The Effect of Acute Coronary Artery Occlusion on Subepicardial Transmembrane Potentials in the Intact Porcine Heart

EUGENE DOWNAR, M.D., MICHEL J. JANSE, M.D., AND DIRK DURRER, M.D.

SUMMARY Subepicardial transmembrane potentials were recorded from intact pig hearts to observe the changes induced by acute ischemia. Ischemia shortened action potential duration, and decreased its amplitude, upstroke velocity, and resting potential. The cells were unresponsive after 12 to 15 minutes of coronary artery occlusion, yet near normal action potentials could be restored by flushing the occluded artery with saline as late as 40 minutes after occlusion. The unipolar extracellular electrogram reflected unresponsiveness by a monophasic potential. Local refractory periods initially shortened by up to 100 msec. Later, postrepolarization refractoriness occurred and refractory periods lengthened often in excess of basic cycle length, thus resulting in 2:1 responses. The onset of early ventricular arrhythmias often coincided with a period of alternation and 2:1 responses, especially when these got out of phase in different regions. Reperfusion frequently led to ventricular fibrillation, and was associated with marked inhomogeneity in cellular responses. Re-entry within ischemic myocardium was the most likely mechanism for arrhythmias.

TO UNDERSTAND the mechanism of early ischemic arrhythmias, it is vital to know of the electrophysiological alterations which occur during the initial stages of myocardial ischemia. Several studies have been conducted in which recordings were made with microelectrodes from intact hearts; only relatively minor changes were reported following coronary artery occlusion, such as slight shortening of action potential duration and loss of resting membrane potential.1-4 These changes fail to explain the marked delay and fragmentation of activation that occurs in the ischemic area,5-7 and the arrhythmias which develop in the early stages following coronary artery occlusion.8-9

Marked changes in transmembrane potential have been reported from in vitro studies in which injured parts of the heart were excised and maintained by superfusion in a tissue bath after varying periods of ischemia.10-12 Lazzara et al.12 used this technique to study the effect of a 30 minute period of ischemia, but the study was limited by a delay of 15 minutes before making intracellular recordings. Thus, little is known about the changes in transmembrane potential during the very early stages of myocardial ischemia, cor-

From the Department of Cardiology and Clinical Physiology, University Hospital Wilhelmina Gasthuis, Amsterdam, and the Interuniversity Cardiology Institute, The Netherlands.

Dr. Downar is a Senior Research Fellow of the Ontario Heart Foundation, Canada.

Address for reprints: Dr. Eugene Downar, Department of Cardiology and Clinical Physiology, University Hospital, Wilhelmina Gasthuis, Amsterdam, The Netherlands.

Received September 22, 1976; revision accepted March 31, 1977.
responding to the highly arrhythmogenic phase described by Harris and Rojas.9

Early changes in excitability during ischemia include shortening of refractory periods13, 14 and temporal dispersion of recovery times.14 These changes have been implicated in the genesis of re-entrant arrhythmias. The purpose of the present paper is therefore 1) to document in greater detail the changes in transmembrane potential that occur immediately following coronary artery occlusion; and 2) to relate these changes to the effects of ischemia on a) local refractory periods, b) extracellular electrograms, c) early ischemic arrhythmias.

Methods

Forty-two pigs aged 8–9 weeks and weighing 20–25 kg were premedicated with Stressnil (R 1929 azaperone, 2 mg/kg i.m.) and atropine (0.12 mg/kg i.m.), then anesthetized with Hypnorm (R 7315 metomidat, 4 mg/kg i.v.). A midsternal incision was made and a pericardial cradle constructed. In seven pigs in situ observations were made. In 35 pigs the hearts were first isolated by the following procedure. After intravenous administration of 1 ml heparin, venous blood was collected from a jugular vein in two stages. This blood was mixed with an equal volume of perfusion medium, containing: Na+ 156.5 mmol/L, K+ 4.7 mmol/L, Ca++ 1.5 mmol/L, Mg++ 0.7 mmol/L, H2PO4 0.5 mmol/L, CL- 137.0 mmol/L, HCO3 28 mmol/L, glucose 20.0 mmol/L, heparin 5250 I.U./L, insulin 10 U/L, dextran (macrodex MW 70,000) 60 g/L. The amount of perfusion fluid thus obtained was about 2 liters, and was recirculated in the perfusion apparatus. The arterial line of the perfusion set-up consisted of a bubble oxygenator (poly-stan-Rygg Kwyżgota disposable oxygenator), a roller pump, a heat exchanger, a 1.5 m hydrostatic column with overflow, a filter (intercept arterial extracorporeal blood filter, Johnson and Johnson) and a lock for the aortic cannula. The different components were connected by tygon tubing. Oxygenation was effected by a mixture of air (1000 ml/min), carbogen (95% O2, 300 ml/min) and CO2 (50 ml/min). The amount of CO2 could be varied, guided by the pH, which was constantly monitored and kept at 7.35 ± 0.05. The pO2 was in the order of 120 mm Hg. Following the collection of venous blood, the heart was rapidly removed and submerged in cooled perfusion medium where the aortic root was cannulated. After the heart had been connected via the aortic cannula to the perfusion apparatus, coronary flow rapidly stabilized at about 200 ml/min. Disc electrodes, sutured on the right atrium, or needles inserted into right or nonischemic left ventricular wall and containing several electrode terminals, were used for regular stimulation. Basic cycle length varied from 390 to 500 msec. Electrode terminals had a diameter of 0.1 mm and were separated by 2 mm. When local refractory periods were determined, a floating bipolar stimulating electrode, consisting of a double spiral of 0.1 mm diameter wire, insulated except at the tips, was positioned within 1 mm of the recording microelectrode. Inter electrode distance of the stimulating electrode was 0.5 mm. Stimuli were rectangular current pulses of 2 msec duration and a strength of twice diastolic threshold for basic stimuli and of four times diastolic threshold for test stimuli which were given after every eighth basic stimulus. The epicardium overlying the area of future ischemia was removed. Conventional microelectrodes (resistance 10 to 30 megOhm) were mounted on Ag-AgCl coated silver wire spirals in order to be able to follow the movements of the heart.16 In the perfused hearts, contractions tended to be less vigorous than in the in situ heart and intracellular impalements were relatively easy to maintain. In the in situ hearts, recordings were less stable and it was sometimes necessary to reduce local movement by the method of Czarnecka et al.,9 which involved suturing a perspex ring to the subepicardium and holding it rigidly. The ring was filled with agar to further damp the movements and to prevent breaking the microelectrode tips. The recordings obtained in this way were from impalements that were not always ideal, especially when two or more microelectrodes were used simultaneously. However, the information from such recordings was sufficient to indicate that we included it in our figures, although we did not include a calibration. In order to minimize interference from the electrocardiogram, a differential method of recording was used, in which the local extracellular signal was subtracted from the intracellular signal. A clip on the aortic root was used as an indifferent electrode for both the intra and extracellular recordings. In the illustrations, the transmembrane potential is always the differentially recorded signal. The local extracellular recording was obtained from a very thin Ag-AgCl coated silver spiral positioned as closely as possible to the intracellular microelectrode. High impedance, capacity compensated amplifiers were mounted on the microelectrode holders. Hydraulic micromanipulators were used. All signals were recorded on an Ampex FR 1300 taperecorder and written out on an Elema inkwriter.

Results

Figure 1 shows the typical time course and character of changes which occur in a subepicardial cell in the center of an ischemic region. Although this example is from a heart in situ, it is also representative of the isolated perfused hearts. As can be seen by the baseline distortion and the amplitude of the control action potentials, the impalement was less than ideal.

The heart was paced from a remote ventricular site at a basic cycle length of 390 msec. After 5 min of occlusion of the left anterior descending artery, the action potential is reduced in amplitude and duration, and upstroke velocity is decreased. The interval between stimulus artifact and beginning of action potential upstroke is increased. One minute later, the plateau disappears and the other changes are accentuated. At 9 min an alternation in amplitude appears which evolves into 2:1 responses. The activation time of the responses is delayed by 100 msec and their total duration is about 100 msec. Even these responses degenerate further into small spikes which disappear altogether by 13 min of ischemia. In the figure the last pacemaker artifact is indicated by an arrow. It produced no response before after a pause of 1170 msec an action potential is produced by a sinus escape. Failure of an ischemic fiber to respond at a given rate could be overcome initially by either a pause or by a sufficient slowing of the pacing rate. Action potentials elicited in this way were sustained only for a few cycles before unresponsiveness supervened.
Oclusion of the proximal left anterior descending artery always produced unresponsiveness in the center of the ischemic region within 10–15 min. In the regions less severely affected, ischemic changes took longer to occur and were less extensive. On several occasions spontaneous improvement occurred after approximately 30 min of occlusion. However, this improvement was never sustained, and by the end of one hour action potentials had virtually disappeared over a large portion of the ischemic region. Depending upon the duration of ischemia, unresponsiveness could be reversed by reperfusion. Within a few beats of releasing coronary artery occlusion, action potentials of near normal amplitude were re-established. Even flushing the occluded artery with saline bubbled for 20 min with N2 could temporarily restore near normal action potentials (fig. 2). Such rapid return of activity was seen if the duration of occlusion was less than 40 min. Occlusion which lasted longer than one hour resulted in unresponsiveness in the center of the ischemic region which could not be reversed by reperfusion.

Relationship to Local Extracellular Unipolar Electrogram

Figure 3 is from an in situ heart and shows simultaneously recorded intracellular action potentials and the unipolar electrogram recorded from the same site during a few minutes of left anterior descending artery occlusion (left hand panel). The right hand panel contains recordings taken after a subsequent 4 min occlusion in the same heart, and show the changes produced by the release of that occlusion. At the height of ischemia (seen best in the top right hand panel, just before release) there is a 2:1 intracellular response. The extracellular manifestation of intracellular unresponsiveness is a monophasic complex reflecting remote activity. When there is still a small response in alternate beats, this is expressed in the extracellular signal by a small downward deflection (indicated by arrows in the bottom left hand panel at 3'50" of occlusion) on essentially monophasic complexes. The alternate large amplitude action potentials produce a large downward deflection in the extracellular complex, whereas the longer action potential duration is reflected in the isoelectric ST segment. When there is alternation in upstroke velocity, the steepness of the upstrokes of the action potentials is reflected in the steepness of the negative downstrokes (indicated by the arrows in the right hand panel 1' after release) of the extracellular complexes.

Changes in Local Excitability

In 12 isolated hearts we determined local changes in excitability. No significant difference was found between measurements made with unipolar cathodal stimuli and bipolar stimuli. The onset of ischemia produced an initial shortening in refractory period which at first followed the shortening in action potential duration. In two isolated hearts, however, the shortening of the refractory period was preceded by a transient lengthening of 30 msec (fig. 4). The degree of initial shortening in refractory period was very variable but could measure as much as 100 msec. Subsequently, although action potential duration continued to decrease, the
refractory period began to increase, thus displaying the phenomenon of postrepolarization refractoriness (fig. 5). During this stage premature stimuli elicited graded responses over a wide range of coupling intervals. In figure 5, for example, this range extended from 230 msec, which hardly produced any response, to 380 msec which still failed to produce a response comparable in amplitude to the basic response. The increase in recovery time eventually encroached on the next basic stimulus. When this happened rapidly it resulted in an alternation in action potential duration and refractory period (in fig. 4 the refractory period alternates between 240 msec and 300 msec). The longer refractory period eventually exceeds the basic cycle length and the alternation is transformed into 2:1 responses (fig. 6). Eventually these responses disappear and the cells become unresponsive even to stimuli of 20 mA strength. The changes described are those which occur in the center of a large ischemic region as it becomes unresponsive. The rate at which the changes developed varied from location to location and at any moment widely disparate refractory periods coexisted in cells in close proximity to one another. In figure 5 for example, a test stimulus at a coupling interval of 180 msec resulted in a response at the site of stimulation about 100 msec later, suggesting that there were cells with a refractory period of 180 msec adjacent to site of stimulation and the wave of excitation spread from these cells back to the

**Figure 3.** Transmembrane potentials (lower trace) and local extracellular electrogram (upper trace). The left panel shows control situation (top) and sequence of events following coronary artery occlusion. Note relationship between intracellular potentials and extracellular electrogram, especially when alternation and 2:1 responses occur (arrows). Right hand panel shows sequence of events following release of another occlusion of 4 min duration. Top shows situation just before release.

**Figure 4.** Changes in local excitability following coronary artery occlusion. Two simultaneously recorded action potentials from cells 2½ cm apart. Premature stimuli indicated by arrows. There is initial lengthening of refractory period and action potential duration at 1½ min of ischemia. At 6 min, marked alternation in action potential duration has developed in the upper cell, with a 60 msec difference in refractory period between the long and short action potentials. Some baseline distortion is present due to movement artifacts.

**Figure 5.** Postrepolarization refractoriness. Stimuli delivered within 1 mm of the cell recorded from. In control situation, recovery of excitability closely follows repolarization. After 12 min of ischemia, the heart responds to a test stimulus 100 msec shorter than in control situation. However, the latency between stimulus and response is more than 100 msec. At 230 msec there is minimal latency but a very small response. Reasonable action potentials without any latency occurred only when the coupling interval was increased to 380 msec, well after completion of repolarization.
site from which the action potential was recorded. This situation is seen more clearly in figure 6 where a cell at the site of stimulation responds only to alternate stimuli while a more remote cell responds to every stimulus.

At the border of the ischemic region, refractory periods, like action potential duration, shortened and remained short. The effect of reperfusion on the refractory period of such cells was paradoxical in that instead of lengthening (back to control values) they tended to shorten first. This shortening could be quite striking as shown in figure 7 where the refractory period measured 190 msec immediately before release of the occlusion and 120 msec 1½ min after release.

Inhomogeneity

We have frequently observed relatively good intracellular responses in cells only a few millimeters from cells which were practically unresponsive. Even when two cells are both capable of generating good responses, and are located within 1 mm of each other, they may be prevented from responding synchronously by conduction disturbances due to the interposition of more severely affected cells. An example of this is shown in figure 8. This composite record shows action potentials of cells located within 1 mm of each other. Stimulation at cell 3 resulted in good action potential which was conducted to cell 1 with a delay of about 100 msec. A premature stimulus, although initiating a large action potential in cell 3, is blocked in cell 2. The double potentials of cell 2 may to a large extent represent electrotonic potentials caused by the regenerative action potentials of cells 1 and 3. A smaller electrotonic prepotential is seen in cell 1 and a small after-potential in cell 3 indicating electrotonic coupling in all three cells.

Arrhythmias

Spontaneous ventricular fibrillation occurred 25 times in 42 occlusions (13 times in 17 in situ occlusions and 12 times in 25 occlusions performed in isolated hearts). The time to onset of ventricular fibrillation varied from 3 to 15 min. Spontaneous alternation in the duration and amplitude of ischemic action potentials was seen in 30 of the 42 occlusions, between 3 and 9 min of ischemia. Such alternation was seen to precede spontaneous ventricular fibrillation in 17 of the 25 instances. Although our techniques did not allow us to establish a causal relationship between the occurrence of alternation and that of ventricular fibrillation, certain additional observations suggested its existence. In two in situ hearts, occlusion of the proximal LAD failed to produce either alternation or fibrillation until the heart rate was increased abruptly. At that point, marked alternation developed followed within a few beats by ventricular fibrillation.

Loss of synchrony between two alternating regions was observed on several occasions just before a premature ventricular beat emerged. This is seen in figure 9 which shows two ischemic action potentials with their respective extracellular electrograms recorded from sites 2 cm apart. Cell 1 shows 2:1 responses to the basic atrial drive while cell 2 shows alternation between small (A) and large (B) responses. The extracellular signals reflect this activity. In response to basic beat C, cell 2 gives a large action potential when a small one was expected. This is followed by a prematu-
tured ventricular beat D, evident in the extracellular electrograms. Cell 1 then gives a large response which is followed by a small complex in cell 2. The origin of the premature ventricular beat appears to be the unexpectedly good response in cell 2 at a time when cell 1 fails to respond. Such spontaneous desynchrony of 2:1 responses may open up a circuit pathway that may lead to re-entrant arrhythmias. A similar loss of synchrony could be brought out by an increase in pacing rate which would convert 2:1 responses to 3:1 responses or even to infrequent intermittent responses.

Ventricular fibrillation frequently occurs on reperfusion.9,16,17 Figure 10 shows four simultaneous action potentials recorded on release of a 6 min LAD occlusion. The heart was paced from a location on the nonischemic myocardium with slightly suprathreshold stimuli. Within a few beats, 2:1 responses occur in cell 2 while large and small potentials alternate in cell 3. A single premature ventricular beat occurs (marked with an asterisk) and is followed by synchronized responses to the first postextrasystolic stimulus. The following stimulus fails to evoke a significant response in cell 2. There is loss of synchrony and a chaotic tachyarrhythmia follows.

The term “local fibrillation”18,19 might be used to describe the initial activity in cells 1, 2 and 3 since the responses in cell 4 remain fairly regular for seven beats before it too clearly participates in the fibrillation. The precise pathways of activation in figure 10 are of course completely unknown. However, one of the factors responsible for the reperfusion arrhythmias seems to be the different rate at which cells regain, or improve, their electrical activity. Particularly cell 2, which during ischemia was quiescent and therefore could not contribute to the generation of ectopic beats, shows in the initial stage of recovery very slow and late responses, which may be instrumental in setting the stage for re-entry. Alternation of such depressed action potentials was frequently, though not consistently, seen on reperfusion of ischemic myocardium.

Discussion

Previous workers have recorded myocardial transmembrane potentials during ischemia resulting from coronary artery occlusion.1-4 They reported only a decrease in resting membrane potential and slight shortening in action potential duration. More striking ischemic changes were observed by Kardesch et al. who produced ischemia by stopping total perfusion in Langendorff preparations.20 In the in vitro studies in which the early ischemic effects were investigated, intracellular recordings could only be made 15 minutes after excision of the tissue. By that time some of the ischemic effects may have been reserved by superfusion.22 Also, these studies were concerned with subendocardial cells, whereas several studies have shown the subepicardium to be a region of marked delay in activation,4,5,21,22 and a likely site of release of occlusion

1
2
3
4

1sec

Figures 9 and 10. Two simultaneously recorded action potentials (transmembrane 1 and 2) and the corresponding local unipolar extracellular electrogram (extra cell 1 and 2) from sites 2 cm apart in the subepicardium of an in situ pig heart. Due to movement artifacts there is considerable baseline distortion. After 8 min of occlusion of the left anterior descending artery, cell 1 shows 2:1 responses, cell 2 shows alternation. At beat C, cell 2 shows an unexpectedly large action potential leading to the ventricular premature beat D.

Figure 10. Release of coronary artery occlusion in a perfused heart leading to ventricular fibrillation. Four simultaneously recorded action potentials are shown. Within beats following reperfusion, cell 2 shows 2:1 responses, and cell 3 shows alternation between large and small action potentials. After the pause following the ventricular premature beat (asterisk) this alternation between cell 2 and 3 gets out of phase; note also sudden increase in amplitude of action potential in cell 1 (arrow).
origin of re-entrant arrhythmias. By recording from the intact heart we were able to observe subepicardial ischemic changes and their time course from the moment a coronary artery is occluded. Perhaps surprisingly, we found no striking differences in either the time course or character of the ischemic changes in isolated hearts and in hearts in situ.

Because the movements of the heart prevented ideal palements, no statements can be made about the exact level of membrane potential in the different stages of ischemia. However, we can confirm the findings of others that loss in membrane resting potential occurs but are unable to say whether this factor alone is responsible for the progressive decrease in amplitude, and rate of rise of the upstroke and the duration of the ischemic action potential. Part of the ischemic changes are due to accumulation of substances released by the ischemic myocardium in the extracellular space, as shown by the rapid return of near normal action potentials following a saline flush (fig. 2). As first suggested by Harris et al., potassium is one of these substances, but there is evidence that other factors are involved. Recording intracellular potentials from ischemic myocardium allows a correlation to be made with the corresponding changes in extracellular electrograms. Unresponsiveness can be recognized on the local unipolar electrogram by a purely monophasic potential which reflects the activity of remote, still responding tissue. It follows that the duration of the local unipolar electrogram is of no value in determining the duration of the local intracellular potential. Downward deflections superimposed on the monophasic unipolar electrogram do reflect intracellular potentials. Apart from timing, the deflections reveal to a certain extent the upstroke velocity, amplitude and duration of the underlying intracellular potentials. In view of the inhomogeneity of ischemic tissue, the extracellular electrode has to be very small to avoid averaging effects produced by contact with disparate cells. As illustrated in figure 8, on occasion activation times of cells very close to one another may differ by more than 100 msec. It is not surprising therefore, that even when small extracellular recording electrodes are used, the signals may show considerable fragmentation. In the initial stages of ischemia the refractory periods changed concomitantly with the changes in action potential duration, and we confirmed the well-known shortening that occurs. On two occasions, both in isolated hearts, we observed a very early lengthening in both parameters which preceded the shortening. This transient lengthening in refractory period has been observed previously and was attributed to cooling due to cessation of perfusion. It has also been reported that after initial shortening the refractory period in later stages of ischemia lengthens again to well in excess of control values. We observed that as the refractory period began to lengthen action potential duration continued to shorten. Such discrepancy between action potential duration and recovery of excitability has been reported in isolated fibers of the His-Purkinje system excised after several hours of coronary artery occlusion; the term postpolarization-refractoriness has been used to describe this phenomenon. We found that such increases in refractory period could even exceed the basic cycle length, at which point 2:1 responses occurred. A slight degree in dispersion of refractory periods in ischemic myocardium was reported by Han and Moe.

Williams et al. suggested that the dispersion in recovery of excitability was much greater, since they could on the one hand excite ischemic myocardium with marked premature stimuli, while adjacent areas could not be excited by strong stimuli applied late in diastole. Our results are clearly in agreement with these findings since we found refractory periods varying from 180 to more than 500 msec (figs. 5 and 6). Simultaneous recordings from different but close locations showed that cells at any one stage could be affected to markedly different extents by ischemia. This suggests that the rate of ischemic change was not uniform. Thus, grossly disparate recovery times could coexist in cells in close proximity to one another. A practical consequence of this is that the test stimulus method of refractory period measurement has serious limitations when applied to ischemic myocardium, since it always reflects the shortest recovery time in the vicinity of the stimulation site.

The ischemic changes described have obvious arrhythmogenic implications. We never found any evidence for the emergence of spontaneous pacemaker activity due to phase 4 depolarization or oscillations during phase 3, such as have been reported. On the other hand, direct proof for the existence of re-entrant circuits is practically impossible to obtain. However, the available information favors re-entry in ischemic myocardium as one of the mechanisms which underlies early ischemic ventricular arrhythmias. Dispersion of recovery times of ischemic myocardium, slow conduction and the presence of local conduction blocks may set the stage for re-entry. Recent studies have emphasized the relationship between delayed and fragmented subepicardial activation and the onset of ventricular arrhythmias. Our observations re-emphasize these well-recognized arrhythmogenic factors but also bring attention to the arrhythmogenic capability of the graded response of the ischemic myocardium. Depending on stimulus strength and the length of the preceding cycle, the ischemic action potential can vary from a small local response to large amplitude action potential capable of a regenerative response. The capacity of delayed potentials to produce re-entry is therefore a function of both the quality of the response and the delay involved. With progression of ischemia, the arrhythmogenic effect of an increasing delay in activation is offset by the decreasing size of the ischemic response. However, even in the setting of small late potentials we have seen intermittent large responses and these may be capable of producing re-entry.

Local Wenckebach block and 2:1 responses have been seen to precede ventricular arrhythmias. Although the exact arrhythmogenic significance of 2:1 responses remains to be established, the frequency and extent to which it occurred just before the onset of ventricular fibrillation was striking. No special significance would be expected as long as the alternating regions remained synchronized and in phase. However, as soon as this synchrony is lost, a potential circuit for re-entry is created.

Ventricular fibrillation frequently occurs on release of a coronary occlusion. This may be due to abruptness and diversity of changes in intracellular responses which reperfusion can initiate. Cells in the center of the ischemic region can regain action potentials within seconds of being unresponsive. Some of these cells have action potentials with
slow upstrokes and long durations which may alternate, while other cells undergo more rapid improvement without a period of alternations. By contrast, cells in the border zone with already shorter than control action potential duration and refractory period, respond paradoxically by undergoing a further substantial shortening in these parameters, without any apparent change in upstroke velocity. Upon reperfusion, border cells temporarily may be subjected to increased concentrations of substances released by ischemic cells. These substances are capable of shortening normal action potentials. Shortening of refractory periods upon reperfusion has been observed previously. Reperfusion thus can produce a sudden inhomogeneity in responses which may be severe enough to preclude organized activation and result in fibrillation. Gradual reperfusion on the other hand avoids this abrupt precipitation of gross inhomogeneity and probably as a consequence drastically reduces the frequency of reperfusion arrhythmias.

Finally, although we have examined the changes in cardiac action potentials during ischemia and reperfusion, we cannot make a statement about the nature of ischemic potentials. Because of the uncertainty of the exact level of resting membrane potential during different stages of ischemia we do not know either the relationship between membrane potential and upstroke velocity or the level at which unresponsiveness occurs. The intriguing question of whether the ischemic action potential is a depressed fast response or a true slow response remains unanswered.

Acknowledgment

The authors wish to thank Wim ter Smitten for excellent technical assistance and Dr. A. G. Kleber for his help in some of the experiments.

References

27. Han J, Goel BG, Hanson CS: Re-entrant beats induced in the ventricle during coronary occlusion. Am Heart J 80: 778, 1970
37. Naimi S, Avitall B, Levine HF: Abrupt shortening of effective refractory period (ERP) following coronary ligation: Possible mechanism of reperfusion arrhythmias. (abstr) Circulation 50 (suppl III) III-385, 1974
The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart.

E Downar, M J Janse and D Durrer

Circulation. 1977;56:217-224
doi: 10.1161/01.CIR.56.2.217

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/56/2/217

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/