively, and were displayed on an eight-channel direct ink recorder and stored on FM magnetic tape (Hewlett-Packard Co.). The system permits playback of recordings and analysis at equivalent paper speeds of 800 mm/s. Voltage and time alterations in the QRS complex were characterized by the following measurements: Peak R wave voltage (V) before (V_N) and during (V_I) coronary occlusion was measured from the base to the peak of the R wave with a pair of calipers. Ventricular activation time (CT) before (CT_N) and during (CT_I) coronary occlusion was defined as the time from base to the peak of the R wave. Some investigators have alternatively referred to this measurement as "epicardial activation time" (15). The manner in which V and CT were experimentally determined is illustrated in Fig. 2. In the presence of a discernible Q wave, V and CT were measured from the deepest portion of the Q wave to the peak of the R wave. Changes in V and CT were respectively expressed by the ratios V_I/V_N and CT_I/CT_N. At equivalent paper speeds of 800 mm/s, CT could be determined within ±3%.

According to Scher (9), the genesis of the R wave recorded by an electrode overlying the left ventricular free wall is primarily determined by the depolarization of the underlying ventricular muscle mass in an endocardial to epicardial direction. Any ischemia-induced changes, then, in the depolarization process of the underlying myocardium should be reflected by alterations in the magnitude of the R wave. Similarly CT was measured because it yields the relative, though not absolute, time required by the wave of activation to move through the thickness of the ventricular wall (16). Although measurements of the duration of the QRS complex are more common, such estimates taken during ischemia are difficult because marked ST segment elevation prevents a clear differentiation between the end of the QRS complex and the beginning of the ST segment.

Verification of Purkinje network. The intramural distribution of Purkinje fibers in a few of the hearts was detailed post-mortem. 1-cm^2 sections of left ventricular free wall approximating 1.1 cm in thickness were fixed for 24 h with 10% neutral-buffered formalin. These were embedded and used to prepare 6-μm serial sections. Sections were cut in an endocardial to epicardial direction and every 30th through 32nd stained with hematoxylin and eosin, Weigert-Van Gieson, and Gomori-trichrome aldehyde fuchsin (GTAF) stains. This method yielded approximately 100 slides for examination of Purkinje fiber location in each section taken from the ventricular free wall.

All statistical analysis was carried out using the *t* test for unpaired samples (17).

RESULTS

The characteristic temporal sequence of changes in the QRS complex during a 150-s coronary occlusion (slow and fast speeds) is shown in Fig. 3. TQ-ST segment deflections were observed within 10 s after the occlusion and were seen to rise progressively with the duration of the ischemia. In addition, there was an immediate decrease in peak V after the occlusion, which was followed later by a dramatic increase which reached a plateau after approximately 120 s. With the release of the occlusion V and TQ-ST segment deflections rapidly returned towards normal within 2–4 beats.

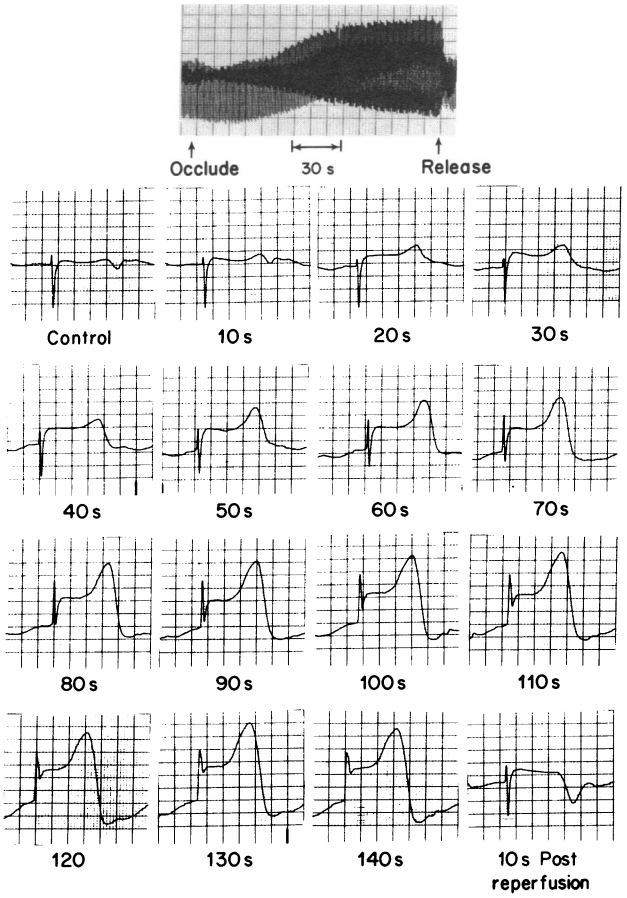

FIGURE 3 Epicardial electrograms during myocardial ischemia. Slow (0.5 mm/s) and fast (50 mm/s) tracings recorded with an epicardial electrode after acute coronary artery occlusion are illustrated. A decrease in peak V was observed early (20 s) and was followed later (50 s) by a dramatic increase. With the release of the occlusion V and TQ-ST segment deflections rapidly returned towards normal within 2–4 beats.

In Fig. 4 a beat-to-beat analysis of changes in both V and CT was made by plotting V_I/V_N and CT_I/CT_N vs. time. An initial decrease below the control line of reference was observed in V_I/V_N and CT_I/CT_N 5 s after occlusion, which suggested that a transient increase in the conduction velocity of the ischemic myocardium had occurred. At approximately 50 s after occlusion both V and conduction time increased to comparable values which were several times greater than unity and which now indicated a marked decrease in the conduction velocity of the ischemic myocardium. After reperfusion both V_I/V_N and CT_I/CT_N rapidly returned towards unity within a few beats.

The period of time from the beginning of the occlusion to that point when CT_I/CT_N first exceeded unity was designated "Tc" and was found to vary with the

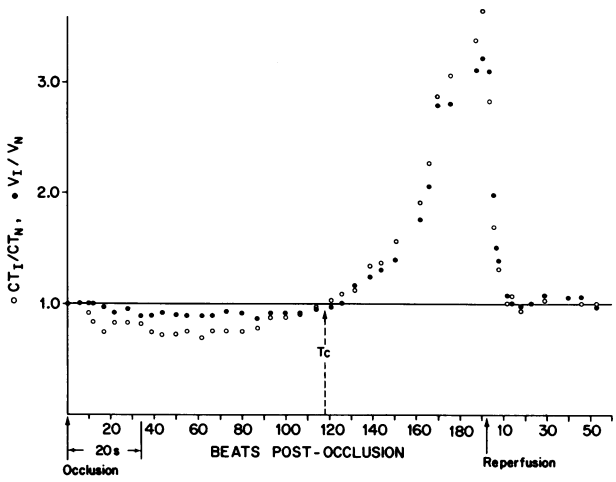

FIGURE 4 Changes in CT (CT_I/CT_N) and V (V_I/V_N) during myocardial ischemia. Changes in CT_I/CT_N and V_I/V_N were measured and plotted versus time after acute coronary artery occlusion and subsequent release. CT_I/CT_N and V_I/V_N decreased to values < 1.0 early and later increased to several times unity. CT_I/CT_N is first observed to exceed 1.0 at time Tc. With the release of the occlusion CT_I/CT_N and V_I/V_N rapidly returned towards normal within 2–4 beats.

area of ischemia (group I) and the pharmacologic status of the animal (group II). Cumulative data illustrating the alterations in Tc as a function of the area of ischemic

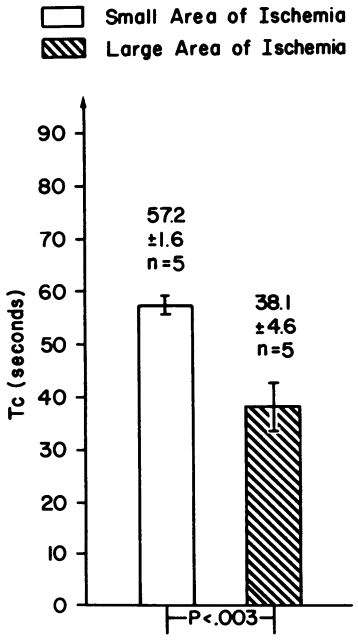

FIGURE 5 The effect of changes in the area of ischemic involvement on the parameter Tc. A large area of ischemia (12–25 cm^2) is seen to shorten Tc when compared to a smaller area (2–6 cm^2).

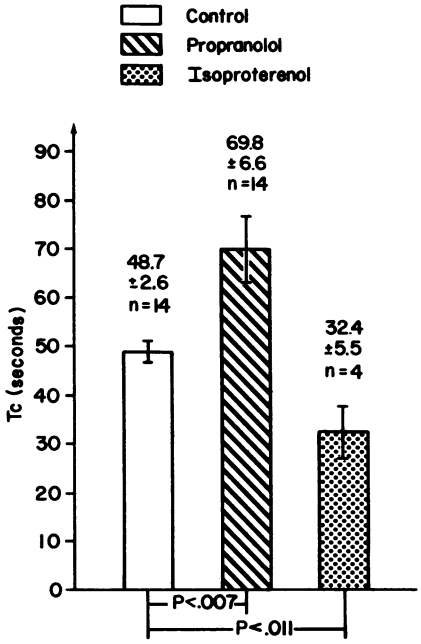

FIGURE 6 The effect of selected pharmacologic interventions on the parameter Tc. The β-agonist isoproterenol (0.4 μg/kg per min) shortens Tc and the β-antagonist propranolol (1.0 mg/kg) lengthens it.

involvement and of isoproterenol and propranolol infusion are shown in Fig. 5 and Fig. 6, respectively. Tc was significantly and consistently shortened after occlusion of a large coronary artery ($P < 0.003$) and isoproterenol infusion ($P < 0.011$). Conversely, it was consistently lengthened with an occlusion of a small coronary artery or propranolol administration ($P < 0.007$).

The effect of changes in extracellular potassium concentration of Tc was evaluated in the group III experiments. In these animals, $[K^+]_o$ was progressively raised by a slow, steady KCl infusion with the epicardial electrode being left in place and repeated occlusion of the same artery made. The cumulative data from a representative animal after 26 reversible occlusions at varying $[K^+]_o$ levels are shown in Fig. 7. Tc is seen to be inversely proportional to $[K^+]_o$ in the range 3.4-8.8 mM. At $[K^+]_o$ levels greater than this the initial decrease in either V or CT was no longer present, and V_I/V_N and CT_I/CT_N began to rise to values > 1.0 within 2–4 beats after coronary artery occlusion. In the absence of KCl infusion, control $[K^+]_o$ levels in the pig averaged 3.7± 0.15 mM.

Purkinje fibers were identifiable with all three stains, but the GTAF stain provided the best means to differentiate these specialized cells from ordinary cardiac muscle. Cell shape resembled a round cylinder of ap-

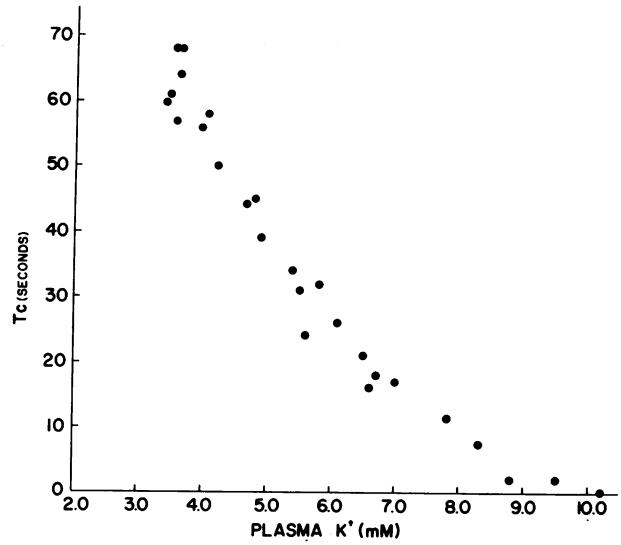

FIGURE 7 The effect of increasing $[K^+]_o$ levels on the parameter Tc. Tc is inversely proportional to $[K^+]_o$ in the range 3.4–8.8 mM. No biphasic alterations in CT or V were observed at $[K^+]_o$ levels greater than 8.8 mM.

proximately 60 μm diameter. The cytoplasm was clear, suggesting a rich glycogen content. With serial sectioning the concentration of the fibers was found to be the greatest in the subendocardial layers with gradual thinning and branching out as the epicardial surface was approached. Single, slender fibers were clearly visible through 8 mm in the average 11-mm section of the wall, but could not be identified immediately underneath the epicardial surface of the heart. The presence and concentration of Purkinje fibers at subendocardial and subepicardial levels in the left ventricular free wall of a representative heart are depicted in Fig. 8. Fibers were observed to travel in various radial and tangential directions throughout the ventricular free wall without regard for the orientation of the neighboring bundles of cardiac muscle.

DISCUSSION

Effects of ischemia and hyperkalemia on the QRS complex. These experiments demonstrate a characteristic relationship between acute myocardial ischemia and the QRS complex. The temporal sequence described herein for the first time in the intact porcine heart is unequivocal and reproducible. The QRS complex alterations are biphasic with an initial small decrease in CT and V (CT_I/CT_N; $V_I/V_N < 1.0$), which is followed by a rapid return to the base line ($CT_I/CT_N = 1.0$), and consequently, a characteristic and dramatic increase (CT_I/CT_N; $V_I/V_N > 1.0$) to several times the control levels. With release of the occlusion and reperfusion there is very rapid return to control levels.

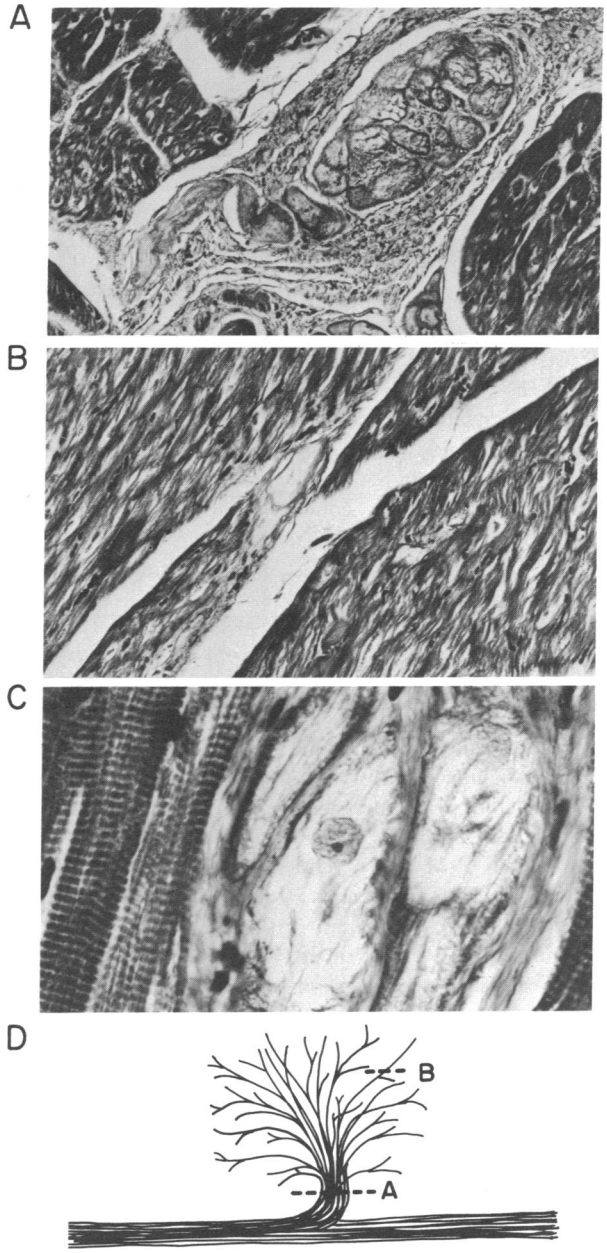

FIGURE 8 Purkinje fiber innervation of the left ventricular free wall in the porcine heart. (*a*) Subendocardial bundle of Purkinje fibers surrounded by thick connective tissue sheath (GTAF, × 250). (*b*) Two Purkinje fibers located in the subepicardium (GTAF, × 250). (*c*) Purkinje fibers and neighboring cardiac muscle. Cytoplasm is generally clear containing only prominent nucleus and scattered fibrillar material (GTAF, × 1,000). (*d*) Model of Purkinje fiber innervation in the left ventricular free wall. The concentration of the fibers is greatest in the subendocardial layers gradually thinning and branching out as the epicardial surface is approached.

The observed changes in activation time indicate that the conduction velocity in the ischemic myocardium is initially accelerated (before Tc) and then later depressed (after Tc) by the ischemic process (18). In addition, the corresponding and near simultaneous change in V suggests that it also is in some manner related to the alterations in the conduction velocity of the depolarizing wave as it travels through the ischemic myocardium.

Potassium leakage from the ischemic cells into the surrounding extracellular space is assumed to be responsible for these biphasic QRS complex alterations. In vitro studies with Purkinje fibers and isolated heart preparations (19, 20) in which $[K^+]_o$ were gradually increased from 2.5 to 7.0 mM have also demonstrated the phenomenon of biphasic conduction velocity. Enhanced conduction velocity and a shortened conduction time is observed within the range of 2.5–5.4 mM. At levels greater than 5.4 mM conduction velocity is depressed. The biphasic conduction velocity (time) response with hyperkalemia has also been shown to exist in vivo in dogs (21), where conduction times decreased with increases in $[K^+]_o$ up to 8.8 mM. At levels above 8.8 mM conduction times were prolonged.

The phenomenon is also observed at the Purkinje fiber-muscle (P-M) junction. Matsuda et al. (22) noticed a slight but distinct and rather abrupt delay of 5-10 ms in impulse conduction from the terminal Purkinje fiber to the ventricular muscle fiber. Mendez et al. (23) then observed that with increases in $[K^+]_o$ up to 6 mM, the P-M delay decreased. With an increase in $[K^+]_o$ up to 8 mM, the P-M delay increased and with further increases in $[K^+]_o$ to 11 mM a total conduction block was observed. Thus, potassium appears to exert its effects on conduction velocity in at least three different locations within the conduction system of the heart: the Purkinje fibers, the muscle fibers, and the P-M junction.

The evidence which implicates potassium as the agent most likely responsible for the biphasic alterations in CT observed during the course of ischemia is as follows: (*a*) Potassium is known to be released from ischemic myocardial cells after coronary artery occlusion (24-26). (*b*) The changes seen here in activation time in the ischemic porcine heart are identical to the changes in conduction time observed in the nonischemic but progressively hyperkalemic canine heart. With either increasing duration of the ischemia or a steady infusion of KCl, activation time first decreases and then increases (21). (*c*) Injection of KCl into a single coronary artery in the normal (nonischemic) heart results in widening of the QRS complex and increases in R wave height in those leads overlying the distribution of the artery (27). And (*d*) Tc is a function primarily of the extracellular potassium concentration as was demonstrated in our group III experiments. If $[K^+]_o$ is raised to values greater than 8.8 mM, essentially no biphasic alterations in either activation time or V are observed after coronary occlusion. This value of $[K^+]_o$ is higher than those values seen in vitro with Purkinje fibers (19) and at P-M junctions (23) but is the same as that reported in vivo in the canine heart (21).

It remains unclear as to how a slight increase in $[K^+]_o$ effects an increase in conduction velocity. The addition of KCl to a solution bathing ventricular muscles produces a lowering of the resting potential, a reduction in amplitude and upstroke velocity of phase 0, and a decreased duration (28, 29). An increase in the $[K^+]_o$ would, by reducing the magnitude of E_K, tend to move the transmembrane potential towards the Na^+ potential, i.e., in the direction of depolarization. However, the observed effect is the opposite, which suggests that an increase $[K^+]_o$ may increase Na^+ extrusion (30) or increase K^+ permeability (31). Recently, Dominguez and Fozzard (19) have calculated that membrane resistance decreases with increasing $[K^+]_o$. This change in the passive properties of the membrane did not appear to change sufficiently to account for the enhanced conduction velocity in the range of 2.5–5.4 mM $[K^+]_o$. They suggested that with the cell partially depolarized by the increase in $[K^+]_o$ the change in voltage necessary to raise the membrane to threshold is less and the current required is less. If less current is required to excite the membrane, it might be activated sooner. The earlier activation would then presumably be reflected by an increase in conduction velocity.

Tc and the rate of ischemic injury. Since control $[K^+]_o$ levels in the pig (3.7 mM) fall clearly within the range of $[K^+]_o$ where further increases in concentration enhance conduction velocity (19-21, 23), and since elevations in $[K^+]_o$ to values exceeding 8.8 mM result in a loss of biphasic QRS changes, we propose that the parameter Tc identifies that point in time after the coronary occlusion when the average $[K^+]_o$ of the ischemic tissue first exceeds 8.8 mM.

If such an assumption is valid, then Tc is an indicator of the rate at which potassium accumulates extracellularly within the ischemic tissue. As illustrated in Figs. 5 and 6, a shortened Tc induced by either a large coronary artery occlusion or isoproterenol infusion suggests a more rapid rate of potassium leakage and accumulation, ventricular activation abnormalities, and probable membrane injury. An increase in Tc, as observed after propranolol administration, suggests in turn that the rate at which potassium accumulates and ischemic injury occurs has been slowed.

Tc is then a *temporal* parameter identifying the relative rate of potassium leakage and membrane injury in the ischemic tissue. Tc should be distinguished from

other measurements made during ischemia, i.e., the area of cyanotic discoloration and ventricular bulging, and sites of TQ-ST segment elevation and CPK depletion which characterize the ischemia in *spatial* terms identifying its location and extent in the ventricular wall. For instance, in the group I animals occlusion of the larger artery resulted in a larger area of ischemic involvement as determined by the area of cyanotic discoloration. In addition to this spatial change, the rate of potassium leakage was accelerated in the larger area as indicated by a shortening of Tc. How a spatial change in the ischemic process effects a temporal change is not altogether clear. The potassium leakage is believed due to increased membrane permeability brought about by either the lack of adequate oxygen supply and/or the production and accumulation of inhibitory end products of glycolysis such as H^+ ion and lactate in the ischemic tissue (32, 33). Presumably a lower oxygen tension, faster production, and slower removal of the inhibitory materials, or a slower removal of the leaked potassium from the larger area could account for the observed difference in Tc. The effect of changes in area on Tc are, however, rather modest. A four- to fivefold increase in the area of ischemia shortened Tc by only 33%.

Although both an increase in the area of ischemia and the administration of isoproterenol resulted in similar decreases in Tc (− 33%), it does not necessarily follow that isoproterenol shortened Tc by increasing the area of ischemic involvement, especially not by effecting a fourfold increase (34). Instead it might have had a more direct effect on the myocardial cell. For example, the heart rate increase induced by isoproterenol could have accelerated the potassium flux out of the ischemic cells just as it does in normal ones (35, 36). In addition, the greater myocardial metabolic demands imposed by isoproterenol (37) could have accelerated the decline in oxygen tension or the accumulation of end products in the ischemic segment without necessarily effecting a large increase in the area of ischemia. It is significant that anoxia-induced potassium loss in the rat ventricle is enhanced by stimulation (38).

In a similar manner the lengthening of Tc with propranolol present might be attributable to (*a*) a decrease in the area of ischemia (39) and/or (*b*) a decrease in heart rate and in the metabolic demands of the ischemic segment (37). Furthermore, as observed by Choi et al. (40), propranolol decreased potassium flux out of normal cells and it may do the same in ischemic ones as well.

The assumptions concerning the effects of changes in both the area of ischemia and pharmacologic intervention on the rate of potassium leakage in the ischemic tissue may have important clinical implications. In many experimental studies the TQ-ST segment deflection which is also strongly potassium dependent (41-43) has been utilized to judge the efficacy or detrimental effects of various interventions on their ability to decrease the area of ischemia (34, 44). A decrease in the magnitude of the TQ-ST segment is nearly always attributed to a reduction in the area of ischemia, and although this is often shown to be the case by way of other criteria, some interventions may have merely slowed down the rate of potassium accumulation and have had no demonstrable effect on the area of ischemia and eventual infarct size. Of even more immediate concern, however, are those interventions which change neither the area of ischemia nor the rate of tissue injury but still give the electrocardiographic illusion of doing so. Potassium for instance shortens Tc, suggesting that the rate of tissue injury has been accelerated. At the same time it can severely reduce or even obliterate the TQ-ST deflection (43), thus suggesting that a reduction in ischemic injury has taken place. At present there is no reason to believe that potassium either increases or decreases the area of ischemia or the rate of tissue injury. Failure to consider the importance of potassium in the genesis of either the QRS or TQ-ST alterations may result in the inappropriate classification of certain interventions as efficacious when, in fact, they may be harmful. The observation that glucose-potassium-insulin administration reduced TQ-ST deflections (45) and histologic evidence of ischemic necrosis (46) is contrary to the clinical findings of Lesch et al. (47) in which it was concluded that tolerance to ischemia was not extended but instead adversely affected by glucose-potassium-insulin administration.

Changes in the pathway of ventricular activation during ischemia. The shape of the ventricular complex recorded at the heart's surface is determined by the pattern of ventricular activation, heart mass, electrode position, and the magnitude and upstroke velocity of the action potential of the muscle cells (48, 49). Since ischemia and progressive hyperkalemia effect similar changes in CT, the corresponding biphasic sequence of V changes seen during ischemia is presumably the result of alterations in the conduction velocity of the activation wave as it travels through the ischemic region. According to Schaefer and Haas (49) concomitant changes in R wave amplitude and QRS duration are due, in most cases, to an inhomogeneous change in conduction velocity. Changes in action potential configuration cannot account for the R wave alterations because they occur somewhat later in ischemia and, unlike the QRS complex, do not exhibit any biphasic character (32).

There are at least two different mechanisms by which local changes in conduction velocity may influence the R wave. First, it is recognized that the QRS complex is the result of strong mutual cancellation. In the pig,

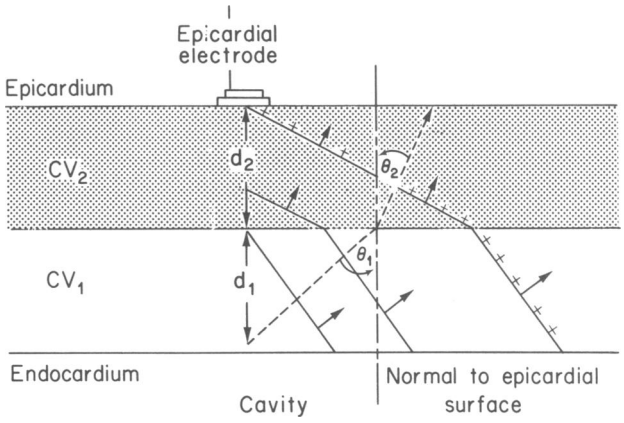

FIGURE 9 Model of the pathway of activation in an ischemic segment of the left ventricular free wall. In the nonischemic (clear) portion of the segment the depolarizing wave travels with normal conduction velocity CV_1 and at an oblique angle θ_1. When the wave encounters the ischemic tissue (shaded) with conduction velocity CV_2 it is refracted according to Snell's Law and assumes a different pathway θ_2. See text for additional details.

because of its extensive transmural Purkinje fiber ramifications (50), the free wall of the ventricle is activated more or less simultaneously in an apex to base direction (51). This "single burst" of mutually cancelling depolarization accounts for the normally small R/S ratio found in leads overlying the free wall (7). With the development of ischemia, Hamlin et al. (8) and Durrer et al. (52) suggested that with delayed or "tardy depolarization" the ischemic tissue would be depolarized with a wave front proceeding in an endocardial to epicardial direction, but relatively unopposed because of that "tardiness." This "tardiness" would then account for the observed increase in CT and the unopposed wavefront for the large R waves recorded by electrodes overlying the ischemic tissue. A small decrease in CT, as is observed early in ischemia, would increase the degree of cancellation in the wall and thus decrease the height of the R wave.

The second mechanism supposes that, late in ischemia, not only is the wave of depolarization delayed and CT prolonged, but the direction of wave transmission through the wall is also altered. Pruitt (53) and Durrer et al. (54) concluded that the depolarization wave is normally oriented tangentially in the pig as it moves in an apex to base direction. This concept is illustrated in Fig. 9. In the pig, the wave would then normally travel from the endocardium towards the epicardium at a relatively oblique angle Θ_1, and with conduction velocity CV_1. We suggest that in the presence of ischemia the normal wave is refracted as it enters the ischemic tissue which has a conduction velocity CV_2, different from that in the normal myocardium. The new pathway Θ_2 that the wave now assumes can be obtained by applying Snell's Law of Refraction or

$$\sin \Theta_1 / \sin \Theta_2 = CV_1 / CV_2$$

With an increased conduction velocity during early ischemia (before Tc) Θ_2 becomes greater than Θ_1 and the wave assumes a more tangential pathway with the V initially decreasing. Later in ischemia (after Tc) a decrease in CV_2 occurs, with Θ_2 now less than Θ_1 and the depolarizing wave now assuming a more radial pathway, with V dramatically and progressively increasing. According to Durrer and van der Tweel (10), because of the widespread Purkinje fiber ramifications and wave front cancellation found in the inner layers of the pig heart, slight changes in the activation process of the subepicardial layers are expected to have considerable influence on the height of the R wave, as suggested by the second mechanism. Thus, the observed R wave changes in the pig may be due to a change in the degree of cancellation in the ischemic tissue, an actual change in the pathway of the activation process, or both.

In conclusion, it is reasonable to characterize the sequence of QRS complex alterations observed in the pig after coronary artery occlusion in the following manner: (*a*) Changes in CT (CT_I/CT_N) and V (V_I/V_N) occur within seconds after occlusion. (*b*) Changes in V_I/V_N and CT_I/CT_N are biphasic with an early decrease and a later increase to several times unity. (*c*) Changes in V are due to either temporal and/or spatial alterations in the pathway of the activation process in the ischemic tissue. (*d*) The changes in both CT and V are due to an immediate and steadily increasing extracellular accumulation of potassium in the ischemic tissue. (*e*) Tc is a measure of the rate of extracellular potassium accumulation in the ischemic tissue. And (*f*) the rate of potassium accumulation can be altered by changes in the area of ischemic involvement and with the use of selected pharmacologic agents.

ACKNOWLEDGMENTS

The authors thank Dr. Morton Arnsdorf for his helpful suggestions in reviewing the manuscript. We also thank Barbara Lidl for technical assistance and Michelle McMillion for help in the preparation of this manuscript.

This work was supported by grants from the U. S. Public Health Service (HL 4368133), The Louis Block Fund, and Sinton Charitable Associates of the University of Chicago.

REFERENCES

1. Braunwald, E., and P. R. Maroko. 1974. The reduction of infarct size—an idea whose time (for testing) has come. *Circulation.* **50**: 203–209.
2. Holland, R., and H. Brooks. 1975. Precordial and epicardial surface potentials in myocardial ischemia: a theoretical and experimental analysis of the TQ and ST segments. *Circ. Res.* **37**: 471–480.

3. Sayen, J. J., G. Peirce, A. H. Katcher, and W. F. Sheldon. 1961. Correlation of intramyocardial electrograms with polarographic oxygen and contractility in the nonischemic and regionally ischemic left ventricle. *Circ. Res.* **9**: 1268–1279.
4. Rakita, L., J. L. Bordans, S. Rothman, and M. Prinzmetal. 1954. Studies on the mechanism of ventricular activity. XII. Early changes in the RS-T segment and QRS complex following acute coronary artery occlusion. Experimental study and clinical applications. *Am. Heart J.* **48**: 351–372.
5. Hellerstein, H. K., and R. L. Hamlin. 1956. Studies in differential vectorcardiography of the dog. II. Early changes in QRS vectorcardiogram and electrocardiogram following experimental left circumflex coronary artery occlusion. *Circulation.* **14**: 953. (Abstr.)
6. Hamlin, R. L., F. S. Pipers, H. K. Hellerstein, and C. R. Smith. 1968. QRS alterations immediately following production of left ventricular free-wall ischemia in dogs. *Am. J. Physiol.* **215**: 1032–1040.
7. Hamlin, R. L., and A. M. Scher. 1961. Ventricular activation process and genesis of QRS complex in the goat. *Am. J. Physiol.* **200**: 223–228.
8. Hamlin, R. L., C. R. Smith, H. K. Pellerstein, and R. S. Pipers. 1969. Alterations in QRS during ischemia of the left ventricular free-wall in goats. *J. Electrocardiol. (San Diego).* **2**: 223–228.
9. Scher, A. M. 1964. The sequence of ventricular excitation. *Am. J. Cardiol.* **14**: 287–293.
10. Durrer, D., and L. H. van der Tweel. 1957. Excitation of the left ventricular wall of the dog and goat. *Ann. N. Y. Acad. Sci.* **65**: 779–803.
11. Holland, R., F. Pashkow, and H. Brooks. 1974. Atraumatic epicardial electrode and rapid sampling switch for cardiac surface mapping. *J. Appl. Physiol.* **37**: 424–427.
12. Eastman Chemical Products, Inc. 1974. Three new cyanoacrylate adhesives. Product brochure. R-206A.
13. Brooks, H., J. Al-Sadir, J. Schwartz, B. Rich, P. Harper, and L. Resnekov. 1975. Biventricular dynamics during quantitated anteroseptal infarction in the porcine heart. *Am. J. Cardiol.* **36**: 765–775.
14. Schaper, W. 1971. The collateral circulation of the heart. North Holland Publishing, Amsterdam. 259 pp.
15. Daniel, T. M., J. P. Boineau, and D. C. Sabiston, Jr. Comparison of human ventricular activation with a canine model in chronic myocardial infarction. 1971. *Circulation.* **44**: 74–89.
16. Schaefer, H. The general order of excitation and of recovery. 1957. *Ann. N. Y. Acad. Sci.* **65**: 743–767.
17. Snedecor, G. W., and W. G. Cochran. 1967. Statistical Methods. Iowa State University Press, Ames. 6th edition. 593 pp.
18. Gambetta, M., and R. W. Childers. 1969. The initial electrophysiologic disturbance in experimental myocardial infarction. *Ann. Intern. Med.* **70**: 1076. (Abstr.)
19. Dominguez, G., and H. A. Fozzard. 1970. Influence of extracellular K^+ concentration on cable properties and excitability of sheep cardiac Purkinje fibers. *Circ. Res.* **26**: 565–574.
20. Swain, H. H., and C. L. Weidner. 1967. A study of substances which alter intraventricular conduction in the isolated dog heart. *J. Pharmacol. Exp. Ther.* **120**: 137–146.
21. Schreiner, E., M. F. Arnsdorf, M. Gambetta, and R. W. Childers. 1969. Electrophysiological changes in hyperkalemia. *Circulation Suppl. III.* **40**: 181. (Abstr.)
22. Matsuda, K., A. Kamiyama, and T. Hoshi. 1967. Configuration of the transmembrane potential of the Purkinje-ventricular fiber junction and its analysis. *In* Electrophysiology and Ultrastructure of the Heart. T. Sano, I. Mizuhira, and K. Matsuda, editors. Grune & Stratton, Inc., New York. 267 pp.
23. Mendez, C., W. J. Mueller, and X. Urguiaga. 1970. Propagation of impulses across the Purkinje fiber-muscle junctions in the dog heart. *Circ. Res.* **26**: 135–150.
24. Harris, A. S., A. Bisteni, R. A. Russell, J. C. Brigham, and J. E. Firestone. 1954. Excitatory factors in ventricular tachycardia resulting from myocardial ischemia. Potassium a major excitant. *Science (Wash. D. C.).* **119**: 200–203.
25. Case, R. B., M. G. Nasser, and R. S. Crampton. 1969. Biochemical aspects of early myocardial ischemia. *Am. J. Cardiol.* **24**: 766–775.
26. Regan, T. J., M. A. Harman, P. H. Lehan, W. M. Burke, and H. A. Oldewurtel. 1967. Ventricular arrhythmias and K^+ transfer during myocardial ischemia and intervention with procaine amide, insulin or glucose solution. *J. Clin. Invest.* **46**: 1657–1668.
27. Ekmekci, A., H. Toyoshima, J. K. Kwoczynski, T. Nagaya, and M. Prinzmetal. 1961. Angina Pectoris. V. Giant R and receding S wave in myocardial ischemia and certain nonischemic conditions. *Am. J. Cardiol.* **7**: 521–532.
28. Déleze, J. 1959. Perfusion of a strip of mammalian ventricle. Effects of K-rich and Na-deficient solutions on transmembrane potentials. *Circ. Res.* **7**: 461–465.
29. Bammer, H., and K. E. Rothschuh. 1952. Über die Erregungsleitung im Froschherzstreifen unter der Wirkung von Kalium-ionen und anderer herzmuskeleigenen Substanzen. *Z. gesamte. Exp. Med.* **119**: 402–414.
30. Weidmann, S. 1956. Shortening of the cardiac action potential due to a brief injection of KCl following the onset of activity. *J. Physiol.* **132**: 157–163.
31. Cranefield, P. F., and B. F. Hoffman. 1958. Electrophysiology of single cardiac cells. *Physiol. Rev.* **38**: 41–76.
32. Trautwein, S., and J. Dudel. 1956. Aktionspotential und Kontraktion des Herzmuskels im Sauerstoffmangel. *Pfluegers Arch. gesamte Physiol. Menschen Tiere.* **263**: 23–40.
33. Webb, J. L., and P. B. Hollander. 1956. Metabolic aspects of the relationships between the contractility and membrane potentials of the rat atrium. *Circ. Res.* **4**: 618–626.
34. Maroko, P. R., J. K. Kjekshus, B. E. Sobel, T. Watanabe, J. W. Covell, J. Ross Jr., and E. Braunwald. 1971. Factors influencing infarct size following coronary artery occlusions. *Circulation.* **43**: 67–82.
35. Langer, G. A., and A. J. Brady. 1966. Potassium in dog ventricular muscle: kinetic studies of distribution and effects of varying frequency of contraction and potassium concentration of perfusate. *Circ. Res.* **18**: 164–177.
36. Parker, J. O., M. A. Chiong, R. O. West, and R. B. Case. 1970. The effect of ischemia and alterations of heart rate on myocardial potassium balance in man. *Circulation.* **42**: 205–217.
37. Braunwald, E. 1971. Control of myocardial oxygen consumption. Physiologic and clinical considerations. *Am. J. Cardiol.* **27**: 416–432.

38. Hercus, V. M., R. J. S. McDowall, and D. Mendel. 1955. Sodium exchanges in cardiac muscle. *J. Physiol.* **129**: 177–183.
39. Reimer, K. A., M. M. Rasmussen, and R. B. Jennings. 1973. Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. *Circ. Res.* **33**: 353–363.
40. Choi, S. J., J. Roberts, and G. J. Kelliher. 1972. The effect of propranolol and quinidine on ^{22}Na- and ^{42}K-exchange in the cat papillary muscle. *Eur. J. Pharmacol.* **20**: 10–21.
41. Kardesch, M., C. E. Hogancamp, and R. J. Bing. 1958. Effect of complete ischemia on the intracellular electrical activity of the whole mammalian heart. *Circ. Res.* **6**: 715–720.
42. Prinzmetal, M., A. Ekmekci, H. Toyoshima, and J. K. Kwoczynski. 1959. Angina Pectoris. III. Demonstration of a chemical origin of ST deviation in classic angina pectoris, its variant form, early myocardial infarction, and some noncardiac conditions. *Am. J. Cardiol.* **3**: 276–293.
43. Holland, R., and H. Brooks. 1975. ST segment mapping: fact and fallacy. *Circulation. Suppl. II.* **52**: 6. (Abstr.)
44. Maroko, P. R., P. Libby, J. W. Covell, B. E. Sobel, J. Ross, Jr., and E. Braunwald. 1972. Precordial S-T segment mapping: an atraumatic method for assessing alterations in the extent of myocardial ischemic injury. The effects of pharmacologic and hemodynamic interventions. *Am. J. Cardiol.* **29**: 223–230.
45. Sodi-Pallares, D., M. R. Testilli, B. L. Fishleder, A. Bisteni, G. A. Medrano, C. Friedland, and A. DeMicheli. 1962. Effects of an intravenous potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. Preliminary clinical reports. *Am. J. Cardiol.* **9**: 166–181.
46. Maroko, P. R., P. Libby, B. E. Sobel, C. M. Bloor, H. D. Sybers, W. E. Shell, J. W. Covell, and E. Braunwald. 1972. The effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. *Circulation.* **45**: 1160–1175.
47. Lesch, M., L. E. Teichholz, J. S. Soeldner, and R. Gorlin. 1974. Ineffectiveness of glucose, potassium, and insulin infusion during pacing stress in chronic ischemic heart disease. *Circulation.* **49**: 1028–1037.
48. Scher, A. M. 1962. Excitation of the heart. *Handb. Physiol. (Sect. 2).* **1**: 287–322.
49. Schaefer, H., and H. G. Haas. 1962. Electrocardiography. *Handb. Physiol. (Sect. 2).* **1**: 323–415.
50. Glomset, D. J., and A. T. A. Glomset. 1940. A morphologic study of the cardiac conduction system in ungulates, dog, and man. Part I: the sinoatrial node. *Am. Heart J.* **20**: 389–398.
51. Hamlin, R. L., and C. R. Smith. 1965. Categorization of common domestic mammals based upon their ventricular activation process. *Ann. N. Y. Acad. Sci.* **127**: 195–203.
52. Durrer, D., A. A. W. Van Lier, and J. Büller. 1964. Epicardial and intramural excitation in chronic myocardial infarction. *Am. Heart J.* **68**: 765–776.
53. Pruitt, R. D. 1962. Electrogram of bundle-branch block in the bovine heart. *Circ. Res.* **10**: 593–597.
54. Durrer, D., L. H. van der Tweel, S. Berreklouw, and L. P. van der Wey. 1955. Spread of activation in the left ventricular wall of the dog. IV. Two and three dimensional analysis. *Am. Heart J.* **50**: 860–882.