Polarographic Oxygen, the Epicardial Electrocardiogram and Muscle Contraction in Experimental Acute Regional Ischemia of the Left Ventricle

By JOHN J. SAYEN, M.D., WARNER P. SHELDON, M.D.,
GEORGE PEIRCE, M.S., AND PETER T. KUO, M.D.

With the assistance of Clarence S. Gilbert, M.D., Aaron H. Katcher, M.D., Harry F. Zinsser, M.D., and Orville Horwitz, M.D.

This study is the first attempt to correlate myocardial oxygen availability by the polarographic method with direct electrocardiographic leads and cinematographic records of muscle contraction during experimental acute coronary branch occlusion and narrowing. The comparative insensitivity and slowness of the epicardial electrocardiogram as an index of acute regional ischemia is demonstrated. Special attention is given to the rates of myocardial oxygen change immediately following attainment of a significant degree of coronary obstruction, the effects of pure oxygen inhalation on the experimental situations, and alterations in coronary vein color following release of arterial occlusion.

In previous studies it has been shown that measurements of oxygen availability by the platinum electrode provide stable values in nonischemic myocardium as well as sensitive indices of ischemia produced by coronary occlusion. The borders of ischemic areas responded to oxygen inhalation by significant rises of myocardial oxygen, whereas the centers failed to show such a response. A "physiologic" classification for ischemic muscle, based on the depth of myocardial oxygen fall, distinguished central zones (levels 25 per cent or less of the control) from border zones (levels 25 to 85 per cent of the control). This classification was roughly consistent with the anatomic extent of the ischemic area as judged from inspection. In these experiments we did not attempt to determine the rate of change in myocardial oxygen or to correlate electrocardiographic or muscle contraction changes with the polarographic findings.

METHODS

Acute regional ischemia was produced in 22 dogs weighing from 15 to 20 Kg. by an experimental technic previously described. Under morphine-pentobarbital-dial-urethane anesthesia, the heart was exposed, a coronary branch isolated, and an array of oxygen electrodes inserted, so as to sample muscle within and, insofar as possible, beyond the vessel's apparent left ventricular distribution. We utilized medium-sized or small arterial branches, which in these experiments were always derivatives of the left anterior descending. We considered a small branch to be any of the terminal surface rami beyond the last major bifurcation, and a medium-sized branch to be a rami just proximal to such a bifurcation. Larger branches were not used, in order to avoid blood pressure or heart rate changes. In all animals continuous epicardial electrocardiograms were obtained. In the 8 most recent animals cinematographic records were obtained.
were made. Polarographic, electrocardiographic and cinematographic techniques are described separately.

**Alterations of Previous Experimental Technic.**

The technic of coronary obstruction was refined with the use of a screw forceps with a small foot resting gently on the epicardium beneath the isolated coronary ramus and between its accompanying veins. The screw of the forceps could be adjusted to produce sudden occlusion, or gradual narrowing with subsequent prompt release of the vessel. This method avoided the undesirable effects of traction on a coronary ligature which were suspected of interfering with the stability of electrode reading in our previous work. Slight increases of heart rate and blood pressure often resulted from dissection of the coronary artery or from placement of the forceps. Because of this, several minutes were allowed to elapse before initiation of any experimental procedure.

Certain changes in gas administration and surgical technic were made in the 6 animals most recently used. A mechanical respirator was used instead of a rebreathing bag. Gases were delivered directly into the intake opening of the respirator, through a reduction valve, whereas expiration was passive. Shifts from room or compressed air to pure oxygen could be made within a few seconds by an interchange of appropriate tubing.

**Experimental Procedures.** In 6 pilot animals the array of 6 to 10 oxygen electrodes was read in rotation as rapidly as possible, so that each electrode was read at 30 to 60 second intervals. These intervals proved to be too widely spaced to follow the rapid descent of polarographic oxygen during occlusion.

In 9 animals (nos. 50, 51, 54, 133, 134, 135, 137, 138 and 140) the changes at a single oxygen electrode were followed at 2 to 5 second intervals during coronary occlusion, and during shifts from air to oxygen inhalation or oxygen to air under nonischemic and regionally ischemic conditions. Rotational readings from the entire electrode array could of course be interspersed among these semi-continuous records.

In 7 animals (nos. 42, 49, 51, 63, 64, 66 and 67) satisfactory studies of critical coronary narrowing were obtained. The forceps were tightened a little at a time, the array of electrodes being read in rotation, and the heart was observed for 30 to 60 seconds between each stage of narrowing. Evidence of ischemia was always initiated by a decline in oxygen availability at one or more of the electrodes in the array. It was important not to tighten the clamp further, once the oxygen fall had begun, and because of this the data from a number of ischemic episodes had to be discarded. Neither semicontinuous oxygen determinations nor motion picture records were obtained in the critical narrowing experiments.

**I. Polarographic Myocardial Oxygen Technic.**

The oxygen electrodes inserted into the left ventricular myocardium were made, as described by Montgomery and Horwitz,

\[0.2 \times 10^{-10} \text{amp.} (1 \text{mm. on a 100 mm. galvanometer scale).} \]

In determining the degree of change in oxygen availability for each experimental procedure, the mean of at least 2, and generally 3 or more, consecutive control readings on air was taken as 100 per cent. Base-line variation that was more than 15 per cent was unacceptable. The commonest oxygen electrode artefact was caused by sudden alterations in position or pressure of the electrode shaft. This was usually due to striking of the edge of the sternum-splitting incision. Such electrodes usually recorded sudden high values followed by sudden falls to very low levels. Subsequent read-
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Coronary Occlusion. Polarographic oxygen in medium-sized ischemic areas fell rapidly during the first 30 to 60 seconds following occlusion. Thereafter relatively stable values were recorded.

In central zones, the most ischemic portion of the coronary distribution, the period of rapid change was characterized by a fast fall to less than 25 per cent of the control. This fall was 50 per cent complete within 4 to 21 sec. and 90 per cent complete in 11 to 52 sec. (12 ischemic episodes in 5 animals). The rates of fall were quite consistent (fig. 1). Occasionally small rises preceded the oxygen fall, but a 15 per cent drop regularly occurred within 1 to 13 sec. After the period of rapid change, myocardial oxygen stabilized at low levels, slowly declined still further, or showed minor fluctuations.

At the borders of medium-sized ischemic zones the rate of polarographic oxygen fall was comparable to that at the centers, but a higher plateau was reached, between 25 and 75 per cent of the control. Occlusion of small coronary branches usually produced a slower polarographic oxygen fall and sometimes a slightly delayed onset or a transient rise. The oxygen falls, even though relatively slow, were ultimately as severe as in larger areas.

Critical Coronary Narrowing. Narrowing by stages of a medium-sized branch ordinarily produced no discernible change in heart fun-
Critical narrowing: polarographic oxygen

At central electrodes there was then a prompt, yet comparatively slow, fall of polarographic oxygen in the ischemic area. This began before any other evidences of ischemia appeared, and continued until there was a low, relatively stable polarographic oxygen level, less than 25 per cent of the control.

This required from 1 to 5 min. (fig. 2). Occasionally oxygen availability increased briefly, just before a critical degree of narrowing was attained. However, spontaneous sustained rises of polarographic oxygen were not seen, once a critical degree of narrowing had been maintained for 60 sec. or more.

In border zones the depth of polarographic oxygen fall was less than in the central zones, but the rate of fall was similar in the same ischemic episodes (fig. 2). In the case of very small coronary branches, the oxygen electrode could not distinguish the effects of critical narrowing from those of total occlusion. Both procedures produced slow falls below 25 per cent of control levels at central zones. Occasionally no central zone could be located, slow falls to between 75 and 25 per cent of the control being the largest recorded. However, we did not sample such ischemic areas at a sufficiently wide variety of positions and depths to exclude the possibility that profounder oxygen falls had occurred somewhere in the unsampled muscle.

Release of Coronary Obstruction. With release of coronary occlusion polarographic oxygen at central zones increased rapidly, generally overshooting the preobstruction control value (fig. 1). It might remain elevated 30 sec. to several minutes. The eventual recovery level was sometimes lower or higher than the control. After release of critical narrowings the oxygen rise was prompt, but less often overshot the control level and sometimes did not attain it. This was also true of border areas following release of an occlusion.

Response to Oxygen Inhalation. In non-ischemic hearts, increases of polarographic oxygen began within 5 to 10 sec. of oxygen inhalation (fig. 3). There were steep rises for 25 to 30 sec. with attainment of a plateau within less than 1 min. Commonly these plateaus were 50 to 100 per cent above the control, but occasional electrodes rose several hundred per cent. A consecutive series of observations is shown in figure 3. The return from pure oxygen inhalation to room air reversed the changes produced by shifts from air to oxygen, the rate and amplitude of the
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Fig. 3. Effect of pure oxygen inhalation on polarographic oxygen in nonischemic hearts. Semi-continuous determinations at 2 to 5 sec. intervals at 7 electrode sites in 5 consecutive animals. Note that the electrode changes are largely complete within 35 sec. following the change of inhaled gas mixture.

fall being quite similar, as shown on the right side of figure 3.

Certain types of responses did not occur in this restricted series. In our total experience (including the pilot animals and previous experiments) roughly one electrode area in 10 showed no significant rise during oxygen inhalation. In such instances there were sometimes slight falls of oxygen, not exceeding 15 per cent.

In ischemic areas the response to oxygen inhalation differed considerably and depended upon the size of the vessel obstructed and whether it was completely occluded or not. Occlusions of medium-sized vessels were studied only in the pilot animals. The oxygen responses reproduced our earlier results.1 Central zones rarely showed any rise at all and never a large or a sustained rise, whereas roughly two thirds of the border zones regained one third or more of their initial fall. At outside electrodes the oxygen response resembled that of nonischemic hearts.

In the other dogs pure oxygen was admin-
### Table 1. Critical Narrowing: Polarographic Oxygen, the Epicardial Electrocardiogram and the Effect of Oxygen Inhalation

Each line gives data for one electrode. Border and central electrode data are grouped together for each ischemic episode. Column 1 identifies animal, episode and electrode, column 2 the absolute oxygen reduction current during the control period for each episode (taken as 100%). The effects of narrowing are tabulated in 3 sections: the period of rapid oxygen fall, the period of oxygen stability, and the period of 100% oxygen inhalation. For the first period are given the rate of oxygen fall, as indicated by the time required for completion of 50% (column 3) and of 90% (column 4) of the total fall; and the time of appearance of RS-T segment elevation (column 5) with the oxygen level at that time (column 6). For the stable period, the maximum RS-T elevation (column 7) and average oxygen level (column 8) provide a base line for evaluating the effects of inhaling 100% oxygen. The effects upon the mean oxygen level (column 9) and any RS-T segment abnormality (column 10) in the first and second halves of the 100% oxygen inhalation period are indicated.

Five critical narrowings and one small vessel occlusion are tabulated. Note that epicardial electrocardiographic results are given only with the oxygen electrode nearest to which the surface record was obtained. Determinations of myocardial oxygen were made at 15 to 30 second intervals, with the older type of oxygen electrode being used (see methods), and without motion picture records.

<table>
<thead>
<tr>
<th>Dog, episode and electrode</th>
<th>Control O₂ reduction current</th>
<th>O₂ fall period</th>
<th>Stable O₂ period</th>
<th>100% O₂ inhalation</th>
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<td></td>
<td>X10^-4 asp.</td>
<td>50% sec.</td>
<td>90% sec.</td>
<td>Onset sec.</td>
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<td>180</td>
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</table>

*For oxygen curves in nos. 42, 49 and 63 see figure 2.

**Duration of oxygen inhalation:** no. 42, 4 and 3 min.; no. 49, 10 and 5.5 min.; no. 63, 6 min. and no. 140, 4.5 min.

Myocardial oxygen increased invariably at electrodes in central zones, although such rises were not always well sustained. At border areas and the centers of very small ischemic areas, oxygen inhalation caused polarographic oxygen to rise slightly, moderately, or even...
above control levels, but not as high as the levels that could be produced at the same electrodes by oxygen inhalation with intact coronary blood supply.

**COMMENT**

Our amperometric measurements are believed to reflect the reduction of molecular oxygen as it diffuses to the platinum cathode. The availability of oxygen to the cathode, however, will be the resultant of 3 major factors: arterial oxygen tension, local coronary flow and myocardial oxygen utilization. In addition, many local factors probably play a role in determining the absolute or relative current level recorded from a given electrode: proximity to arterial capillaries, edema, or extravasated blood. Temperature and pH presumably are additional determinants.

**Arterial Oxygen Saturation.** We have assumed that arterial oxygen saturation has followed its usual pattern when air or pure
oxygen is administered. Measurements of saturation have not been made. The wide variety in magnitude of oxygen response is mainly attributable to local factors. It requires roughly 30 sec. or less for the great majority of electrodes in the heart to complete their response to inhalation of pure oxygen or to return to control levels when air breathing is resumed.

Myocardial Oxygen Utilization. Following occlusion of medium-sized coronary branches the rapid fall in polarographic oxygen reflects the rate of myocardial oxygen utilization. Ischemic myocardium can use up all the oxygen measurable by our technic within 30 sec. We do not know to what extent the rapid rise and overshoot of polarographic oxygen with release of coronary obstruction are reflections of diminished utilization of oxygen by the ischemic muscle, but we presume that most of the rise is due to increased coronary flow, since this has been shown to follow release of occlusion.6

Coronary Flow and Collateral Circulation. When pure oxygen is administered it is clear that the increased arterial tension, even though it involves a very small amount of dissolved oxygen, outweighs any tendency by oxygen to cause a decreased general coronary blood flow.6 This appears to be true both in ischemic and nonischemic situations. Compensatory flow in localized ischemic areas consequent on arterial occlusion must depend on collateral circulation alone, whereas with critical narrowing there would also have to be appreciable, though residual, flow through the obstructed main vessel. We had no way of separating these two components of compensatory flow. It was possible that the transient rise of polarographic oxygen which sometimes preceded attainment of the critical stage of narrowing (fig. 4) reflected increases of flow through collateral channels. However, we could not exclude either a transient blood pressure increase with better coronary perfusion or some alteration in myocardial metabolism that might have caused oxygen utilization to diminish.

Temperature. Local temperature must also be a determinant of oxygen availability insofar as it affects tissue oxygen tensions and oxyhemoglobin dissociation. We do not believe that temperature changes are important as far as the results of the present experiments are concerned. In hearts exposed to ambient air temperatures, the ventricular muscle soon becomes cooler than its perfusing blood. Hence arterial obstruction might be expected to cool it further, while cessation of local muscle contraction should cool it further still. However, the fall of local temperature has been found to begin later and progress more slowly than the rapid decline of polarographic oxygen.7 The delay may be due in part to temporary continuation of muscle contraction despite cessation of main artery flow. When color motion pictures were recorded during ischemia, the lights raised temperatures in the exposed heart, with a greater rise in the ischemic area than in the nonischemic muscle. Yet the rapidity of the initial fall of polarographic oxygen was not more than slightly decreased.

Heart Rate and Blood Pressure. Induced tachycardia decreases, and slowing of the heart rate increases, polarographic oxygen, whereas blood pressure variation produces changes in the same direction as the pressure change. These variations (which do not exceed 25 per cent) could be ignored in the studies reported here because of the negligible rate and blood pressure changes associated with medium-sized or small coronary branch occlusions.

II. Epicardial Electrocardiography

Technic

Electrocardiograms were recorded from a wick of cotton moistened with normal saline solution and attached by an insulated wire to the chest lead cable of a Sanborn or Cambridge direct-writing electrocardiograph. This wick was allowed to rest on the epicardial surface of the exposed heart. The reference electrode usually was the right foreleg. Records obtained in this fashion will be referred to as epicardial electrocardiograms.

Warming or cooling the ventricular surface by as little as 0.5 C. respectively reversed or exaggerated the T-wave inversion characteristic of ex-
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posed dog hearts but did not alter polarographic oxygen valves. We made no attempt to abolish the T-wave inversion. The second commonest electrocardiographic artefact was RS-T segment elevation caused by such surface irritants as 5 per cent glucose, procaine, blood, abrasion or mechanical pressure. These segment shifts, however, could usually be avoided. They were never accompanied by significantly altered polarographic oxygen in the underlying myocardium.

In the pilot series, electrocardiograms were obtained from the borders of the ischemic area and from a point thought to be well outside. We found, however, that no changes occurred during ischaemia or oxygen inhalation at the "outside" lead positions and that changes were rare and inconsistent at the border positions. In the subsequent two series of dogs, electrocardiograms were recorded from the apparent center of the ischemic area.

RESULTS

Coronary Occlusion. Epicardial electrocardiographic abnormalities appear 15 to 45 (commonly 20 to 25) sec. after occlusion of medium-sized branches (6 dogs and 15 episodes) rarely appearing before the period of rapid oxygen change was at least half over. The electrocardiographic changes consisted of contemporaneous progressive RS-T segment elevation and T-wave reversal (steadily decreasing negativity, then positivity) as illustrated in figures 5 and 6. During the period of stable, low myocardial oxygen levels, electrocardiographic abnormality in ischemic areas progressed gradually, so that within a few minutes high elevations of the RS-T segment and tall positive T-waves had developed (fig. 6, second occlusion). Occasionally there might then be an increase of amplitude of the R wave, with diminution of the S-wave amplitude and disappearance of R waves when present, but no measurable change in the QRS duration. Negative U waves often appeared.

At the borders of medium-sized ischemic zones, electrocardiographic change was not seen unless polarographic oxygen had fallen below 65 per cent of control values (fig. 7). Often there was no measurable change. With occlusion of small coronary branches, electrocardiographic changes were delayed even more than oxygen changes, and not infrequently were absent or insignificant. RS-T-segment depression was almost never seen and never proved reproducible.
Fig. 6. Coronary occlusion, central electrode: two occlusions of same vessel (dog no. 133, tables 2 and 3). Electrocardiograms are placed along abscissa with left edge of each section at correct time interval. Earliest significant electrocardiographic change (RST segment and T-wave) occurs 26 sec. after first occlusion, with the changes well established by 40 sec. First change after the second occlusion is at 45 sec. and by 85 sec. considerable RST segment elevation has developed, together with a slight diminution in S-wave amplitude—an unusually early time for any QRS change.

Critical Coronary Narrowing. Epicardial electrocardiographic abnormality was not seen after narrowing until oxygen availability had declined at least 35 per cent at underlying electrodes (fig. 2). Occasionally it was absent. When present, it consisted of R-S-T segment elevation with contemporaneous T-wave reversal. As with occlusion, progression of electrocardiographic abnormality continued long after polarographic oxygen had reached steady, low levels. In border zones electrocardiographic changes were absent or greatly delayed and slight. With occlusion of very small coronary branches electrocardiograms were usually unchanged (fig. 4).

Release of Coronary Obstruction. After release of any short occlusion the R-S-T segment of the electrocardiogram returned to
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Fig. 7. Coronary occlusion, border electrode: three successive episodes plotted simultaneously. (dog no. 134, table 1). Stable levels average about 30% of the control. Electrocardiograms from an epicardial electrode somewhat nearer ischemic area's center (see map) show changes only after polarographic oxygen has completed most of its fall. The lack of T-wave negativity in control tracing preceding the tie-off (lowest row of electrocardiograms) is a temperature artefact due to the application of warm normal saline to the heart shortly before. The ordinate shows heart rate/min. as well as per cent polarographic oxygen.

"normal" in 10 to 20 sec. (fig. 5). The T waves required somewhat longer to return to a control configuration, especially when lighting for motion pictures was in use. The overshoot of polarographic oxygen, when this occurred, had no electrocardiographic reflection.

Response to Oxygen Inhalation. Abnormal
electrocardiograms recorded from the central zones of medium-sized ischemic areas never showed significant improvement in response to pure oxygen administered after the start of coronary occlusion in our pilot series of animals. Abnormal tracings were so rarely recorded from the border zones of such hearts that the effect of oxygen could not be tested satisfactorily.

When pure oxygen was administered after attainment of a critical narrowing (medium-sized branch) severe electrocardiographic abnormalities were sometimes reduced, but never abolished (Table 1). However, only in rare instances could completely satisfactory correlation be achieved. The borders of the ischemic areas (and the centers of very small areas) regularly failed to show significant electrocardiographic abnormality nor did any changes develop after oxygen inhalation.

**Disturbances of Rhythm.** One or more extrasystoles, nodal or ventricular in origin, commonly occurred following coronary occlusion (15 of 20 episodes in 9 dogs). The first extrasystole was recorded 7 to 15 sec. after the onset of ischemia and almost always preceded any epicardial surface electrocardiographic abnormality.

In critical narrowing extrasystoles were rare. One or two extrasystoles occurred 10 to 20 sec. after release, following about half the ischemic episodes, usually the longer ones. Oxygen administration did not appear to change the frequency of extrasystoles.

Three animals of the 29 reported in this and the preceding paper developed ventricular fibrillation. Two were breathing pure oxygen at the time. In these 2 dogs a rather large coronary ramus had been occluded. In the other dog (no. 133) the clamp had just been released from a medium-sized branch after almost 10 min. of occlusion. Shortly after ventricular fibrillation developed, polarographic oxygen fell to zero at all electrodes.

**Comment**

The epicardial electrocardiogram proved a slow and an insensitive index of early localized ischemia as compared with polarographic oxygen. The smaller the ischemic area and the more gradual the onset of evidences of ischemic dysfunction the more inadequate the surface electrocardiogram's performance became.

On the other hand epicardial electrocardiograms, aside from their obviously useful identification of arrhythmias, were invaluable for following advanced ischemic situations. RS-T segment and T-wave abnormalities continued to increase in severity after disturbance of polarographic oxygen had become maximal. Still later, QRS changes and negative U waves might appear.

It has been reported that increased T-wave negativity is the earliest electrocardiographic evidence of ischemia and that this may develop within a few seconds of coronary occlusion. We have found no changes prior to the development of RS-T segment elevation 15 to 25 sec. after occlusion. While T-wave changes were occasionally seen earlier than this, we could always account for them by variations of the epicardial surface temperature. Indeed, we have not found T-wave abnormalities of importance as specific indices of ischemia. When significant they invariably were accompanied by RS-T segment displacement. The larger amplitude of T waves make changes in them easier to see during the course of an experiment than small RS-T segment shifts, but in the final analysis of records we have not derived any new information from T-wave measurements.

Depression of the RS-T segment is known to be a characteristic of the borders of large ischemic areas as well as of the ventricular myocardium opposite the center of such areas. In the experiments reported here we rarely found RS-T segment depression. Most of our border areas showed no electrocardiographic change during short occlusions. We recorded RS-T segment depression (slight in degree) in only 3 ischemic episodes and 2 animals of the series reported here and these phenomena did not prove reproducible.

The epicardial electrocardiogram has long been known to be disturbed only by great decreases of local coronary flow. Wegrza, et
al., have shown that, even with large ischemic areas, epicardial electrocardiographic change could be discerned regularly only when coronary flow had been reduced by 70 to 100 per cent. We do not know the degree of flow reduction produced by our critical narrowing procedures, but estimated that we were reducing the coronary diameter by 75 per cent. Whatever the degree of main trunk coronary flow disturbance, it was clear that reductions that did not affect the overlying surface electrocardiogram could nevertheless profoundly alter polarographic oxygen.

Oxygen administration during ischemic episodes did not increase electrocardiographic abnormality when this was present or cause it to appear when absent. We have therefore no evidence suggesting that oxygen inhalation makes ischemic areas worse despite any diminution of general coronary flow which might be expected to accompany this procedure.4 Nevertheless oxygen produced not more than slight improvement of any severely abnormal electrocardiographic pattern. The frequency of extrasystoles was not significantly altered by oxygen, nor was ventricular fibrillation prevented. The physiological significance of the rises of oxygen in ischemic areas consequent on oxygen inhalation cannot be definitely assessed by these experiments.

III. Muscle Contraction Studied by Cinematography

TECHNIC

For muscle contraction studies Kodachrome motion pictures of the exposed heart were made at 32 frames per sec. so as to slow the cardiac movements to one half of normal speed during projection. Damage to the heart by the required lighting (2 Eastman photospot bulbs at 3 ft.) could be prevented by interposing heat-absorbing glass (Edmund Scientific Corp. no. 4057). The photographed field included the coronary artery with its accompanying veins, the jaws of the occluding forceps, the anterior wall of the heart, a watch, and an image of a direct-writing electrocardiograph's paper and stylus, permitting correlation of electrical and mechanical events.

Simple inspection of the films permitted easy recognition of the onset of localized muscle contraction abnormality following coronary occlusion. For more precise measurement of contraction the distance between the white depth stops of any pair of oxygen electrodes could be measured frame by frame from the projected film and plotted against time.4-5 Here we shall be concerned only with muscle contraction disturbance easily discerned by the eye.

RESULTS

All animals in which adequate motion picture records were obtained are listed in table 2. Muscle contraction changes following occlusion are correlated with the fall of polarographic oxygen and with the electrocardiographic abnormalities.

Six to 9 sec. following occlusion, sudden late systolic bulging of the ischemic muscle could regularly be discerned. This usually occurred after a 15 to 25 per cent oxygen fall but was sometimes present before oxygen had fallen significantly. There appeared to be no exact correlation of the amount of the oxygen change and the first muscle contraction abnormality. By the time oxygen had fallen 50 per cent or more and epicardial electrocardiographic disturbance was beginning in medium-sized ischemic areas, muscle contraction began to fail earlier in systole. Early in the period of relatively stable, low myocardial oxygen levels there was holosystolic bulging of the ischemic area. When the first extrasystole occurred (7 to 15 sec. after the occlusion) it followed in every instance just after the first visible muscle contraction disturbance.

Occlusion of small coronary branches produced muscle contraction disturbance about as promptly as occlusion of large branches. Spontaneous improvement in muscle contraction was observed after small branch occlusion, without any rise of myocardial oxygen. Such a response, consisting of late systolic shortening, was sometimes demonstrable after the first 60 to 120 sec. of the stable ischemic period. The improvement was always gradual and a normal contraction pattern was never reestablished prior to release of the coronary obstruction.

At the borders of ischemic zones, disturbance of muscle contraction was more complex.
because increased shortening occurred in some areas in association with failure of contraction in central, adjacent muscle.

Coronary Narrowing. Following the attainment of critical narrowing, muscle contraction abnormality always appeared but we do not as yet have complete motion picture records of such situations. Systolic bulging had developed within the early minutes of the period of steady myocardial oxygen values. Slow spontaneous improvement was frequent.

Release of Coronary Obstruction. The speed of recovery of myocardial contraction and changes in vein color in all release sequences recorded by motion pictures are tabulated in table 3.

Table 2.—Coronary Occlusion: Polarographic Oxygen, Muscle Contraction and the Epicardial Electrocardiogram

Each horizontal line lists data for a separate occlusion. The columns (number at bottom) identify the animal, the ischemic episode and electrode number (column 1), and the absolute oxygen reduction current during the control period for each electrode (column 2), taken as 100%. The next 8 columns (nos. 3 to 10) contain information about the period of rapid oxygen change that followed occlusion: the speed of fall, indicated by the time required for values to decline by 15, 50 and 90% of the total fall (columns 3, 4 and 5); the time of appearance of visibly abnormal muscle contraction (column 6) and the oxygen level at which this began (column 7); the time of appearance of the first extrasystole (column 8); the time of onset of RS-T elevation in the epicardial electrocardiogram (column 9) and the oxygen level at which this developed (column 10). Column 11 gives the average oxygen level during the stable ischemic period.

Ten episodes in 6 animals are tabulated. In the upper 7 ischemic episodes, a branch of moderate size was occluded; in the rest, a small branch was occluded. Electrode data have been given only for electrodes that could be followed semicontinuously. Depths of electrode insertion varied from 3 to 6.5 mm.

Other electrodes in the array for each dog were read during the stable ischemic period. The tabulated electrodes in animals 134, 135, and 140 are considered as placed in a border zone since, although they did not fall below 25%, another electrode in the same array did.

For oxygen curves in nos. 133 and 134 see figures 6 and 7.
After release the epicardial veins draining the ischemic area invariably began to redden by 7 to 12 sec. This progressed rapidly so that they became almost as red as the arteries by 30 sec. The phenomenon was most conspicuous in veins which accompanied the obstructed arterial branch. As a rule the veins accompanying adjacent branches also reddened but to a much slighter degree. There was no visible change of color in the veins draining more remote portions of the myocardium. Articularization of the veins occurred regardless of the degree of polarographic oxygen response in the affected muscle.

Muscle contraction was restored to normal much more gradually than any of the other functions measured. Following release of any short occlusion, at about the time venous reddening was first seen (7 to 12 sec.) the visible muscle bulge began to disappear. By 12 to 20 sec. it could not longer be discerned (table 3). Thereafter recovery progressed steadily, with prolonged contraction of the formerly ischemic muscle beginning late in systole and reaching a maximum early in diastole. At this time the delayed relaxation of the ischemic area still clearly differentiated it from surrounding nonischemic muscle.

Table 3—Release of Coronary Occlusion: Effects on Polarographic Oxygen, the Epicardial Electrocardiogram, Muscle Contraction and Epicardial Vein Color

The animals, occlusion episodes and electrodes (column 1) are the same as in table 1 except as specified in the foot note.* The other columns record: the interval until the R-S-T segment returned to normal or stability (column 2); the time of the first extrasystole (column 3); the time when myocardial oxygen began to rise (column 4); the height and time of the peak (column 5); and of the stable level (column 6); the time venous color changes, reddening (column 7), and later darkening (column 8) began; the time when the muscle clearly ceased to bulge (column 9) and the total interval during which muscle contraction abnormalities were observed (column 10), a limit being imposed by the run of the movie camera.

Prerelease values for oxygen can be found in table 2, (column 11), or the foot note.*

<table>
<thead>
<tr>
<th>Dog episode and electrode</th>
<th>Electrocardiogram</th>
<th>Myocardial oxygen</th>
<th>Vein color</th>
<th>Muscle contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal RST(sec.)</td>
<td>Extrasystoles (sec.)</td>
<td>Start of rise (sec.)</td>
<td>Peak level (%/sec.)</td>
</tr>
<tr>
<td><strong>Medium-sized Vessels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>133-1-5</td>
<td>10</td>
<td>none</td>
<td>3</td>
<td>300 : 40</td>
</tr>
<tr>
<td>133-2-5</td>
<td>†</td>
<td>3</td>
<td>3†</td>
<td>9 : 3†</td>
</tr>
<tr>
<td>134-1-8</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>61 : 10</td>
</tr>
<tr>
<td>134-2-8</td>
<td>12</td>
<td>none</td>
<td>3</td>
<td>87 : 85</td>
</tr>
<tr>
<td>137-3-4**</td>
<td>20</td>
<td>21</td>
<td>15</td>
<td>334 : 295</td>
</tr>
<tr>
<td><strong>Small Vessels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>135-1-1</td>
<td>11</td>
<td>none</td>
<td>5</td>
<td>127 : 155</td>
</tr>
<tr>
<td>138-2-6**</td>
<td>12</td>
<td>47</td>
<td>3</td>
<td>400 : 60</td>
</tr>
<tr>
<td>140-1-4</td>
<td>0</td>
<td>21</td>
<td>5</td>
<td>373 : 186</td>
</tr>
</tbody>
</table>

For control oxygen reduction currents and pre-release oxygen levels for all electrodes, see table 1, except as noted.

* 30 X 10⁻¹⁰ amp. = 100%, prerelease oxygen level = 7%.
** 39 X 10⁻¹⁰ amp. = 100%, prerelease oxygen level = 1%.
† Ventricular fibrillation at 7 sec.
§ End of continuous motion picture record.
When the vein color and polarographic oxygen values were beginning to stabilize or return toward the control, muscle contraction frequently appeared normal to the eye. However, it could be shown by cinematographic plots that contraction patterns reproducing the control were not present until 2 to 5 min. after release, at about the time when polarographic oxygen and vein color restabilized.

**Response to Oxygen Inhalation.** So far we have not been able to demonstrate any improvement in muscle contraction following administration of pure oxygen during coronary occlusion. In the few instances in which there was improvement of electrocardiographic patterns as well as the usual improvement of myocardial oxygen following pure oxygen inhalation, no improvement of muscle contraction could be discerned exceeding what could properly have been ascribed to spontaneous improvement with passage of time.

**COMMENT**

Muscle contraction at the center of any ischemic area was disturbed very early after occlusion, with a remarkably constant time of onset. Surprisingly, this occurred before the initial drop of myocardial oxygen was well established. Often oxygen was lowered (not more than 35 per cent), but sometimes it was unchanged or even slightly elevated at the time contraction abnormality began (table 2). The lack of relationship between the onset of contraction failure and the myocardial oxygen level suggests a mechanism initially independent of oxygen deficit. We have repeatedly noted that similar, though transient, disturbances of muscle contraction are produced at the time of insertion of the oxygen electrodes into the heart. The contraction abnormality of ischemia, however, is progressive and soon becomes associated with low oxygen values.

The slow recovery of muscle contraction following release of occlusions contrasts with the rapid arterialization of the coronary venous blood, with the high myocardial oxygen values, and with the rapid return of the epicardial electrocardiogram to normal.

The dramatic arterialization of the veins following release of obstruction presumably is a reactive hyperemia. To what extent this

### Table 4.—Characteristics of Two Common, Easily Producible Regional Ischemia Situations.

<table>
<thead>
<tr>
<th>Regional Ischemia Situations (defined by the Central, Most Ischemic, Muscle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal ischemia</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Measurable oxygen rapidly exhausted (below 25% in 30 to 60 sec)</td>
</tr>
<tr>
<td>Failure of muscle contraction, first late systolic (6 to 9 sec.), then holosystolic</td>
</tr>
<tr>
<td>Extrasystoles, usually one or more, just after muscle contraction abnormality begins</td>
</tr>
<tr>
<td>Epicardial electrocardiographic abnormality uniformly (RS-T segment elevation in 15 to 30 sec.)</td>
</tr>
<tr>
<td>Muscle contraction abnormality shows no improvement, or else slow progression during the &quot;stable&quot; period</td>
</tr>
<tr>
<td>Oxygen inhalation has no effect</td>
</tr>
<tr>
<td>Produced by occlusion of a medium-sized coronary branch</td>
</tr>
<tr>
<td>No effectual compensatory (collateral) blood flow</td>
</tr>
<tr>
<td>Sequence of events is consistent and reproducible</td>
</tr>
</tbody>
</table>
is due to simple vascular dilatation, to failure of muscle contraction, to lack of oxygen utilization, to the accumulation of metabolites or even to opening of arteriovenous anastomoses, is not clear. The reddening of veins accompanying other arterial branches indicates either overlap in the normal drainage areas or disturbances of local distribution by the effects of ischemia.

Although cyanotic discoloration of ischemic muscle frequently could be seen, it was difficult to record consistently in motion pictures, and we have not as yet been able to make use of this sort of information. Frequently there was no discernible change of color.

**DISCUSSION**

The results of these studies define, preliminarily, two easily produced regional ischemia situations that cannot be differentiated adequately by the behavior of any single anatomic or physiologic index. We call these *maximal* and *critical* ischemia. Their characteristics are listed in table 4.

Maximal ischemia is characterized by a fast fall of the myocardial oxygen and a pattern of dysfunction showing great uniformity from animal to animal and episode to episode (upper portions of tables 1 and 2). It thus represents a rough standard for comparison of critical ischemia with its slower falls of myocardial oxygen. Particular instances of critical ischemia show considerable variation in the time required to attain stable oxygen levels. Consequently the differentiation of degrees of severity should be possible, although in these experiments we have not attempted it.

A number of general factors are known to affect coronary flow and the state of the myocardium, e.g., falls of blood pressure, extreme changes in heart rate, anoxia, and anemia. In these experiments we wished to avoid all factors that might tend to complicate the regional ischemic situation.

Uncomplicated maximal and critical regional ischemia would seem to represent the simplest experimental analogs of acute myocardial ischemia in man. They presumably correspond to situations that give rise to many of the small regional lesions we have distinguished in human clinicopathological studies.

These studies have not attempted to define minimal degrees of critical ischemia precisely, in part because our technic of narrowing an artery is not sufficiently delicate. With our method, when coronary obstruction becomes critical, central myocardial oxygen declines slowly to levels quite comparable with those found in maximal ischemia. While it may well be possible to produce ischemic dysfunction without such a profound oxygen fall, in our experience (with small or medium-sized coronary arterial branches) it is not easy. Acute obstruction has resulted either in maximal ischemia, in critical ischemia, or in no significant disturbance of function.

Border zone muscle in both maximal and critical ischemia shows important differences from central muscle. The fall of border oxygen is less profound than in the centers, and there is little tendency for surface electrocardiographic change. Although spontaneous improvement is common, muscle contraction disturbances are complex and cannot be studied by simple inspection of motion picture records but require analysis by cinematographic plots. As with central zones, there is little or no tendency for spontaneous improvement of either oxygen or electrocardiographic abnormality.

For experimental analysis of pharmacologic agents we have found both maximal and critical ischemia situations valuable. In general, the border zones of maximally ischemic areas and the central zones of critically ischemic areas are most useful. They provide myocardium showing comparative stability of dysfunction yet appreciable compensatory
blood flow, so that drugs are able to reach and influence the ischemic muscle. The inadequate compensatory flow to central zones in maximal ischemia, and the lack of reproducibility and slight degrees of dysfunction shown by the border zones in critical ischemia make these less suitable for studies of the effects of experimental procedures and pharmacologic agents. Studies of the effects of levaterenol have been recently completed and will be reported in a subsequent communication.

Conclusions

Localized myocardial dysfunction consequent on acute obstruction of a coronary arterial branch in the dog has been analyzed by simultaneous determinations of polarographic oxygen, epicardial electrocardiograms and cinematographic records of muscle contraction and surface vein color.

Polarographic measurement of oxygen availability is a sensitive indicator of regional myocardial ischemia. With occlusion of a medium-sized artery there is a prompt and rapid fall of oxygen in the affected muscle. With critical narrowing of the vessel the fall is slower but the depth is comparably profound in the central, most ischemic, zone. At the borders of ischemic regions the fall is less profound. With the initial period of rapid change in polarographic oxygen there ensues a long period of relative stability.

Muscle contraction abnormality is an index of regional ischemia comparable in promptness and sensitivity to myocardial oxygen change. Late systolic bulging can be observed 6 to 9 sec. following coronary occlusion. Failure of muscle contraction increases progressively after its inception. Disturbance occurs, regardless of the size of the area.

The epicardial electrocardiogram, generally believed to be a good index of regional ischemia, is much less sensitive than polarographic oxygen. RS-T segment elevation and significant T-wave abnormality are not found until polarographic oxygen has fallen below 65 per cent of the control level and gross disturbance of contraction has begun. Significant epicardial electrocardiographic changes are generally confined to the central zones, and are consistently seen only with occlusion of medium-sized vessels. The borders usually show few surface electrocardiographic alterations or none at all. With smaller ischemic zones electrocardiographic changes on the epicardial surface may be entirely absent, despite profound falls of myocardial oxygen.

With release of coronary obstruction the return of the electrocardiogram to normal is rapid. Myocardial oxygen rapidly approaches, or temporarily exceeds, the control. The epicardial veins redden until their color resembles that of the arteries. Muscle contraction recovers quite slowly and is the last index of ischemia to become entirely normal.

Inhalation of pure oxygen during regional ischemia usually causes oxygen availability to rise in border zones. Central zones may respond when the artery of supply has been incompletely obstructed or when the ischemic area is small. Only rarely has a severely abnormal electrocardiogram been improved by oxygen and reversal of contraction abnormalities has not been observed. Oxygen does not prevent arrhythmias or ventricular fibrillation.

Study of the effects of coronary branch obstruction has led us to distinguish two stable, easily produced situations, maximal ischemia and critical ischemia. These concepts are of value in the assessment of the effects of procedures or pharmacologic agents on experimental ischemia, and have theoretical application to coronary disease in man.

Summary in Interlingua

Localsatte dysfunction myocardial, resultante del obstruction acute de un branca del arteria coronari del can, esseva analyzate per le effectuation simultanea de determinaciones de oxygeno polarographic, registrationes electrocardiographic epicardial, e cinematographias del contraction muscular e del color superficial del venas.

Le mesuration polarographic del disponibilitate de oxygeno es un indice sensibile de regional ischemia myocardial. Post occlusion de un arteria de dimensiones intermediari il
ocurre un prompte e rapido reduction de oxygeno in le musculo afficite. In caso de restriction critic del vaso, le reduction es plus lente, sed su profundor es comparabile in le zona central que es le plus ischemie. Al margione del regiones ischemic le reduction es minus profunde. Post le periodo initial de alteration rapide in le oxygeno polarographic, il seque un longe periodo de stabilitate relative.

Le contraction muscular es un indice de ischemia regional comparabile in promptitude e sensibilitate con le alteration de oxygeno myocardial. Excavation termino-systolische pote esser observate 6 a 9 secundas post le occlusion coronari. Non-occurrentia del contraction muscular deveni progressivamente plus frequente post su inception. Le disturbance occurre sin reguardo al dimension del area.

Le electrocardiogramma epicardial—generalemente considerate como un bon indice de ischemia regional—es muito minus sensibile que le oxygeno polarographic. Elevation del segmento RS-T e grados significative de anormalitate del unda T non es incontrate ante que le oxygeno polarographic ha descendite a infra 65% del nivello de controlo e ante que un grossier disturbance del contraction ha commenciate. Significative alteratioues del electrocardiogramma epicardial es restringuite normalmente al zonas central. Illos non occurre unifomemente excepte post occlusion de vasos de dimensiones interme-deiari. Usualmente le margiones exhibi pauc o nulle alterationes electrocardiographic superficial. Quando le zona ischemie es miere, alterationes electrocardiographic al superficie epicardial pote esser completamente absent in despecto de profunde reductions del oxygeno myocardial.

Quando le obstruction coronari es eliminate, le retorno del electrocardiogramma a un configuration normal es rapide. Le oxygeno myocardial approcha rapidemente le nivello de controlo o mesmo exceede lo temporarimente. Le venas epicardial rubesce usque lor color es simile a illo del arterias. Le contraction muscular se restabili satis lentemente. Illo es le ultime del indices de ischemia que rede-veni completamente normal.

Le inhalation de oxygeno pur durante ischemia regional resulta usualmente in un augmento del disponibilitate de oxygeno in le zones marginal. Zonas central responde quando le arteria de accesso es obstruite in-completamente o quando le area ischemic es miere. Casos in que sever anormalitates electrocardiographic esseva meliorate per oxygeno ha essite rar. Nulle reversion de anormalitates contractional como efecto de oxygeno ha essite observate. Oxygeno non preveni arrhythmias o fibrillation ventricular.

Le studio del effectos de un obstruction in un del brancais del arteria coronari ha duite nos a distinguire duo stabile conditiones que es facile a producer: ischemia maximal e ischemia critic. Iste conceptos es de valor in le evaluation del effectos exercite per manovras technic o per agentes pharmacologic in ischemia experimental. Illos es de appli-bilitate theoretic a morbo coronari in humanos.

REFERENCES


Polarographic Oxygen, the Epicardial Electrocardiogram and Muscle Contraction in Experimental Acute Regional Ischemia of the Left Ventricle
JOHN J. SAYEN, WARNER F. SHERDON, GEORGE PEIRCE and PETER T. KUO

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