Activation of the Ischemic Ventricle and Acute Peri-Infarction Block in Experimental Coronary Occlusion

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Changes in left ventricular activation during the first 10 min. following occlusion of the anterior descending branch of the left coronary artery of dogs were studied by using multiple intramural electrodes. Intramural block and an increase in the amplitude of R were observed routinely in the outermost layers of muscle in the central zone of maximal ischemia as long as the occlusion was maintained. These changes were distinct from those produced by left bundle-branch block. Failure to propagate the accession process in normal fashion seems to be characteristic of ischemic heart muscle.

During the course of a series of experiments to study the acute changes produced by coronary occlusion on the recovery process of the electrocardiogram of the dog, an increased amplitude of R and a delayed intrinsic deflection were observed. These changes have not been studied in detail, though reported previously. In order to evaluate the significance of these changes experiments were designed to examine (1) the supposition that a form of intraventricular block distinguishable from left bundle-branch block is produced by coronary artery occlusion, (2) the reason for an increased amplitude of R in the ischemic region, (3) the incidence of local ventricular block associated with occlusion, (4) the duration, extent, and disappearance of block when the occlusion is released, and (5) the general order of activation of the left ventricle during the first few minutes of experimental coronary artery occlusion.

Methods

Experiments were conducted on healthy mongrel dogs anesthetized with intravenous injection of pentobarbital sodium, the initial dose being 25 mg./Kg. A Harvard animal respirator sufficed to maintain adequate ventilation. The heart was exposed through a horizontal trans-sternal incision and was cradled in reflected pericardial flaps. Its surface was kept moist with normal saline solution. A segment of the anterior descending branch of the left coronary artery was exposed to permit application of either a spring clamp or a small screw clamp to produce occlusion of the vessel. Either clamp could be released within a few seconds. In one experiment the artery was securely ligated with a cotton suture. Obliteration of the arterial lumen was confirmed at the end of several experiments by dividing the artery distal to the clamp.

After placing the arterial clamp, an occlusion of 2 to 4 min. duration was performed and the ischemic region of the left ventricle explored with a cotton-pledget electrode to find the region of greatest change in the form of QRS. After release of the occlusion, a multipole electrode was inserted and fixed in position in the myocardium at the selected site. Similar electrodes were then fixed in the wall of the left ventricle at varying distances from the first electrode. The insertion of the electrodes is illustrated in figure 6. The total number of electrodes in any one experiment ranged from 2 to 6. A reference electrode was fixed to the surface of the right ventricle. The electrodes were similar to those described previously except that the distance between the 3 fixed points was 3 mm. The electrodes were inserted so that the first point lay in the inner region of the ventricular wall where the first R appeared. The fourth point touched the epicardial surface. The positions of the electrodes were identified anatomically at the conclusion of the experiment by direct visualization. They could not move during the experiment. After several minutes injury effects and T wave changes appeared to be stabilized. The effects of a second occlusion were then recorded. Subsequent
osculations were performed after control values had been re-established.

The recording equipment used was a Hathaway oscilloscope and a 5-channel oscillograph with amplifiers modified to provide an infinite input resistance, a convenient lead selector switch, and proper attenuation. All records were obtained at a paper speed of 4 inches/sec. The Wilson central terminal was used as the reference potential for the unipolar leads. Bipolar leads from points on the electrode were recorded so that when the potential differences \( V_n - V_{(n+1)} \) were positive, an upright deflection was inscribed.

Left bundle-branch block was produced at the end of 5 occlusion experiments by severing the bundle with a curved iridectomy knife introduced through a stab wound in the lateral-posterior wall of the left ventricle. Completeness of block was judged by the appearance of initial maximally positive deflections recorded from the subendocardial surface, and the presence of a broad, slurred and notched R together with the absence of Q at VF.

In the last experiment, a d.c. stimulus obtained from a Grass stimulator was applied to the endocardial point in the ischemic region. The stimulus was 0.004 sec. in duration and of sufficient intensity to pace the heart.

All tracings were analyzed by measuring the peak of R and comparing the time of its inscription to the peak of R of the reference electrode. Measurements were made on a Cambridge Universal Measuring Machine and were reproducible to 0.0004 sec. The general method, as well as a critique of this method of analysis has been described previously.²

A total of 17 consecutive experiments were performed. The changes described below were observed in 16 animals, 4 of which died during the experiments due to ventricular fibrillation. Complete data were obtained in the remaining 12 experiments. Data on 2 or more occlusions were obtained in 5 of these experiments. In the one experiment where changes were not seen, significant electrocardiographic changes (injury and ischemia) were not produced by occlusion of the anterior descending branch of the left coronary artery followed by ligation of the posterior descending branch of the left coronary artery. Ventricular fibrillation occurred after ligation of the circumflex artery.

**RESULTS**

Results are summarized in figure 1.

**Control Observation**

There was an orderly progression in the amplitude of R from the subendocardial lamina of muscle to the epicardial surface of the anterior and lateral free wall of the left ventricle (fig. 2). A sharp upright deflection was recorded in each corresponding bipolar lead. An R was present at every point, the only exception occurring when the electrode was plunged into the papillary muscle. Even in these instances the wall proper could be identified by the appearance of a small R at the innermost point when the electrode was withdrawn slowly. It was usual for the R to be preceded by a small negative deflection, but at times this was absent at the epicardial point particularly in the anterior apical region of the ventricle. The time at which the peak of R was inscribed at electrode points from the subendocardial to the epicardial surface increased by regular increments except when points 3 and 4 were anatomically juxtaposed. The time differences between successive electrode points were less in the basal region of the ventricle compared with the remainder of the anterior free wall. An S of varying breadth was recorded from all points explored over the anterior and lateral walls. Activation of all innermost electrode points occurred within an average
ACTIVATION OF ISCHEMIC VENTRICLE

ISCHEMIC

CONTROL 5'OCCL  CONTROL 20hOCCL  CONTROL 5'OCCL  CONTROL 20hOCCL

NORMAL

FIG. 2. Left: Potential variations at 4 points of an intramural electrode in the region of greatest intensity of ischemia in two experiments. Point 1 was located just beneath the endocardial surface and point 4 touched the epicardial surface of the left ventricle. The times of inscription of the peaks of R are noted with reference to the peak of R at the reference electrode. After 5 min. occlusion (experiment 6) there is a noticeable delay in the peak of R at points 3 and 4. The Q has disappeared at point 1. The amplitude of R at points 3 and 4 is somewhat increased. A minute Q has appeared at points 2 through 4. There is a decrease in voltage of the intrinsic deflection. After 20 hours' occlusion (experiment 5) a prominent Q is present at all points. It is followed by a broad late R. At this time activation reaches the epicardial surface before the subendocardial region is activated (point 4 before point 1). Right: Activation of 4 points of an intramural electrode in the "normal" zone distant from the central zone of maximal ischemia. Same experiments. At the end of an occlusion 5 min. in duration there are no significant changes in the time of activation of muscle adjacent to the 4 electrode points. In the occlusion of 20 hours' duration the R has disappeared at point 1 and has left only a vestigial slur; it is greatly reduced in amplitude at point 2 where it is preceded by a small Q. At points 3 and 4 the amplitude of R has decreased and a prominent Q is present. There is no delay in intramural activation. In this and all subsequent tracings the interval between time lines is 0.1 sec. and the standardization is 1/20 normal.

interval of 0.0096 sec. However, considerable variation was encountered due to the fact that exact replicate placement of the electrodes from dog to dog was not possible.

Experimental Observations

During Occlusion. For convenience results were grouped arbitrarily according to the anatomic position of the electrodes in regard to their proximity to the central zone of ischemia and to the duration of the occlusion. Some overlapping of data is recognized because the change in intensity of ischemia from the central zone of maximal ischemia to the periphery is gradual.

Central zone of ischemia (fig. 2). During the first few seconds the R at the innermost electrode point became smaller and quickly disappeared leaving a vestigial slur on the initial downstroke of S to indicate that only a few electromotive forces remained intact in the subendocardial regions. Many times there was a slight decrease in amplitude of R at the epicardial point. There was no significant change in the time of activation of the endocardial point (when it was of sufficient amplitude to measure), and no change was apparent in the time of activation of the epicardial point. At 2 minutes the R at the epicardial point increased in amplitude and became noticeably broader so that at the end of 3 minutes its summit was delayed by 0.0181 sec. and at the end of 5 min. by 0.0267
FIG. 3. Changes in activation at 4 intramural electrode points in the region of greatest intensity of ischemia produced by occlusion of 5 min.

A continuous recording during occlusion was obtained. The values at 15 sec. intervals are shown. After release the only values shown are those which represent significant change up to 25 seconds. At point a (1 min. following occlusion) an R could no longer be noted at the innermost point. It reappeared at c within 21 sec. after release of the occlusion. There is a delay in radial spread between points 2 and 3 beginning about 2 min. after occlusion. It persists for several seconds after release of occlusion. At point b the difference in time between activation of points 3 and 4 has become less. Six seconds after release point 4 on the epicardial surface is activated before the subjacent point.

sec. (range 0.0203 to 0.0442 sec.). Its amplitude was 23 mm. as compared with the control mean of 13 mm. (at N/20 standardization). By the end of the second minute the R at the subendocardial point had vanished so that only a few observations could be made. In these instances there was no significant change in the time of activation of the subendocardial point. At times there was a reversal of the normal order of activation of the subepicardial and epicardial points (points 3 and 4). The form of the bipolar leads reflected the same change. The initial negativity at the subendocardial point increased and delays on the adjacent point (point 2) were encountered at 5 to 10 min. There was no further prolongation of the time of the inscription of the peak of R at the epicardial surface. Its amplitude was 24 mm. One experiment was carried to conclusion at 24 hours with interval recordings (fig. 2). At the end of 15 min. the delay at the epicardial point was 0.0161 sec. There was a further progressive delay until at 24 hours it attained a magnitude of 0.0397 sec. In the last few hours a late R was inscribed at the subendocardial point. Its peak was sometimes as much as 0.0061 sec. after the peak of R at the epicardial point, but usually averaged 0.0037 sec. earlier. (The corresponding control value was 0.0143 sec. before the peak of R at the epicardial point.)

Boundary zone of ischemia. Only 2 observations were made in the 0 to 2 min. interval. There was a slight delay (0.0010 sec.) at the subendocardial point and no significant change at the epicardial point. Nine observations during the 2 to 5 min. interval showed a short delay at the subendocardial point although there was great variation. There was a delay of 0.0009 sec. at the epicardial surface. A slight increase in the amplitude of R was seen occasionally; however the mean value of 7 mm. was slightly less than that of the control period. There was no significant change in time of activation of the subendocardial point in 3 instances during the 5 to 10 min. interval. In the fourth case, there was a delay of 0.0115 sec. In most cases there was a significant delay (0.0100 sec.) at the epicardial point although 2 of 7 observations showed no significant change. The mean amplitude of R was 15 mm. No observations were made after 10 min.

Relatively normal zone (fig. 2). There were no significant changes in the magnitude of R or in the time that activation reached the electrode points in the ventricular wall. Minor degrees of R-ST junction displacements indicated that the myocardium in these regions was "normal" only in the sense that the intensity of ischemia was much less than in those areas directly irrigated by the occluded vessel. In one experiment there was no delay of activation of the R at the subendocardial point at 15 hours. Later a prominent Q appeared. The time of activation of the epicardial point had not changed from the control value when the experiment was terminated at 24 hours.
Release of Occlusion. The amplitude and breadth of R at the epicardial point diminished so that within 4 min. control values were re-established. The R at the subendocardial point reappeared within 20 to 60 sec. Changes in T took longer to revert. In about 10 min. after release the electrocardiogram could not be distinguished from the control tracing in any respect after the usual 5 to 10 min. occlusion (fig. 3).

Repeated Occlusions. Consecutive occlusions produced characteristic sequential changes of comparable magnitude. Interval control values did not differ significantly from the originals. At times there appeared to be slight diminution in the amplitude of R at the subendocardial electrode in the central zone in the interval tracings suggesting the possibility that with occlusions of short duration some muscle death had occurred even though the remainder of the muscle was intact and activated in normal fashion. Block was observed in 29 consecutive occlusions including the trial ones. The probability that this would occur as a result of chance is 1/2^29.

Left Bundle-Branch Block (fig. 4). Complete left bundle-branch block was produced at the end of 5 occlusion experiments. In one case a form of incomplete left bundle block was seen in addition. Bundle-branch block forms other than those produced intentionally were not observed.

Left Bundle-Branch Block and Occlusion. In 2 experiments occlusion superimposed on left bundle-branch block produced no further changes.

Occlusion and Stimuli. Two experiments were done (fig. 5). In the central ischemic zone there was an average delay in activation of the epicardial point of 0.0085 sec. after the stimulus was applied to the subendocardial point as compared with values obtained with stimulation of the same point without occlusion. The amplitude of R was greater with stimulation after occlusion.

Changes in Limb Leads. The duration of QRS in Vf in the control period was 0.080 sec. After occlusion it measured 0.078 sec.

Discussion

In view of the extensive biophysical and biochemical changes which must occur in ischemic muscle when the ischemia is of a degree to progress ultimately to infarction, it is not surprising that propagation of the excitation process should be impaired in the involved region. After occlusion the first evidences of a local ventricular block were limited to the most intensely ischemic region. Delays in activation of the surrounding muscle were observed later. The magnitude of delay was greatest in the central ischemic region. Activation of relatively normal muscle at a greater distance from the center of ischemia was unchanged. Delay increased progressively in the deeper region of the wall.
CONTROL 8' OCCL

![Waveform Diagram]

**Fig. 5.** Activation of 4 intramural electrode points in the region of maximal ischemia when a d.c. stimulus was applied to the innermost point before and after an 8 min. occlusion. R is represented by slurring and notching of the downstroke of S at points 2 through 4 in the control tracing. After occlusion the magnitude of R is much greater. The potential difference induced by the d.c. stimulus at Vr is shown. The nadir of this deflection (F) served as the reference time for this experiment. Activation of the right ventricle (RV) is late in each instance.

of the central ischemic region where the first QRS evidences of infarction would eventually appear. Activation of these regions maintained a normal radial direction, moving from the endocardial surface toward the epicardium. Activation of the superjacent muscle became tangential in direction as access spread into it from less ischemic surrounding regions presumably because ample time for radial activation of the less ischemic region plus tangential activation of subepicardial layers overlying the ischemic zone had been provided by delayed activation in

the underlying ischemic region. Tangential spread in the outer regions was indicated by a lesser time difference for activation to reach electrode points 3 and 4. Often it was oriented so that it reached point 4 before point 3. When this occurred a reversal in polarity of the corresponding bipolar lead resulted. In the one experiment of 24 hours' duration late tangential spread through whatever viable muscle remained in the infarcted region was observed.

During the period when intramural block was developing no significant delay to indicate altered endocardial spread at the innermost point occurred in either the central ischemic zone (when an R deflection remained to be measured) or in the surrounding, less ischemic region. The apparent resistance of the Purkinje fibers to ischemic changes has been commented on before.

The constancy with which local intravenous block due to ischemia appears in the dog following coronary occlusion suggests that identical changes occur regularly in the initial ischemic stage of myocardial infarction in man. Evidences of block would disappear concomitantly with the appearance of actual infarction and inability of those muscle units previously ischemic to be activated. It would persist when muscle units surrounding the infarct remained intensely ischemic and blocked. When the infarct extended through the ventricular wall only the negative cavity potential would be transmitted to the superjacent electrode and the manifestations of local block would depend upon the persistence of a degree of ischemia sufficient to produce significant block in the muscle immediately surrounding the infarct. If infarction is limited to the innermost layers the appearance of local block would depend again upon block in the surrounding ischemic region unless the infarct is of sufficient size to result in late tangential activation of overlying muscle units. In this circumstance block may persist even though ischemia subsides. In most instances the temporal relationship between block and ischemia
dictates that block will be a temporary phenomenon because it is likely that ischemia of a degree sufficient to produce block must either culminate in infarction or be followed by at least partial recovery. It is supposed that the transitory nature of block associated with ischemia and the limitations posed by the small area of the blocked region are sufficient to preclude its being recorded except fortuitously during the early stages of infarction in man. The appearance of peri-infarction block in the course of myocardial infarction has been described. It is due presumably to tangential activation of normal muscle overlying an infarct of reasonable size. It was observed in the one experiment of 24 hours' duration where QRS changes diagnostic of infarction had been allowed to develop.

Ready explanation for the increased amplitude of R in the ischemic region is difficult. Stimulation of the endocardial point was done to observe the effect of dissociating the activity normally occurring at more remote regions in the septum and ventricles from that in the local ischemic zone. The presence of an R of greater amplitude after occlusion in this experiment suggests that the cause is local rather than due to the absence of opposing forces elsewhere in the myocardium at the time when activation of the ischemic region occurs. The results would be anticipated because direct leads are relatively insensitive to distant effects. The increased amplitude of R cannot be due to an increased accession moment because there is a subnormal intensity of repolarization after occlusion as evidenced by a decreased R-S voltage. This conclusion is substantiated by studies of intracellular potentials recorded during ischemia. It is unlikely that a phase of supernormal intensity of polarization exists. It seems more likely that the sum of multiple accession forces demonstrated in the ischemic region accounts for the increased amplitude of R (fig. 6). One of these forces is represented by a boundary drawn to the surface of accession spreading in a normal endo-

![Diagrams](http://circres.ahajournals.org/)

**Fig. 6.** Order of activation of the ischemic and early infarcted ventricle. In A the muscle mass is activated when the excitation impulse reaches its endocardial surfaces almost instantaneously (a). Radial spread of activation is indicated by arrows (b) leading from the endocardial to epicardial surface. Electrode E in a plastic support is shown. Its 4 intramural points are in the muscle mass. The electromotive forces produced during activation of M result in the form of QRS shown above the diagram. In B an ischemic region is present. The intensity of ischemia is indicated by the shading. Activation begins at the endocardial surface (a). In the relatively normal zones radial activation is unchanged (b). In the central ischemic zone a marked delay of radial activation is indicated by the shortened arrow. Slighter delay is seen at c' in the adjacent ischemic region. Sufficient block at the subendocardial regions has occurred to permit tangential spread (c) through the outer less ischemic regions. In D an infarct extends through the wall from the endocardial to epicardial surface. Radial activation occurs (b) in the relatively normal regions and tangential spread into the blocked zone is depicted at c.

epicardial direction. Another is represented by a boundary drawn circumferentially to the surfaces of tangential spread. Other forces in addition to those demonstrated may exist in this region.

Previous electrocardiographic studies of experimental coronary occlusion and myocardial infarction in dogs have differed from our study in several respects. In many the chest has been closed after occlusion, to be reopened hours or days later to permit re-examination of the heart. The electrodes have not been fixed in situ in the myocardium
necessitating reinsertion of the electrodes. The surface of the heart was not carefully explored so that the region of peri-infarction block which is of small area (at least for 24 hours) may have been overlooked. In addition the ischemia must be of sufficient intensity and duration to permit the characteristic changes to develop.

Left bundle-branch block differs significantly from the block observed as a result of myocardial ischemia. Changes in the order of activation of the left ventricle in left bundle-branch block are of a magnitude and direction not seen with local intraventricular block due to ischemia (fig. 1). Previous studies of the activation of the ventricles in experimental bundle-branch block of right or left form have shown that endocardial spread is completely altered after bundle-branch block. In local block due to ischemia endocardial spread to the less ischemic zone is unaltered and apparently is not changed in the more intensely ischemic regions.

An initial positive deflection was observed in all regions of the left ventricular wall (with the exception of the papillary muscle) from just beneath the endocardium to the epicardium. We have been unable to confirm the observations of others that there may be normal regions in the left ventricular wall (with the exception noted) in which an R deflection is not present. We cannot substantiate the conclusions that an R occurs only in the outermost muscle layers and that there is no consecutive appearance of the intrinsic deflections in the innermost layers or that only cavity potentials are found in the inner two-thirds of the ventricular wall.

We believe, apparently as others do, that an initial positive deflection by definition is an R. The peak to peak voltage of R to S is not significantly different in the subendocardial regions as compared with other regions of the muscular wall normally. Since the accession moment can be calculated from this voltage, the data suggest that the moment of accession is the same for all regions of the left ventricular wall.

**Summary**

Changes in left ventricular activation during the first 10 min. following occlusion of the anterior descending branch of the left coronary artery were studied in dogs by using multiple intramural electrodes. Intramural block in the region of maximal ischemia occurred within 2 min. after occlusion in all 29 occlusion episodes. Delay in activation progressed to an average value of 0.0267 sec. at the end of 5 min. in this region while a delay of lesser magnitude (about 0.0040 sec.) was observed later in the surrounding zone. Least ischemic regions showed no change. During the 10 min. observation period there was evidence of increasing delay in activation of the innermost muscle layers in the region of greatest intensity of ischemia so that opportunity was provided for tangential activation of the superjacent outer muscle layers. In one experiment, tangential activation persisted after the appearance of characteristic changes of infarction until the experiment was concluded 24 hours after occlusion.

In the third minute after occlusion the amplitude of R in the outermost layers of muscle in the central ischemic zone was observed to increase. By the end of 5 min. it had doubled in height and remained so until the occlusion was released. The increased amplitude of R was attributed to the presence of multiple accession boundaries in and adjacent to the most intensely ischemic zone. The results of stimulation of the endocardial point in the ischemic region were valuable in supporting this conclusion.

The zone of maximum block effect and the zone displaying greatest increase in the amplitude of R were coincidental but appeared only in a small area which could be overlooked unless the ventricular surface was carefully explored. There were no distinctive changes in lead V6.

Repeated occlusion and release in the same dog yielded the same results without significant differences in control or occlusion values.

Left bundle-branch block was produced by severing the left bundle and differed in all de-
tails from acute peri-infarction block resulting from coronary occlusion.

It is believed that these observations in dogs are pertinent to an understanding of the order of activation of the ischemic and freshly infarcted ventricle in man. The significance of these events for the development of peri-infarction block is apparent.

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**Summary in Interlingua**

Alterationes in le activation sinistro-ventricular durante le prime 10 minutias post occlusion del branca antero-descendente del arteria sinistro-coronari esseva studiate in canes per medio de multiple electrodes intraparietal. Bloco intraparietal in le region del maximo de ischemia occurreva intra 2 minutias post le occlusion in omne le 29 episodios occlusional del presente serie. Le retardo del activation progredeva a un valor medie de 0,0267 secondas al fin de 5 minutias in iste region, durante que un retardo de un plus basse magnitude (circa 0,0040 secondas) esseva observate plus tarde in le zona circumjacente. Le regiones del minime ischemia manifestava nulle alteration. Durante le 10 minutias del periodo de observation, indicationes esseva manifeste de un crescente retardo in le activation del plus interior stratos muscular in le region del plus grande intensitate de ischemia, de manera que le opportunitate esseva providite pro le activation tangential del superjacente stratos de musculo exterior. In un experimento, le activation tangential persisteva post le apparition de caracteristic alteraciones de infarcimento usque le experimento esseva concluside 24 horas post le occlusion.

In le terti minuta post le occlusion, le augmentate amplitude de R esseva attribuite al presentia de multiple frontieras de accesio intra e adjacent al zona del plus intense ischemia. Le resultatos de stimulation del puncto endocardial in le region ischemic esseva de valor como supporto de ille conclusion.

Le zona del bloco maximal e le zona manifestante le plus marcate augmento del amplitude de R coincideva, sed illos appareva solmente in un miocre area que poteva facilemente escappar al observation a minus que le superficie ventricular esseva explorate meticulosemente. Nulle alterationes distincte esseva notate in le derivation V_R.

Repetite occlusiones e relaxations in le mesme can produceva le mesme resultatos sin significative differentias in le valores de controlo o le valores occlusional.

Bloco de branca sinistre esseva producite per secar le fasse sinistre. Illo differeva in omne detalios ab le bloco de peri-infarccimento acute que es le resultato de occlusion coronari.

Es opinate que iste observationes in canes es de importantia pro le comprension del ordine de activation del ventriculo ischemic e novemente infarcite in humanos. Le significacion de iste eventos pro le disveloppamento de bloco peri-infarccimental es evidente.

**References**

4. —, HILL, I. G. W., AND JOHNSTON, F. D.: The form of the electrocardiogram in experimental myocardial infarction. III. The
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