Effects of Experimental Regional Ischemia and Levarterenol on the RS-T Segment and Baseline of Ventricular Surface Electrocardiograms Obtained by Direct-Coupled Amplification

By A. H. Katcher, M.D., G. Peirce, M.S., and J. J. Sayen, M.D.

Conventional electrocardiographic equipment (capacitance-coupled amplification) cannot distinguish between RS-T segment and baseline shifts of the ventricular complex. The so-called RS-T segment displacement is the net difference between the undetermined levels of those components. Using direct-coupled amplification, the absolute changes of baseline and RS-T segment on the surface of the exposed left ventricle during levarterenol administration and during regional ischemia and release-recovery were studied in dogs. Ten significant patterns of displacement were observed. These permitted clear differentiation of the effects of levarterenol injection and hyperperfusion from those of ischemia. The centers and borders of an ischemic area could be distinguished and the change with prolonged ischemia described. The relationship of these observations to the literature and pertinent studies of intracellular action potentials are discussed.

The clinical and experimental value of "RS-T segment" shifts for body or ventricular surface electrocardiography has been sufficiently appreciated. However, the relationship of the "RS-T segment" shifts obtained with capacitor-coupled amplifiers, in which baseline shift is compensated for within a few seconds at most, to the behavior of direct-coupled amplification systems has received little or no attention. By considering only the direction of change, and the relative magnitude of change, when baseline and RS-T segment were displaced in the same direction, records from direct current amplifiers can be ordered into 12 patterns qualitatively different from control (table 1). This permits a potential fourfold gain in precision over the three patterns of the capacitor-coupled amplifier—"RS-T segment elevation," "RS-T segment depression," and "isoelectric RS-T segment."1

It seemed important to us to study "RS-T segment" shifts such as can be produced reversibly in the exposed beating heart with minimal disturbance of general circulatory dynamics and intraventricular conduction, so as to find out where and when these 12 patterns might occur. We selected acute regional left ventricular ischemia and the effects of small doses of levarterenol as situations with which our investigative group has some familiarity and facility for comparative study of the behavior of other parameters of ventricular function.1

The purposes of this communication are to describe the circumstances under which 10 types of pattern disturbance were found and in particular the sharp distinction between the effects of levarterenol** and those of ischemia on direct-coupled amplifier records. Mention will also be made of the difficulties of explaining our results from known features of the behavior of ventricular action potentials.

*At the beginning of certain rapid potential changes, occurring within not more than 1 or 2 cardiac cycles, it can sometimes be discerned whether baseline or segment begins its shift prior to restoration of a zero baseline by a capacitance coupled amplifier. Otherwise, due to the self-centering feature of the instrument a millimeter of shift in baseline produces exactly the same effect as an equal but opposite shift of the RS-T segment. With a direct-coupled amplifier only the affected portion of the record will shift.
**Preliminary findings were presented to the Physiological Society of Philadelphia, November, 1958.
Prolonged Coronary Occlusion: Single, Continuous Sweep Record from Central, Border and Outside Areas.

The electrode was not removed from the heart while passing from position A (outside) through the ischemic area to position E (outside) and back again. There is no potential difference between baselines (level indicated by heaviest lines on record) and RS-T segments between areas A and E. The heavy lines indicated the level of the baseline of the control areas. Slight differences of T-wave and QRS configuration are present due to differences of electrode placement.

The borders of the ischemic region (just within the area of cyanosis) show slight segment elevation without baseline depression. Along the line of this sweep there are no intervening islands of RS-T segment depression between outside and border areas. The centers show both elevation of the RS-T segment and depression of the baseline. Baseline depression in the center of the area reached a maximum 55 min. after the occlusion, when it was twice the amplitude seen in this record.

Methods

The heart was exposed in a pericardial cradle in 12 dogs and prepared for coronary branch occlusion using methods previously described. Surface electrocardiograms were obtained from a chlorided silver wire electrode tipped with a cotton wick saturated with normal saline, the over-all dimensions of the heart surface contact being 5 by 10 mm. Care was taken to keep the exposed heart surface dry and free from extravasated blood. The exploring electrode was connected to 1 terminal of a small differential direct-coupled preamplifier (input impedance greater than $10^{10}$ ohms). To the other input of the preamplifier was connected the reference electrode which was a chlorided silver wire inserted into a saline bath in which the animal's left hind foot was immersed.

This high input impedance was much greater than necessary and could equally well have been obtained with any of the usual arrangements used with microelectrodes for intracellular recording.

**Since the whole body surface is essentially iso-electric compared to the large potentials being measured on the heart, the site of a remote reference electrode is unimportant. The behavior of any such reference electrode will be mainly determined by the weighted sum of all the connections between heart and body, hereinafter referred to as the heart-body contact.
Table 1

<table>
<thead>
<tr>
<th>Capacitance-coupled (AC) Amplifier:</th>
<th>DC Amplifier:</th>
<th>Circumstances of Observation</th>
</tr>
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<tbody>
<tr>
<td>RS-T segment</td>
<td>RS-T Segment</td>
<td></td>
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<tr>
<td></td>
<td>Base-line</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>— (1)</td>
<td>early ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trauma</td>
</tr>
<tr>
<td>+</td>
<td>0 (2)</td>
<td>center of ischemic areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+ (3)</td>
<td>release of prolonged occlusion</td>
</tr>
<tr>
<td></td>
<td>0 (4)</td>
<td>trauma</td>
</tr>
<tr>
<td>—</td>
<td>— (5)</td>
<td>transiently immediately after occlusion</td>
</tr>
<tr>
<td>+</td>
<td>(6)</td>
<td>about margins of ischemic areas (pink muscle)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>(7)</td>
<td>centers or borders after release of short occlusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>+ (8)</td>
<td>norepinephrine injections</td>
</tr>
<tr>
<td></td>
<td>— (9)</td>
<td>posterior surface of heart during ischemic period</td>
</tr>
<tr>
<td>—</td>
<td>&lt; + (10)</td>
<td>not observed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>+</td>
<td>+ (11)</td>
<td>release of prolonged occlusion</td>
</tr>
<tr>
<td></td>
<td>= — (12)</td>
<td>transiently immediately after occlusion</td>
</tr>
<tr>
<td></td>
<td>(0)</td>
<td>(many normals)</td>
</tr>
</tbody>
</table>

*Circumstances under which these patterns were obtained experimentally. Ten of the possible twelve patterns were observed, resulting in a greater than threefold gain in precision over the AC amplifier.

**RS-T depression may increase transiently after release.

The output of the preamplifier was fed into an Edin DC amplifier, records being obtained from a Brush ink-writing oscillograph at a sensitivity of 30 mV. for 7 mm. of pen deflection.

Repeated checks for amplifier drift were made by connecting both preamplifier inputs to the reference electrode with the exploring electrode out of circuit. However, amplifier drift proved to be negligible in comparison to electrode drift consequent on changes of local temperature and ion concentration at the exploring electrode. The immediate effect of applying the electrode previously moistened with saline (under room temperature) was a rapid negative shift of the electrocardiographic trace, followed by a slow positive drift which grew progressively slower. From previous experience we presume most of this drift was due to electrode temperature change. It required several minutes for complete disappearance of electrode drift and we did not always wait long enough. When we did, records entirely free of drift were obtained, as in figure 1. However, the effects of a small steady drift could easily be corrected, and we did not reject such records. We of course always waited until the period of rapid drift was over before beginning any control period.

Procedures
Since the levaterenol injections would necessarily affect the entire heart, one-minute control periods preceded them. The short (1 to 3 min.) periods of maximum drug action there was sometimes a very slow upward drift of the trace which did not differ significantly from the rate and direction of drift in control periods of comparable length.

For short coronary occlusion studies a small or medium-sized branch of the left anterior descending was selected. Control records were obtained from a series of positions along a line running from “outside” muscle, well beyond the apparent distribution of the artery, over muscle in the center of its distribution and out again to the starting point. The electrode was not lifted from the heart in moving from one to another of the 3 or 4 positions along the line of study. This “sweep” technique generally permitted us to obtain records entirely free of electrode drift during the control period. With occlusion of the coronary the same maneuver was repeated so as to obtain records as rapidly as possible during the first 2 or 3 min. of ischemia and the early minutes of release of short occlusions. The amount of RS-T segment...
or baseline deviation was measured by comparison with the baseline of outside muscle from the same sweep.

For more prolonged occlusions, sweep studies were made at less frequent intervals with recording at more positions. The electrode was removed from the heart between sweeps. Generally 2 lines of study positions were followed for each ischemic zone under these circumstances, each crossing the entire distribution area of the occluded coronary branch from unaffected right ventricular to lateral left ventricular muscle on either side. One line traversed the apical and one the more basal portions of the coronary branch's distribution. In addition, records were taken from a variety of points along the borders of the ischemic area and from the back of the heart, which could be exposed satisfactorily by slight traction. It was necessary to wait 15 to 30 sec. after the electrode was applied to the heart for temperature effects to subside before beginning each series of recordings, since the saline transiently displaced the electrocardiographic trace in a negative direction. As in short occlusions, baseline and RS-T segment displacement were measured by comparison with outside areas recorded on the same sweep.

Throughout this report we shall use the terms RS-T segment, the level of the most horizontal portion of the trace after the S-T junction (or the earliest definite shoulder); and baseline, the level of the trace just before the P-wave. "RS-T segment" shifts described on the basis of capacitance-coupled (AC) amplifier records will be distinguished by quotation marks or referred to as net RS-T segment shifts.

As has been previously reported, the surface electrocardiogram is an insensitive index of ischemia in comparison with falls of myocardial oxygen and abnormal muscle contraction. In these experiments the time of appearance of electrocardiographic surface abnormality was not earlier than 15 sec., which was in accord with our previous experience. Three to 5 min. after occlusion a rather sharply defined area of cyanosis developed and this was used to define the margins of the ischemic area for the more prolonged ischemic periods. For the short occlusions there was not time enough for sampling the periphery of the occluded coronary branch's distribution by electrocardiograms, and no visual clue as to the location of the periphery of ischemic disturbance was available. Our previous work would not have led us to expect early electrocardiographic changes on the heart surface except at the central, most ischemic portion of any regional ischemic area.

Polarographic oxygen and muscle contraction were not followed hence it is not known how well even the late-appearing surface cyanosis corresponded with the distinctions between central and border muscle made by Sayen et al on the basis of polarographic oxygen falls. There were no evidences of spontaneous recovery such as we had frequently found in smaller ischemic areas. All the areas studied would be considered as showing maximal ischemia at their centers by criteria previously described. In half the animals small epicardial Q-waves were recorded within 58 to 217 min. after occlusion.

Results

Control Records

Neither the baseline nor RS-T segment levels were affected by spontaneous changes of heart rate or blood pressure and were in this respect similar to AC amplifier records. Surface trauma (pressure), blood or potassium solutions produced prompt baseline depression, and a lesser degree of RS-T segment elevation, both of which were slow to disappear. We did not study these situations and rejected records to which they obviously contributed. The control periods prior to levarterenol injections were always at least 1 min. long and were free of measurable drift.

Injections of Levarterenol

The effects of small intravenous doses (0.25 to 1.0 µg./Kg.) were studied in 5 dogs. Nine of 13 injections showed RS-T segment change within 17 to 30 sec. In all these RS-T segment depression occurred without baseline displacement (fig. 2). The changes in the electrocardiogram and rhythm with these injections were similar to those reported by Sayen et al. with capacitance-coupled amplification. In 2 of the 4 injections in which there was no RS-T segment change the exploring electrode was over the septum or right ventricle (two dogs); while the other 2 injections were given to an animal who showed only a slight RS-T...
ECG AFTER ISCHEMIA AND LEVARTERENOL

Direct Current Amplifier Record of the Effects of Intravenous Levarterenol on the Epicardial Electrocardiogram of a Nonischemic Heart.

There is no drift of baseline throughout the record. RS-T segment depression begins about 10 sec. and is followed closely by diminished T-wave negativity and then reversal. Electrocardiographic effects have begun before the slowing of heart rate.

Ischemia

Early Effects

Fifteen short occlusions (47 sec. to 7 min. duration) were studied in 6 dogs. Study was confined to the center of the ischemic area and a point well outside the apparent distribution of the occluded branch. In 14 out of the 15 the first change was depression of the baseline. The onset time ranged from 10 to 35 sec. (mean 24). In one 47-second occlusion only RS-T elevation was recorded.

RS-T segment change not only began later than baseline depression but was rather variable in its behavior for the duration of these shorter occlusions. Elevation was seen in 11 out of 15 occlusions, its onset being between 28 and 200 sec. (mean 98), and its amplitude always lower than that of the baseline depression. RS-T segment depression was seen in 5 occlusions and 3 dogs (fig. 3). In 3 occlusions it persisted to the end of the ischemic period. In none was it earlier or of greater magnitude than the baseline depression hence RS-T segment depression would not have been recorded by an alternating current amplifier. The data are graphed in figure 4.

Release of Short Occlusions

Following release, in the 9 ischemic episodes so studied, the baseline returned to the isoelectric level in from 6 to 100 sec. (mean 36). After 6 of these releases the RS-T segment returned to the isoelectric level at the same time as the baseline, while in 2 others the elevation persisted for several minutes after release. In 4 releases the baseline, after returning to the isoelectric level, rose 1 to 2 mm. above it, and remained there for 20 to 30 sec. In 2 instances there was transient RS-T segment depression (fig. 3).

More Prolonged Ischemia

Central Areas

Ischemic periods varying from 65 min. to 5 hours and 25 min. duration were studied in 8 animals. The data are graphed in figure 5. As in the short occlusions the initial baseline depression was always greater than the RS-T segment elevation. The depression reached its maximum 10 to 60 min. after oc-
Short Coronary Occlusion and Release.

The illustrated complexes are from the center of the ischemic area. Only the probable center of the ischemic area has been indicated on the map, as early in the ischemic period there was no zone of cyanosis present to define the borders. The heavy line at the left margin of the strips of record are at the level of the baseline of the outside area measured on the same sweeps (the long strip has lines on its right and left margin). Twenty seconds after occlusion both the baseline and RS-T segment are depressed. The baseline depression occurs earlier and is of greater magnitude than the RS-T segment depression (net effect is "SR-T segment elevation"). The RS-T segment is still depressed just before release at 125 sec. Following release there is a rapid return of the baseline and RS-T segment to the isoelectric level. At 19 and 66.5 sec, the baseline is slightly elevated. The RS-T segment is depressed again at 19 sec. and from 19 to 93 sec, after release there is slight net RS-T segment depression.

Figure 3

The elevation of the segment was less regular in distribution and time course than the baseline depression. In 1 animal there was no significant RS-T segment elevation during a two-hour occlusion. In 2 other animals RS-T segment elevation was absent at the time of maximum baseline displacement (fig. 6). In the remaining animals the RS-T segment level either rose slowly and inconstantly throughout the ischemic period or reached a maxi-
ECG AFTER ISCHEMIA AND LEVARTERENOL

mum and then declined but slightly. There was no tendency to wax and then wane such as was observed for the baseline displacement.

**Border Areas**

RS-T segment elevation was confined to the area of visible cyanosis. The baseline depression, which was of greatest amplitude at the center, decreased as the borders of the cyanotic zone were approached. The ratio of RS-T segment elevation to baseline depression was greater at the borders (fig. 1). The variation in depth of baseline depression was not entirely symmetrical, some borders showing as much baseline depression as the centers. There was much less variation in RS-T segment elevation between borders and centers, hence the difference in appearance between center and periphery of the cyanotic area tended to diminish as the baseline approached the isoelectric level.

**RS-T Segment Depression**

This was seen in 2 dogs within 10 min. of occlusion (the earliest time at which we systematically explored the periphery of the ischemic areas) and in 4 others somewhat later. It was observed only outside the area of cyanosis. It occurred in small islands which did not form an unbroken perimeter. These could be found near the basal, lateral or septal borders of the ischemic areas. They were not constant in position from animal to animal, nor did every island persist for the remainder of the ischemic period. In 3 of these 6 animals the islands of RS-T segment depression were found immediately posterior to the vortex (anterior apex) of the left ventricle, extending for varying distances on the posterior surface of the heart but never to the base (fig. 7). When the islands were large enough to determine this, it was found that the amplitude of the RS-T segment displacement was greatest immediately adjacent to the ischemic area and decreased with increasing distance from it. The RS-T segment depression was frequently but not always accompanied by baseline elevation. In 1 animal baseline elevation with an undisplaced RS-T segment was observed over a portion of the posterior surface of the left ventricle.

**Release of Prolonged Occlusions**

In 2 of the 3 released occlusions the artery did not open at once. Flushing of the area occurred suddenly after another 30 to 35 min. Following release there was an increase in amount of RS-T segment depression at the borders and a positive displacement of the baseline (above the control level) in the center of the area. This was accompanied by a slow decline of RS-T segment elevation. In the 2 animals that survived release more than 10 min. baseline and segment elevation at the center of the area persisted for the remaining 1 to 2 hours of the experiment (fig. 6).

**Discussion**

The diagnostic value of diastolic potential differences for the recognition of myocardial injury or physiological disturbance was first

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*Figure 4*

Short Coronary Occlusions: RS-T Segment Deviations and Baseline Depression in Direct-Coupled Amplifier Electrocardiograms from the Centers of the Ischemic Areas.

Data from 15 occlusions in 6 dogs are plotted. The symbols distinguish individual animals but not individual occlusions. Standardization of the electrocardiograph 7 mms. = 50 mvs. Measurements are based on differences from the segment and baseline of records of muscle outside the distribution of the occluded vessel. Occlusion of the coronary branch is at zero time.

The earlier and consistent negativity of baseline deviation contrasts with the delayed and varied response of the RS-T segment.
pointed out 80 years ago by Burdon-Sanderson and Page. Their elegant studies of the exposed frog ventricle showed that uninjured muscle in diastole was isopotential whereas injured areas promptly became negative to uninjured areas. The effects of progressively warming a normal area or applying hypertonic salt solution could become indistinguishable from those of injury. They also observed, though they did not try to explain it, a shortening of the "total duration of the period of variation" following injury or warming. During systole a rapid change of potential was followed by an isoelectric interval and then by a slower change in the opposite direction. Injury abolished the isoelectric interval, the abnormal area becoming less negative during excitation and consequently being relatively positive to the uninjured area. These results were obtained with the slowly reacting capillary electrometer and rheotome. In 1892 Bayliss and Starling working with the exposed dog heart confirmed Burdon-Sanderson and Page's work insofar as the more rapid mammalian heart rate and the necessity of studying the heart with the circulation intact permitted them to do so.

When the string galvanometer came into increasingly wide usage (after 1903) it was scarcely ever used as a type of DC instrument, despite its theoretical suitability for following steady potential differences. Deviations of the baseline of records whether obviously artifactual or relatable to "currents of injury" were compensated as necessary to center the string and not compared with control records. When interest in the isoelectric period of the ventricular complex was revived by studies of myocardial infarction clinically and experimentally, only net RS-T segment levels were reported. It was of course well known that at least part of the RS-T segment elevation associated with trauma or ischemia was due to compensation of a primary baseline shift. Wilson et al. at first suggested that there was no systolic flow of current in association with injury; subsequently it was suggested that incomplete depolarization might cause systolic positivity of the exploring electrode in unipolar leads following coronary occlusion. However, the baseline shifts in the latter report were compensated and no systematic comparison of their deviations with control records seems to have been attempted.

Eyster and Meek in 1938 used direct-coupled amplifiers to study the effects of injury (crushing, heat or suction electrodes) in turtle hearts and the effects of suction electrodes in dog hearts. They found, as had Burdon-Sanderson and Page, that injured areas became negative to uninjured areas in diastole but positive, sometimes to a greater but usually to a lesser degree, in systole; both changes developing at about the same rate. They did not study ischemia. Their work was confirmed by Sugarman et al. the following year. Bayley's string galvanometer records of coronary occlusion demonstrated negative base-
line and positive RS-T segment shifts during the first few minutes of ischemia and recovery. He makes no comments about the exact sequence of events.

The 1957 report of Alzamora-Castro and associates opened the study of injury and ischemia with direct current amplification. Injury was produced by injection of concentrated solutions of KCl, or cocaine into a coronary artery or by tying a large coronary artery. They found depressed baselines with KCl, and high amplitude segment elevation without baseline change following cocaine. Following coronary ligation they illustrated a sequence of changes similar to our observations, that is, baseline depression followed by elevation of the RS-T segment. No waning of the baseline depression was reported, but it is perhaps not to be expected with large areas. On sweeping from the center to the side of an established ischemic area the same transition from RS-T segment elevation with baseline depression to RS-T segment elevation alone was noted.

The only subsequent study of segment and baseline shift is that of Samson and Scher who, unlike Alzamora-Castro, observed an upward RS-T segment shift and a smaller degree of negative T-Q interval shift within 60 sec. after experimental large coronary artery occlusion in dogs. The main interest of the investigators was correlation of their results with simultaneous cellular action and membrane potential data (see below). So far as we know, no one has attempted to make practical use of the theoretical advantages of direct-coupled amplifier records for describing the time course, and distribution of the disturbances consequent on simple coronary occlusion.

RS-T segment depression patterns associated with localized ischemia have not been previously investigated by this method. With capacitance-coupled amplifiers 2 types of "RS-T segment depression" are generally recognized. "Reciprocal" displacement is commonly found over presumably normal muscle remote from a large ischemic area.
Figure 7

Prolonged Coronary Occlusions: Two Continuous Sweeps.

Symbolism is the same as for figure 1 except that the full extent of the basal-apical-basal (no. 1) sweep cannot be shown on the map. In this sweep there is no RS-T segment or baseline displacement at the base posteriorly. On the posterior left ventricular surface there is baseline elevation with no RS-T segment depression. About the apex there is both segment depression and baseline elevation. At the apex (beginning of the zone of cyanosis) there is a rapid transition from depressed to isoelectric, to elevated segment as the electrode advances across the ischemic area.

On the second sweep the electrode was first moved from the lateral wall of the left ventricle parallel to the sweep shown in figure 1, but slightly nearer the base. It again fails to pass through an area of RS-T segment depression (cf. fig. 1). As the electrode moves along an apical-basal line parallel to that of sweep no. 1 there is a sudden transition from RS-T segment elevation to depression. On the posterior surface of the apex near the vortex the RS-T segment depression reaches its greatest amplitude. It rapidly declines as the posterior left ventricle is traversed and there is no depression at the base. In this sweep there is no baseline elevation in the areas sampled.

As compared with figure 2 it can be seen that in the intervening 121 min. there has been a decrease in baseline depression at the center and borders and RS-T segment elevation has increased at the center of the ischemic area. A Q-wave is now present (at D). A Q-wave may also be noted at the apex outside of the zone of cyanosis and at a location where there is segment depression. The relationship of the distribution of the Q-wave to the ischemic area has not been defined by these experiments.

Baseline depression was frequently unaccompanied by baseline elevation. It was observed in small irregular islands of muscle contiguous to the ischemic area. Where negative RS-T segment displacement was distributed over the posterior surface of the heart its greatest amplitude was observed immediately next to the ischemic area, and the base of the heart was never involved. The RS-T depression increased with release of a prolonged occlusion in one animal while RS-T elevation was disappearing at the center of the ischemic area. Furthermore RS-T depression could occur without baseline elevation and in 1 dog there was an area of baseline elevation without RS-T segment depression.
That "reciprocal RS-T segment displacement" was not found in association with regional ischemia is perhaps not surprising. The exact nature of the heart-body contact in an open-chest preparation such as we have used is unknown. Because of the high conductivity of the blood the cavity potentials are presumably major contributors to the heart-body contact. However in our preparations 50% procaine applied to the posterior surface of the left ventricle produced the expected28 RS-T segment elevation locally but reciprocal RS-T segment depression over the entire anterior surface. Whenever we placed a sheet of insulating material between the ventricles and the pericardial cradle the RS-T segment depression vanished. Thus in the open chest preparation the posterior surface of the ventricles also contributes to the heart-body contact. The extent of endocardial pattern change beneath a small or medium-sized ischemic area is also unknown, but it seems likely that the more extensive the ischemic area the greater the extent of "RS-T segment elevation" on the endocardial surface would tend to be.* Presumably the regional ischemic areas studied here are not extensive enough to affect significantly the heart-body contact (via their cavity potential changes). In a closed-chest preparation, with the epicardial surface contributing more to the heart-body contact, relatively much smaller ischemic areas might be expected to produce "reciprocal" effects. Of course where we are concerned only with the difference between 2 patterns, 1 inside and 1 outside the area of physiological disturbance, the nature of the reference electrode is irrelevant.

The immediate electrocardiographic effects of levarterenol in areas we studied (prin-

cipally the anterior surface of the ventricles) were RS-T segment depression without change in baseline. The finding of any pattern change with extracellular electrode (other than a change of timing) when a drug is being supplied to the whole heart, necessitates the assumption that not all of the heart is equally affected. Thus for an exploring electrode on the heart surface to show RS-T depression, a smaller, zero or opposite change must be occurring in at least some of the muscle that contributes to the heart-body contact.

Depression of the RS-T segment alone without baseline depression either in the same area or elsewhere on the heart has not been seen in any of our regional ischemia situations. When this observation is considered together with the reported effects of levarterenol in raising polarographic muscle oxygen and coronary sinus oxygen saturation, and in improving ventricular contraction, reasonable doubt can be cast on any association of levarterenol injections with ischemia. Release of an occlusion, which could result in appearance of RS-T segment depression in the centers and increase of existing segment depression outside of the ischemic area, has likewise been reported as being associated with high polarographic muscle oxygen and increased venous oxygen saturation values. Oxygen tension has not been measured in the islands of segment depression that surround an ischemic area,* and it is possible that subendocardial ischemia may underlie this pink muscle. However, it is also possible that the behavior of these islands may be consequent on hyperperfusion due to channels of collateral circulation.

On the basis of our findings, the RS-T segment depression caused by levarterenol or release of occlusion is not associated with evidence of ischemia, and there is reason to doubt that the islands of RS-T segment depression found peripheral to regional ischemic areas are due to diminished circulation. Conse-

*Prinzmetal et al.7 reported low oxygen tension and increased intracellular potassium in islands of "segment depression" produced by severe hypotension. They did not study ischemic situations comparable to ours or describe their amplifier.
quently we may say that RS-T segment depression, if associated with an isoelectric or elevated baseline, cannot be identified with an ischemic process in the area showing such a pattern.

Two possible patterns of RS-T segment depression were not observed, but we suspect that they might well be recorded even in situations similar to the ones we have studied. RS-T segment depression greater than accompanying baseline depression (pattern 9) is probably the direct-coupled amplifier equivalent of some of the "negative RS-T segment displacements" which have been observed immediately after the occlusion of an artery. Baseline elevation greater than segment elevation (pattern 10) could probably be produced by the superimposition of levarterenol effect on the release of an occlusion.

It has been proposed, at a time when there was no independent measure of membrane or action potential in the heart, that changes in the baseline of heart surface electrocardiograms might be related to changes in diastolic membrane potential, and changes in the RS-T segment with systolic events, such as failure to depolarize or incomplete depolarization. With this theory it was possible to classify any change in the slow components of the extracellular electrocardiogram as a consequence of varying intensities of disturbance in repolarization or depolarization, though of course no predictive power was provided. Now that at least a small body of cellular action potential data is available for anoxic and ischemic situations it is desirable to examine this for possible correlation with the material we have just presented. The work of 3 groups of investigators is pertinent.

With anoxic perfusion of cat papillary muscle strips Trautwein and Dudel found almost immediate shortening of the action potential, reduction of its amplitude (overshoot abolished) in about 10 min., but reduction of the resting potential only after an hour. Failure of depolarization occurred when the membrane potential fell to less than 2/3 of the control Purkinje tissue was more resistant to anoxia. Intact beating perfused dog hearts made "totally ischemic" by Kardesch et al. showed reduced duration and amplitude of the cellular action potential within 6 min. but the resting potential had fallen only 18 per cent. Conduction failed in 15 to 26 min. when the resting potential had fallen to 65 per cent of control values. Neither of the aforementioned situations are closely analogous to localized ischemia. However, in the large ischemic areas produced recently in dogs by Samson and Scher, intracellular electrograms showed rather rapid resting potential reduction. This began within 2 min. of coronary occlusion, being preceded by decreases of action potential duration and amplitude. Consistent findings for all 3 groups were early action potential changes and more delayed membrane potential changes which invariably tended to progress. The latter authors suggest that their epicardial electrophysiologic changes are accounted for by the behavior of the cellular action potentials they obtained: RS-T segment elevation (which in their experiments was greater, prompter and more consistent), reflecting faster repolarization in the ischemic area and the T-Q depression being due to reduction of resting potential.

Consideration of our data, however, makes any simple correlation of T-Q interval with membrane potential and the RS-T segment with action potential level and duration give rise to many contradictions. If the change in baseline is to be identified with change in resting potential, the findings would have to be interpreted as indicating that alteration in resting potential is the first change consequent on ischemia; that it is of greater magnitude than the change in action potential for the first hour or two after occlusion, and that it steadily returns toward normal with persisting ischemia. Indeed this return of the baseline potential to the isoelectric level was demonstrated even in the center of areas which later proceeded to transmural infarction. It can hardly be attributed to muscle cell death, since release of the occlusion after 2 to 3 hours was followed by disappearance of systolic bulging in our animals and has...
been reported to be compatible with almost complete survival of the muscle when care is taken to prevent vascular thrombi. Furthermore, RS-T segment elevation, which we have as a late and inconsistent manifestation of the first minutes of ischemia would have to be in like manner identified with the most labile portion of the action potential.

Failure to depolarize (conduction block) has been offered as an alternative explanation for segment elevation. However, where action potentials have been measured, failure to conduct an impulse occurs only after profound lowering of the membrane potential. If there is any correlation between cellular action potentials and potentials measured on the surface of the heart it is hard to see why a hypothetical ischemic conduction block would progress at a time when the baseline is returning toward the isoelectric level.

There has been no attempt to relate primary RS-T segment depression to action potential phenomena. Pertinent intracellular ventricular action potential studies of catechol amine effects have so far been reported only for isolated sheep Purkinje. At least with the mixture Adrenalin and with dosage large enough to increase the rate, a striking hyperpolarization occurs together with some shortening of repolarization. However, increases of rate shorten guinea pig ventricular action potentials and increases of perfusion pressure decrease amplitude, presumably by inducing changes in the ionic environment of the muscle fibers. Ventricular action potentials of open chest dogs likewise shorten with increases of rate. Furthermore, even were a shortening of action potential duration demonstrated for large doses of levarterenol the response to small doses by the more physiological muscle preparations might well be a prolongation such as has been the case for strophanthin, for digitalis, and for 0.5 normal potassium solutions.

We do not believe it possible at present to correlate our observations of RS-T segment and baseline change during ischemia or levarterenol action with any available theoretical construct or body of data relating to the cellular action potential. Information on intracellular and extracellular conductivity, and ion concentrations and gradients within the ischemic area are lacking, and even the data on action potentials themselves are limited in number and represent a small sampling of only superficial cells.

**Summary**

The effect of levarterenol injections and of left anterior descending coronary branch occlusion on the RS-T segment and baseline of the surface electrocardiogram was studied in dogs with direct-coupled amplification and precautions to minimize and recognize amplifier and electrode drift. It was therefore possible to distinguish between RS-T segment and baseline shifts—a distinction impossible with the usual electrocardiographic equipment.

The initial effect of levarterenol was RS-T segment depression only. The first change following occlusion of a coronary artery was baseline depression. This was maximal within 10 to 60 min. but diminished rapidly and reached the isoelectric line as early as 2 hours after occlusion.

RS-T segment elevation was an inconstant finding early in ischemia but tended to increase throughout the ischemic period. The borders of the ischemic area showed a higher proportion of RS-T segment elevation to baseline depression than the centers. RS-T segment depression with and without baseline elevation was distributed in irregular islands beyond the cyanotic borders of the ischemic areas. It was never present over the entire posterior surface of the ventricles nor was it found at the base.

Following release of short occlusions tran-
sient elevation of the baseline and depression of the RS-T segment regularly occurred at the centers of the ischemic areas.

The occurrence of RS-T segment depression without depression of baseline differentiated levarterenol injection effects from ischemic situations. RS-T segment depression with an isoelectric or elevated baseline has not been observed over demonstrably ischemic muscle or found to be 'reciprocal' to segment elevation elsewhere on the heart surface. Its association with release and levarterenol injection suggest that it may be related to a relative hyperperfusion rather than ischemia.

The increased number of abnormal patterns obtained with a direct current amplifier permits more adequate description of the time course and distribution of ischemic areas than a capacitance-coupled amplifier. The observed combinations and changes of RS-T segment and baseline deviation permit no simple correlation with such cellular action potential data as are available.

**Summario in Interlingua**

Le effecto de iniecciones de levarterenol e de occlusion del branco sinistro-anterior del descendent arteria coronari super le segmento RS-T e le linea de base del electrocardiogramma derivate ab le superficie ventricular esseva studiate in canes con le uso de amplificator per acopulamiento directe e precauciones visante a reducere e a render recogonoscibile le tendentia deviatori del amplificator e del electrode. Asi il esseva possibile distinguere inter le dislocamento del segmento RS-T e le dislocamento del linea de base—an distinction que es imposibile con le uso del usual equipamento electrocardiographic.

Le effecto initial de levarterenol esseva solmente un depression del segmento RS-T. Le prime alteration occurrente post occlusion de un arteria coronari esseva un depression del linea de base. Le magnitude de ist depression esseva maximal intra 10 a 60 minutas, sed postea ilo diminuvere rapidemente e attingeva le linea isoelectric in certe casos intra 2 horas post le occlusion.

Le elevation del segmento RS-T esseva un constatation inconstante durante le prime phases del ischemia sed tendeva a devenir plus marcate in le curso del periodo ischemico. Le margines del area de ischemia monstrava un plus alte proportion inter elevation del segmento RS-T e depression del linea de base que le centros. Depression del segmento RS-T con e sin elevation del linea de base se trovava distribuite in insulas irregular in ultra del margines cyanotic del areas de ischemia. Illo esseva nunquam presente al integre superficie posterior del ventriculos. Similemente illo non esseva incontrate al base.

Post le relaxation de un occlusion de breve duration, un traniente elevation del linea de base con depression del segmento RS-T occorreva regularmente al centro del areas de ischemia.

Le occurrentia de un depression del segmento RS-T sin depression del linea de base differenziava le effectos del injection de levarterenol ab le situation ischemic. Depression del segmento RS-T con linea de base isoelectric o elevate non esseva observate sur demonstrabilemente ischemic musculo, e quando ilo esseva presente, nulle 'reciprocitate' esseva notate con elevation del segmento RS-T in altre portions del superficie cardine. Su association con relaxacion de occlusion e con iniecciones de levarterenol suggere que ilo es possibilemente relacionate con hyperperfusion relative plus tasto que con ischemia.

Le augmentate numero de configurationes anormal que es obtenite per medio de un amplificator a currente directe permette un plus adequate description del curso temporal e del distribution de areas ischemic que un amplificator de acopulamiento a condensator. Le observe combinationes e alterationes de deviationes del segmento RS-T e del linea de base non permette un simple correlation con le currentemente disponibile datos sur potentialis de action cellular.

**References**


ECG AFTER ISCHEMIA AND LEVARTERENOL


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Effects of Experimental Regional Ischemia and Levarterenol on the RS-T Segment and Baseline of Ventricular Surface Electrocardiograms Obtained by Direct-Coupled Amplification

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An erratum has been published regarding this article. Please see the attached page for: