IN 1879, Burdon-Sanderson and Page\(^1\) described the effects of injury to the surface of the frog heart and noted that, during activity, the injured site became positive with respect to the uninjured surface. Since then, many authors have studied the effects of injury, including those of ischemia, on local extracellular electrograms of the heart. Gradually, it was established that S-T elevation as related to fasting values of plasma triglycerides and cholesterol. Lancet 1: 865-868, 1972


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**Mechanism and Time Course of S-T and T-Q Segment Changes during Acute Regional Myocardial Ischemia in the Pig Heart Determined by Extracellular and Intracellular Recordings**

**ANDRÉ G. KLÉBER, MICHEL J. JANSE, FRANS J.L. VAN CAPELLE, AND DIRK DURRER**

**SUMMARY** We recorded transmembrane potentials from subepicardial ventricular cells and local extracellular DC electrograms in isolated perfused pig hearts before and after occlusion of the left anterior descending artery. The first change was a decrease in the resting membrane potential, reflected by T-Q depression in the electrogram. After 3 minutes, action potentials shortened and their amplitude decreased, resulting in S-T elevation until, finally, cells in the center of the ischemic zone became totally unresponsive at resting potentials of about —65 mV. This rendered the extracellular complex monophasic. Determination of extracellular potential distribution at 150-250 epicardial sites after 15-30 minutes of occlusion showed an increase of T-Q depression and S-T elevation toward a central area, with maximum values of —15 and +35 mV, respectively. Comparison of amplitude and configuration of intramural and epicardial potential profiles revealed that the potential distribution was homogeneous throughout ischemic parts of the wall. Extracellular epicardial current originated, therefore, from the epicardial intracellular compartment. Maximal current density during late systole was 1 μA/mm\(^2\), flowing in the border zone towards normal myocardium. After 1 hour of occlusion, there was a marked decrease of extracellular DC potentials which could be attributed to transient recovery of electrical activity in the ischemic zone. After 2 hours, the zone of unresponsiveness was larger than after 15 minutes of occlusion, and the overall amplitude of DC potentials had decreased further, possibly because of healing over.
Further knowledge of the relationship between transmembrane potentials and extracellular potentials in regional myocardial ischemia would be of help in interpreting results obtained by recording extracellular complexes. Also, it would be interesting to obtain information about the flow of injury current and its possible relationship to the occurrence of ventricular arrhythmias. The purpose of the present study was: (1) to measure the extracellular potential distribution on the epicardium and at intramural sites at different times after coronary artery occlusion and to calculate from these data local current densities, and (2) to compare the changes in extracellular potentials to changes in transmembrane action potentials of the ischemic tissue.

Methods

Pigs weighing 20–25 kg were anesthetized by an intravenous injection of sodium pentobarbital (20 mg/kg). The thorax was opened by a midsternal incision. Approximately 1 liter of venous blood was taken from the pig and mixed with modified Tyrode’s solution yielding 2 liters of perfusion fluid. The heart was removed rapidly and fixed to the perfusion setup where it was perfused according to the Langendorff method. The exact description of the perfusion fluid is given elsewhere.

The heart was driven above the spontaneous frequency of the sinus node by bipolar stimuli applied by means of a pair of electrodes fixed to the right atrium. Ischemia in the anterior wall and the septum was produced by clamping the anterior descending branch of the left coronary artery, usually proximal to the origin of the first diagonal branch.

Determination of the Extracellular Potentials

Extracellular DC potentials were measured by means of a cotton wick (diameter, 0.5 mm) which emerged from a polyethylene tube filled with isotonic saline. The saline was in contact with a chlorided silver wire that was connected to a high input impedance buffer preamplifier. A DC amplifier with differential input measured the potential at this electrode with respect to a relative zero reference potential recorded through a second wick electrode fixed to the aortic root.

Prior to and after a series of 10–20 recordings at different sites, the measuring wick was brought into contact with the aortic root to check the level of zero potential. Whenever the control revealed a shift of more than 1 mV, the data were rejected. Epicardial potentials were determined consecutively at different sites on the anterior part of the right and the left ventricles. The following technique was applied to achieve reproducible measurements at different intervals after the occlusion at distinct sites on the epicardial surface. A thin rubber membrane was perforated to obtain a grid of holes 0.7 mm in diameter. The distance between the holes varied in different experiments from 2 to 5 mm. Each hole in the grid was identified by a letter giving its vertical position and by a number indicating its horizontal position. Prior to occlusion of the left anterior descending artery, the membrane was sutured tightly to the anterolateral part of the heart, covering the presumed future ischemic area and an additional zone of the left ventricular anterolateral wall. Potentials were measured by touching the epicardial tissue underlying a hole lightly with the cotton wick. Thus, in a typical experiment, epicardial potentials from 150 to 250 sites could be recorded within 15 minutes. By this method, two adjacent points were connected electrically only by the extracellular bridge under the rubber membrane, and the area of myocardium accessible to the measuring electrode was the same at each site.

A polyethylene tube (diameter, 0.7 mm) of about 10 cm in length through which a fine cotton wick was pulled served as the intramural wick electrode. A tiny hole in its wall at a variable distance from the sealed end allowed electrical contact between the wick and the intramural extracellular space. The tube was driven through the ventricular wall from the epicardial surface. The free end of the tube emerged from the left ventricular cavity and the mitral orifice. Measurements were taken by touching the free end of the tube with the movable wick electrode described above. The level of the zero potential was determined in the same way as for the epicardial sites.

Measurements of Transmembrane Potentials

To determine transmembrane potentials, floating glass microelectrodes filled with 3 M KCl with resistances of 20–30 MΩ were used, together with conventional high input impedance preamplifiers and differential DC amplifiers. The microelectrodes were brought into contact with the extracellular space by advancing them carefully through the holes in the rubber membrane attached to the epicardium. Impalements were performed with a hydraulic micromanipulator. A second microelectrode with a broken tip positioned in the same hole served as extracellular reference. The determination of the value of resting membrane potential on withdrawal of a microelectrode proved to be difficult, because of the great flexibility of the microelectrode tips. Therefore, values of resting membrane potentials will not be given for all transmembrane potentials shown in the Results section. The outputs of the differential amplifiers were connected to an Ampex multichannel instrumentation tape recorder. Signals were printed out on an Elema multichannel inkwriter.

In Situ Experiments

In three control experiments, DC extracellular electrograms were measured from in situ hearts. Holes in a rubber membrane 5 mm apart served as epicardial sites of measurement. Cotton wick electrodes inserted from the epicardium into the left ventricular wall recorded extracellular DC electrograms at a distance of 5–6 mm from the epicardium.

Construction of Isopotential Maps and Computation of Extracellular Current Densities and Laplacian Maps

Amplitudes of DC potentials at fixed intervals of the cardiac cycle (taking the atrial stimulus as zero time) were measured by hand from signals printed out at a sensitivity of 1 mV/mm. From these data, isopotential maps were constructed by hand or by using a computer program. This program calculates the potential by linear interpolation.
from the four neighboring points on the grid. The extracellular potential gradients which appear after coronary occlusion during the T-Q and S-T segments are caused by the flow of injury current through the extracellular compartment. This current is generated by the instantaneous difference in transmembrane potential in adjacent myocardial tissue. The assessment of the epicardial and transmural potential distribution allowed us to (1) calculate the extracellular current flowing between two measuring sites and (2) determine the sources of this current, i.e., determine the net current which, at a certain measuring site, flows between the intracellular and extracellular compartment and is added to or subtracted from the extracellular current flowing at this site.

The principle of the technique is outlined briefly as follows. Consider a point in the grid of holes in the rubber membrane which is not at the border of the grid, for example, F7. It is surrounded by F6, F8, E7, and G7. The current flowing from any of these points to F7 is proportional to the voltage difference between F7 and the point in question. For example, the current density $J_{E7F7}$ from E7 to F7, at time, t, in the cardiac cycle will be:

$$J_{E7F7} = \frac{1}{\rho \cdot L} (V_{E7} - V_{F7}) [A/m^2]$$  \hspace{1cm} (1)

where $\rho = \text{resistivity of the extracellular compartment of the tissue}$, $L = \text{distance between the measuring points}$, and $V_{E7}$ and $V_{F7} = \text{the extracellular potentials at the sites E7 and F7 at time, t, of the cardiac cycle}$. Now consider a small cube of the subepicardial tissue sheet oriented in parallel to the grid lines in such a way that site F7 is the center of its top. Let the length of the edges be $L$, the distance between the sampling points. The amount of current entering this cube through a lateral face will be the product of the current density and the area of the face. The total amount of current entering or leaving the cube through the lateral faces will thus be given by:

$$I_{F7} = L^2 \cdot (J_{E7F7} + J_{F7G7} + J_{F6K7} + J_{F7F7})$$

Introducing Equation 1 and dividing by the volume of the cube yields:

$$I_{F7} = \frac{1}{\rho \cdot L^2} (V_{E7} + V_{G7} + V_{F6} + V_{F7} + 4V_{F7}) [A/m^2]$$  \hspace{1cm} (2)

where $i$ is a scalar quantity representing an extra current which cannot be accounted for by the two-dimensional extracellular potential field measured on the grid. Indeed, as long as the sheet of epicardial tissue behaves as a simple passive resistance network, the total current flow to site F7 is zero. This is equivalent to the condition that the potential of the central point equals the numerical average of the neighboring points. Exactly the same amount of current then is flowing toward the central point as is flowing away from it. As soon as $I_{F7}$ in Equation 1 is not zero, net current must either have been added to or subtracted from the extracellular tissue at site F7. Two biological explanations can be given in this case: (1) a transmembrane current flowing locally between intra- and extracellular compartments and (2) an extracellular current flowing between the epicardial and the underlying intramural layer. As will be shown in the Results section, during ischemia no important transmural gradients occurred in our experiments. Therefore, $i_{F7} = 0$ defines F7 as a current source; $i_{F7} < 0$ defines F7 as a current sink. Equation 2 is the discrete counterpart of the well known electroconduction field equation

$$\mathbf{i} = \nabla \cdot \frac{1}{\rho} \Delta \mathbf{V},$$

where $\Delta$ represents the Laplacian operator. The current source strength can be calculated for all the points on the grid except those situated at the border and presented on a map. For this map, the term “Laplacian map” will be used in the remainder of the text. For actual calculations, a slightly more elaborate version of Equation 2 was used, which takes into account the potentials at eight instead of four neighboring points. The relative weighing factors for the potentials in Equation 2 may be conveniently expressed in the computational molecule $1 - 4 - 1$. The form which was actually used was $4 - 20 - 4$. For numerical calculations, a value of 400 ohm cm was assumed for the extracellular resistivity, $\rho$. The extracellular current density vector, $j$, will be expressed in $\mu A/mm^2$, the current source strength, $i$, in $mA/mm^2$.

Results

The Relationship between the Extracellular DC Electrogram and the Transmembrane Potential during Early Ischemia

Figure 1 depicts the changes in the transmembrane potential and local extracellular DC electrogram during the first minutes after coronary artery occlusion. Each panel is a superposition of the transmembrane potential and the extracellular electrogram recorded at a single site during the control situation and at various intervals during ischemia. The first change to be observed is a shift of the resting membrane potential to a more positive value and a concomitant depression of the T-Q segment of the extracellular potential. In the following minutes, the resting membrane potential decreases further and the upstroke velocity, amplitude, and duration of the action potential diminish. These changes are reflected in the extracellular signal by an increased T-Q depression and S-T elevation, and by a decrease in magnitude and downstroke velocity of the electrogram spike. The decrease in the resting transmembrane potential always was associated with T-Q segment depression at every subepicardial site at which it was measured. The nature of S-T elevation, which, in Figure 1, is due to loss of action potential amplitude and duration, is more complex. The onset of local depolarization in Figure 1 was only slightly delayed during ischemia with respect to the beginning of the ventricular complex. As shown in Figure 2, from another experiment, the onset of local depolarization in the ischemic zone can be markedly delayed. At these sites, the
delay in the onset of local activation seems mainly responsible for the local S-T elevation. The polarity of the local T wave is dependent on both the duration of the ischemic action potential and on the moment of activation. A short action potential which repolarizes earlier than the cells in the nonischemic tissue causes an early and positive T wave. Whenever repolarization of ischemic cells occurs later than that of normal tissue, a negative T wave results.

The electrical alternation shown in Figure 2 is a typical feature of the ischemic cells and occurs within the first minutes of ischemia. In the center of the ischemic zone it precedes the phase of unresponsiveness shown in Figure 3. The absence of local electrical activity is reflected in the extracellular signal by a monophasic potential. At this stage of ischemia, which begins some 7 minutes after ligation, the extracellular complexes have their maximal amplitude, the T-Q depression being about −15 mV and the S-T elevation, about +35 mV. By withdrawing the microelectrode from the unresponsive cell, an estimate could be made of the membrane potential, which in this case was −65 mV.

**Epicardial Potential Distribution during Early Ischemia**

Figure 4 shows maps of isopotential lines constructed from recordings taken between 15 and 30 minutes after coronary artery occlusion at 240 epicardial sites, separated by 3 mm, on the anterior wall of the heart. The upper map shows the potential distribution during diastole; the lower map shows that during early systole (250 msec after the atrial stimulus). Both maps show an arrangement of the isopotential lines around a central region with a maximal T-Q depression of −15 mV and a maximal S-T elevation of +35 mV. In six other mapping experiments, the results were comparable to those of Figure 4 with respect to the arrangement of the isopotential lines and amplitude of the potential changes. Complexes recorded along a line where the potential gradient is steep show a transition from completely monophasic potentials that...
FIGURE 4  Epicardial potential distribution in diastole (top) and early systole (bottom) after 15-25 minutes of occlusion of the left anterior descending artery. Asterisks on the lowest electrogram indicate the moments during the cycle at which the potentials were measured. Signals were recorded from the shaded area on the anterior aspect of the heart shown in the inset, at sites 3 mm apart. The extracellular complexes shown were recorded from sites along the line of steep potential gradients indicated. Square wave pulse indicates a 30-mV calibration. Isopotential lines in both maps represent 4-mV steps.

FIGURE 5  Comparison of epicardial DC potentials and intramural DC potentials recorded 3 mm below the epicardial surface. Inset shows the arrangement of the measuring points: The epicardial sites (triangles) separated by 5 mm form a grid of 3 rows and 12 columns. The intramural electrodes (crosses) are inserted at a distance of 1 mm from the epicardial measuring sites. The 3 pairs of graphs show the potential distribution along the 3 rows during the T-Q segment (open circles) and the S-T segment (filled circles) before and 15 minutes after occlusion. Intramural potentials are connected by an interrupted line; epicardial potentials, by a solid line. The time of diastolic and systolic measurement is indicated by open and filled circles on two redrawn extracellular electrograms, one of which is in the ischemic zone and the other in the normal tissue. Note that, during ischemia, intramural and epicardial potential profiles in the border zone are almost superimposable.
indicate local unresponsiveness to normal extracellular complexes that indicate normal intrinsic activity. In this experiment, the shortest distance measured between areas showing unresponsiveness and areas showing normal activity was 9 mm. Since the recording sites were separated by 3 mm, the actual dimensions of this border zone could be less.

**Intramural Potential Distribution during Early Ischemia**

To interpret the electrical changes on the epicardial surface, we had to know whether the ischemic changes in DC electrograms were uniform throughout the ventricular wall or whether important differences existed between intramural and corresponding surface sites. We therefore performed several experiments, using intramural wick electrodes to record DC potentials in the ventricular wall, at various distances from the epicardial surface. In the experiment shown in Figure 5, intramural wick electrodes were inserted at 5-mm intervals in three parallel rows, and intramural potentials were recorded 3 mm from the epicardial surface. Epicardial electrograms were recorded at a site 1 mm from the insertion point of the intramural electrode.

Potentials at fixed moments during diastole and systole are depicted for the control condition and after 15 minutes of ischemia. Although at certain sites during ischemia there are slight differences in magnitude between intramural and epicardial potentials, it is evident that the transitional zone where the potentials return to normal has the same configuration and occurs at the same sites both at the surface and in the wall. In another experiment in which intramural potentials were recorded at different depths, i.e., 3, 6, and 9 mm from the epicardial surface, the potential profiles at the surface and in the wall also were practically superimposable. We concluded therefore that in the perfused pig heart the ischemic changes in potential are uniform throughout the ventricular wall. Consequently, the main orientation of the extracellular current which causes the potential differences in the epicardial extracellular space is directed parallel to the surface.

**Extracellular Epicardial Current Flow during Early Ischemia**

An isopotential map during the early S-T segment (250 msec after the atrial stimulus) and the corresponding Laplacian map after 15 minutes of occlusion are shown in Figure 6. The steepest potential gradients (left panel) are situated in the border zone, and the potential distribution in the center of the ischemic zone is more uniform. Since the center of the ischemic zone is more positive with respect to the normal area, currents must flow in a centrifugal direction towards the nonischemic area. As can be seen from the computed Laplacian map in the right panel, the main sources of these currents are localized in the borders of the ischemic area. At the site of the main source maximum (point A), the current source has an amplitude of 1.0 \( \mu \text{A/mm}^2 \). The current emerging from point A spreads out into the adjacent sinks. The sinks are distributed over a larger area than the sources and, therefore, have smaller maximum amplitudes. At point B, a current of 0.6 \( \mu \text{A/mm}^2 \) is disappearing from the epicardial layer. In the map of Figure 6, the greatest extracellular current density vector is located between A and B and

![Figure 6](http://circres.ahajournals.org/)

**Figure 6** Epicardial potential distribution (left panel) and computed Laplacian map (right panel) after 15 minutes of ischemia, at a moment in the cardiac cycle indicated by the asterisks on redrawn extracellular electrograms recorded from sites A and B. Shaded area in inset represents area recorded from. In the isopotential maps, lines indicate 4-mV steps. In the Laplacian maps, the shaded area represents current sources; the unshaded area, current sinks. Lines indicate steps of extracellular current change of 200 nA/mm² extracellular space. Since the Laplacian values of sites at the border of the area recorded from cannot be calculated, the Laplacian map is smaller than the isopotential map.
S-T AND T-Q SEGMENT CHANGES DURING ISCHEMIA/Kléber et al.

FIGURE 7 Epicardial isopotential maps during diastole (top) and systole (middle) after 15 minutes, 1 hour, and 2 hours of occlusion. Moments of measurements are indicated by asterisks on the extracellular electrogram recorded from a site in the ischemic area. Isopotential lines indicate 4-mV steps. Area recorded from is shown in the inset. In the lowest panels, the shaded areas represent zones of absent local electrical activity.

The overall amplitudes of the monophasic extracellular potentials indicating local unresponsiveness 2 hours after occlusion were 25% of the amplitude measured between 10 and 15 minutes after occlusion. This decrease in amplitude of the extracellular DC potentials was present in all experiments, and the potential distribution after 2 hours was always very similar to that shown in Figure 7. The initial fast transition from normal electrical activity to unresponsiveness, already demonstrated by intracellular measurements in Figures 1-3, results in two large zones of absent electrical activity, as shown in the left lower panel of Figure 7. Between approximately 30-45 minutes after occlusion, most of the cells in this area regain their excitability. In the experiment shown in Figure 7, only three small areas of unresponsiveness were present after 1 hour. After 2 hours of occlusion, activity had again disappeared from a large zone which exceeded the area of unresponsiveness present after 15 minutes of occlusion. Transmembrane potentials which were measured from nonischemic sites within 2.5 hours of coronary occlusion showed the same amplitude and configuration as the control values before occlusion. At this stage, no electrical activity could be restored by reperfusion. The transient return of electrical activity in previously unresponsive cells was found in every experiment. Its onset occurred at intervals varying from 30 to 45 minutes after occlusion, and unresponsiveness gradually returned between 1 hour and 1.5 hours after occlusion.

Intracellular recordings at different stages of occlusion are shown in Figure 8. In the left panel, a cell in the center of the ischemic area has become unresponsive after 7.5 minutes of occlusion. After 42 minutes, activity has returned. The transmembrane action potential at this stage is of low amplitude and short duration and shows a loss of...
FIGURE 8 The panel on the left shows the transmembrane potentials (top tracings) and the corresponding DC extracellular electrogram (lower tracings) of one cell in the ischemic area before, and 7.5 and 42 minutes after occlusion of the left anterior descending artery. Note return of electrical activity after 42 minutes. The panel on the right shows transmembrane potentials (top tracings) and DC electrograms (lower tracings) in the border zone at different times after coronary occlusion (in lowest panel, the atria were not stimulated).

plateau. The onset of depolarization is markedly delayed. In the panel on the right, the transmembrane action potential from a border site is shown. Although the transmembrane potentials remain virtually the same after 14, 30, and 60 minutes of occlusion, the concomitant extracellular electrogram clearly diminishes in size.

In Figure 9 the time course of potential changes on the epicardium is compared to that at corresponding intramural sites 6 mm from the epicardial surface. Although minor transmural gradients existed during different stages of occlusion, the decrease in T-Q depression and S-T elevation is marked at both epicardial and intramural sites and follows the same time course. The border of the potential changes does not change its site between 15 minutes and 2 hours of occlusion. Similar results were obtained when intramural recordings 3 and 9 mm from the epicardium were compared with corresponding surface recordings. In Figure 9 it can be seen that site A is unresponsive at 15 minutes of ischemia but that intrinsic activity reappears after 30 minutes, while, even after 1 hour, the small downstroke indicates the presence of a small transmembrane action potential. Site B shows activity throughout the first hour. After 2 hours, no intrinsic activity is seen at either site.

Control Experiments in Situ

The in situ control experiments did not allow the measurement of potentials from extracellular sites separated by less than 5 mm, a limit which is needed to obtain accurate information about epicardial extracellular current flow. The distribution and amplitude of both epicardial and intramural DC potentials was similar to that found for the isolated hearts. The only difference was the time course of the changes. Initially, unresponsiveness in the center of the ischemic zone occurred between 5 and 7 minutes after occlusion. Transient improvement of electrical activity in the ischemic zone occurred between 10 and 20 minutes of occlusion. After 1 hour, a large zone of unresponsiveness was present, and the overall amplitude of the extracellular monophasic complexes had decreased to 25% of the values recorded during the initial stage. This corresponds to the amplitudes found in the isolated hearts 2 hours after ligation.

Discussion

Our results confirm previous findings\(^{9,11}\) that cells in the ischemic myocardium undergo depolarization after coronary artery occlusion. The transmembrane action poten-
S-T AND T-Q SEGMENT CHANGES DURING ISCHEMIA/Klèber et al.

...tials show a progressive decrease in amplitude and upstroke velocity and a decrease in duration, until, between 7 and 10 minutes after ligation, no action potentials can be evoked by excitation propagating from normal myocardium. Membrane potentials recorded from unresponsive cells (Fig. 3) indicate that the critical level at which unresponsiveness occurs is identical to the threshold for the rapid inward sodium current.

Our recordings of DC extracellular electrograms obtained simultaneously with the recording of transmembrane potentials show that loss of resting membrane potential is associated with T-Q depression and that loss of action potential amplitude, action potential shortening, and delayed activation are associated with S-T elevation (Figs. 1 and 2). Complete unresponsiveness results in a monophasic extracellular potential (Fig. 3), the amplitude of which is comparable to the monophasic potential recorded after mechanical injury.

The ischemic changes in the experiments on in situ hearts were comparable to the changes in the isolated heart with respect to the magnitude of the T-Q and S-T segment changes and their distribution. The faster time course of their development may reflect the fact that the oxygen demand in the Langendorff-perfused heart is smaller than in a heart working against an external load and, consequently, changes in intracellular metabolism occur more slowly after coronary occlusion in the isolated heart.

The determination of the intramural extracellular potential distribution showed that no major transmural potential gradients were present in the pig heart during ischemia. This is in agreement with the finding that occlusion of the left anterior descending artery in the pig heart results in a transmural infarct, whereas, in the dog heart, the ischemic area is predominantly in the subendocardium. The absence of transmural potential gradients means that extracellular current flow during the T-Q and S-T segments is directed tangentially to the ventricular wall and generated at any layer of tissue by the intracellular compartment of this layer. Extracellular epicardial current flow then is the consequence of intracellular current of opposite direction in the epicardial cellular sheet. The electrical driving force for this current is the instantaneous difference in transmembrane potentials between ischemic and nonischemic cells, as illustrated in Figure 1. This relationship between transmembrane potential and the extracellular DC electrogram already has been shown hypothetically in electrical models of regional myocardial ischemia and experimentally in isolated perfused rabbit hearts.

To quantify the direction, localization, and magnitude of extracellular currents, isopotential maps were constructed from the epicardial surface. An ideal map would be constructed from simultaneous recordings. Several observations showed that the error introduced by sequential recording at different sites did not influence the main conclusions drawn from our data. (1) Although extracellular potentials changed rapidly during the first minutes of ischemia, after 10-15 minutes, potentials remained stable for some 20 minutes, as shown by repeated mapping during this period. The decline in potential amplitude in later stages occurred very gradually. (2) Maps from different experiments made after 15 minutes of ischemia at similar periods showed essentially the same configuration and amplitudes, although the sequence of measurement was different in different experiments. (3) The area covered by points necessary to calculate one value of the Laplacian operator was recorded within 3 minutes or less. The Laplacian maps provide a two-dimensional representation of the origin of the extracellular currents. During the early stage of the S-T segment, and during its later stages, when some fibers have already repolarized, the distribution of current sources and sinks is similar and is localized in the border zone. The maximal strength of the current sources was of the order of 1.0 μA/mm² extracellular space. This current is dispersed into sinks localized toward the normal myocardium. Maximal extracellular current densities are found in the border zone and are of the order of 1 μA/mm². In diastole, the current flows in the opposite direction, is more dispersed over the ischemic area, and has a maximal amplitude of 0.3 μA/mm². These current strengths are scaled by the value we chose for resistivity of the tissue. Values found in the literature range from 800 to 160 ohm·cm. Since we used the value of 400 ohm·cm, which might be on the low side. Consequently, we might have underestimated the actual current strength. Also, the fact that the muscle resistivity may be anisotropic has not been taken into account. Finally, since the Laplacian represents a second difference quotient of the measured values and no smoothing of the data was done, the Laplacian maps are more sensitive for noise than the potential maps. Therefore the Laplacian maps should be interpreted mainly as an indication of the order of magnitude and of the localization of the current sources and sinks.

The onset of local depolarization in the ischemic area can be markedly delayed. This delay may influence the direction of current flow during repolarization, because repolarization in the ischemic area may outlast repolarization in the normal area and produce a negative T wave in the electrogram, as shown in Figure 2. This occurs especially in the transient phase during which ischemic action potentials alternate with respect to amplitude and duration. Because of the transient nature of this phase, maps which would have allowed calculations of current flow could not be made. The occurrence of arrhythmias during the first minutes of ischemia coincides with the period of maximal T-Q depression and S-T elevation, and with the phase of electrical alternans. One might therefore ask whether the extracellular current flow does play a role in the genesis of ectopic ventricular rhythms. Figure 10 shows in diagrammatic form the relationship between local electrical activity and current flow during repolarization at the time alternation occurs in the ischemic area. In the upper panel, current flows during the repolarization of the normal action potential intracellularly into ischemic cells which have already repolarized. The maximal electrotonic effect of this depolarizing current is exerted at sites where the transmembrane current is greatest (maximal source in the Laplacian map). Since, at this stage, excitability of the ischemic zone is depressed and the refractory period is longer than the action potential duration, it is unlikely that local ectopic excitation occurs. However, as indicated in the lower
panel, in the subsequent beat, when repolarization in the ischemic area occurs later than repolarization in the normal zone, current flows in the opposite direction toward the normal zone, where it exerts a depolarizing effect. At that moment in the cardiac cycle, excitability in the normal myocardium has recovered, and the current requirement for excitation at that moment may even be slightly less than later in diastole. In a previous paper it was shown that during the phase of alternation, the conditions required for reentry were present. In view of the above considerations, we should add that reexcitation caused by "currents of injury" may also be a factor in the genesis of arrhythmias. This reexcitation would occur when, primarily because of delayed activation within the ischemic zone, repolarization in the ischemic area outlasts repolarization in the normal zone. This condition is apparent from the configuration of the extracellular electrogram and is represented by a negative T wave.

Time Course of T-Q and S-T Segment Potential Changes

Several factors could account for the gradual decrease in T-Q depression and S-T elevation which begins 30 minutes after ligation. Between 30 and 45 minutes of ischemia, action potentials reappear in previously unresponsive cells, and this may lead to a decline in T-Q depression and S-T elevation. We do not know the reason for this transient improvement of electrical activity, which has been noted before, both in the pig heart and in the dog heart. One might speculate about a delayed increase of collateral flow into the ischemic area. Alternatively, it is possible that, due to diffusion through the extracellular space, the extracellular concentration of substances which leaked out from ischemic cells may diminish with time. Such substances produce inexcitability of normal myocardial cells in vitro and are partially responsible for the early occurrence of inexcitability in the ischemic area. After 90 minutes of ischemia, excitability has again disappeared from a region which, at many sites, exceeds the initial area of unresponsiveness. At 120 minutes, the T-Q depression has about the same amplitude as the S-T elevation, whereas the ratio of S-T elevation to T-Q depression after 15 minutes is about 2.5. This shift can be explained by the loss of polarization of the ischemic cells. When the membrane potential of ischemic cells gradually shifts toward zero, the electrical gradient between ischemic and nonischemic cells increases during diastole and decreases during activity of the normal zone. The overall decrease in extracellular potential at all epicardial and intramural sites within the ischemic area during the first 2 hours after coronary artery ligation can be due either to a decrease in tissue resistivity through which the current is flowing or to a decrease in the amount of current. Extracellular edema may lead to a decrease in extracellular resistivity, and this could occur in the ischemic zone and partially account for our results. It would, however, lead to an increase in conduction velocity, and the marked delays in onset of local depolarization in the border zone where local activity is only moderately impaired would not be expected. A gradual electrical uncoupling of the ischemic cells may be the major reason for the decrease in amplitude of the extracellular potentials.

Wojtczak has shown that the internal longitudinal resistance of bovine myocardial trabeculae increases rapidly when the fibers are immersed in hypoxic, glucose-free medium, and that this increase is related to an increase in intracellular Ca concentration. This process may be similar to the "healing over" observed after mechanical injury of cardiac tissue, which is dependent on the presence of Ca ions at the low resistance intercellular connections.

The decrease in amplitude of S-T elevation and T-Q depression after the initial stage of coronary occlusion thus can be due either to a reappearance of electrical activity in the ischemic area or to electrical uncoupling of damaged cells.

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Mechanism and time course of S-T and T-Q segment changes during acute regional myocardial ischemia in the pig heart determined by extracellular and intracellular recordings.

A G Kléber, M J Janse, F J van Capelle and D Durrer

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