The Effect of Levarterenol on Polarographic Myocardial Oxygen, the Epicardial Electrocardiogram and Contraction in Nonischemic Dog Hearts and Experimental Acute Regional Ischemia

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In open-chest dogs it was found that levarterenol produced primary ST segment depression in epicardial surface electrocardiograms together with increases of ventricular muscle contractility. These effects occurred in nonischemic, regionally ischemic, and hypoxic myocardium and were accompanied by rises of polarographic myocardial oxygen and a reddening of coronary venous blood in all but the lowest dosages. The findings are discussed in the light of the pertinent experimental literature.

In previous studies it was reported that stable values for polarographic myocardial oxygen could be obtained in nonischemic ventricular myocardium and were regularly increased by the administration of large doses of epinephrine—an effect that appeared to be independent of and additive to rises produced by oxygen inhalation. Pilot experiments showed that levarterenol in small doses produced favorable changes in regional ischemic areas.

Certain indices of myocardial function found necessary for following the behavior of nonischemic and ischemic left ventricular muscle have since been correlated. The rate of myocardial oxygen change was found to be a more sensitive and rapid index of early regional ischemia than the epicardial electrocardiogram. Visible muscle contraction disturbance was found to be a comparably delicate index of early ischemia. Artialization of regional veins, which invariably follows release of coronary obstruction, provided an index of reactive hyperemia. The phenomena of acute coronary narrowing episodes in dogs and the sequence of events following coronary occlusion and release have been described in terms of these parameters; the influence of 100 per cent oxygen inhalation on nonischemic and regionally ischemic myocardium has been reported.

The present communication deals with the effects of levarterenol administration to dogs under nonischemic conditions and during regional ischemia as well as the interrelationships of the findings to the pertinent literature.

Methods

Twenty-eight dogs weighing 15 to 20 Kg. were prepared for open-chest study by techniques previously described. The heart was exposed for the placement of an array of 8 to 10 oxygen electrodes and for recording epicardial electrocardiograms. Small or medium-sized ischemic areas were produced by acute coronary occlusion or critical coronary narrowing in 14 of the animals. Blood pressures were recorded with a damped mercury manometer. Anticoagulants were not administered. The anesthesia was morphine (3 mg./Kg., intramuscularly) followed in 45 min. by slow intravenous injection of 0.25 ml./Kg. of a mixture containing equal parts of pentobarbital sodium (60 mg./ml.) and Dial-Crethane (Ciba). Occasionally a small supplementary subcutaneous injection of morphine was required (one half or less of the initial dose) to abolish hypertension and excessive tachycardia. In a number of animals...
oxygen inhalation was instituted during the ischemic period before, after or concurrently with the administration of levarterenol (technic previously described1-6).

Electrocardiographic Technic

A Cambridge direct-writing electrocardiograph was used for most experiments. The exploring electrode was a saline-soaked cotton pledget and the reference electrode the right foreleg or left hindleg. A direct current amplifier driving a Brush ink-writing oscillograph was used for checking the results. In the latter circumstance a chlorided AgCl wire covered with saline-soaked cotton was used for the exploring electrode. No attempt was made to abolish the T-wave inversion characteristic of exposed dog hearts. RS-T segment elevations could be minimized or abolished by keeping the epicardial electrode free of blood and by avoiding even slight trauma to the epicardial surface. However, the responses to both ischemia and levarterenol were not influenced by small RS-T segment elevations in control records.

Polarographic Technic

The depth of oxygen electrode insertion was 2 to 3 mm. beneath the epicardium in the first 12 animals. Thereafter we began using lighter oxygen electrodes provided with depth stops which permitted insertion to depths (fixed for each electrode) from 2.5 to 8 mm. The currents of oxygen reduction were measured either by semicontinuous readings of a sensitive galvanometer (Rubison no. 3418) placed in series with each electrode; by rapid sequential readings, every 15 to 30 sec, from the continuously polarized electrode array; or, in the case of a few of the injections in nonischemic hearts, by summatting the oxygen reduction currents from a small group of electrodes and following the sum semicontinuously.

For the sequential readings we selected electrodes which gave control currents of moderate amplitude (50 to 150 X 10^-10 amps.). All electrode arrays selected for sequential readings included 1 or 2 electrodes in the central portion of the ischemic area, 1 electrode as far as possible outside the area, and 1 or 2 electrodes at its borders. We did not follow electrodes which had given low readings (about 1/3 of those originally inserted), nor those which failed to show at least a 25 per cent rise during a preliminary test of pure oxygen inhalation (approximately 1 electrode in 10). The responses to pure oxygen inhalation of the electrodes in animals no. 133 through 140 have been illustrated previously.6

Cinematographic Technic

The method for making cinematographic records has been described previously.4,6 Briefly, Kodachrome records were made at 32 frames/sec. Heat resistant glass protected the heart from damage by the lighting, and a simultaneously photographed electrocardiogram coordinated electrical and mechanical events. The markers attached to the oxygen electrodes provided an array of points whose motions could be studied by simple inspection or by plotting the changing distances between pairs of points from the projected motion picture frames. As in the previous report,6 we will describe here only changes readily visible in projected film. The results of the muscle contraction analysis by plotted curves are reported elsewhere.5,10

Regional Ischemia Production

Coronary obstruction was produced by a screw clamp as previously described.6 Occlusion or narrowing of small or medium-sized branches of the left anterior descending coronary ramus produced ischemic areas whose limited extent permitted study of ischemic, border, and normal muscle with camera, oxygen electrodes and surface electrocardiogram. The size of the ischemic area could be estimated from the extent of the muscle contraction abnormality, the changes in myocardial oxygen, and, for longer occlusions (over 5 min.), the area of visible cyanosis. At electrodes outside the ischemic area there was either no change or a slight rise; at electrodes in the borders, shallow falls; and at electrodes in the center, falls exceeding 75 per cent of control values. Although with coronary occlusions of limited duration there was good correspondence between muscle contraction abnormality, cyanosis and oxygen falls in delineation of an ischemic area, it was not possible to use surface electrocardiographic abnormalities for this. With brief occlusion of a small branch there was usually no electrocardiographic change. When electrocardiographic abnormalities did develop they were frequently limited to the central areas where deep falls of myocardial oxygen occurred and were absent over the border areas where there were shallow falls in oxygen. Because of the lack of sensitivity to ischemia of the surface electrocardiogram the ischemic area had to be defined in extent (central, border, and outside) primarily by changes in myocardial oxygen and secondarily by the muscle
contraction abnormality and cyanosis when present. But while the surface electrocardiogram did not provide a good spatial localization of the ischemic area it continued to change after the myocardial oxygen had reached a stable level and the contraction abnormality had ceased to progress. With occlusions of longer than about 5 min. duration, the extent of the electrocardiographic abnormality tended more nearly to approximate that of the ischemic area.

Criteria for Severity of Ischemia

Previous studies of localized ischemia suggested a classification or grading of ischemia based on the rapidity of oxygen fall and the response to the inhalation of 100 per cent oxygen. Narrowing of a medium sized artery or occlusion of a small branch produced critical ischemia, while occlusion of a medium sized branch produced maximal ischemia at the center of the vessel's distributional area. Occlusion of larger coronary branches was likely to alter heart rate, lower systemic blood pressure and produce a complex situation. The essential requirement for regional ischemia, fulfilled by all the ischemic situations reported here, is that systemic blood pressure be unaffected by the ischemic episode. Except for extrasystoles, which were common with maximal ischemia, heart rate was likewise unaffected. Critical and maximal ischemia situations provide long stable periods of regional myocardial dysfunction. The behavior of such areas has been described in detail previously.

Experimental Procedures

In 8 pilot animals (nos. 10, 11, 17, 19, 51, 57, and 68), large doses of intravenous levarterenol or Adrenalin were administered (4 to 50 µg./Kg.). In dogs no. 57 and 58, coronary sinus blood specimens were collected by catheter in collaboration with Drs. Elwood Foltz and William West of the Department of Pharmacology.

In 5 animals (nos. 63, 64, 65, 66 and 67) critical coronary narrowing was produced and rotational readings obtained from an array of oxygen electrodes of the older, heavier type. In 7 animals (133 to 135 and 137 to 140) color motion pictures were obtained during the action of levarterenol (or epinephrine) under ischemic and nonischemic conditions. The rate of myocardial oxygen change was followed by a combination of semicontinuous and rapid rotational readings from the electrode arrays. The responses to ischemia and oxygen inhalation of these animals have been previously described. In 2 of the animals intracoronary injections were studied either by catheterization of the left coronary artery (no. 139) or by an indwelling no. 26 gage needle (dog no. 140).

In 8 animals (nos. 147 to 154) the effects of intravenous injection of levarterenol and other catechol amines on blood pressure and precordial electrocardiograms were studied. Subsequently direct electrocardiograms were obtained from the heart surface using a direct current amplifier.

Results

Sinus arrhythmia was common in these animals especially in the early hours of each experiment. Some animals showed phasic variations of blood pressure unrelated to respiration or any other factors we could identify (Traube-Hering waves). Sometimes these occurred without change in heart rate. Spontaneous variations of heart rate and blood pressure were not reflected by any electrocardiographic changes.

Rises of blood pressure or slowing of the heart rate slightly decreased myocardial oxygen. Falls of blood pressure or increases of heart rate slightly decreased myocardial oxygen. However, the greatest magnitude of oxygen change from either of these causes did not exceed 25 per cent of the mean. These phasic oxygen changes varied in amplitude but were consistent for any particular electrode insertion. They could readily be identified when electrodes were read semicontinuously, but could be confusing when arrays of electrodes were read sequentially.

In most hearts, especially with rates exceeding 100/min., an area of systolic expansion could normally be seen proximal to the left ventricular apex. In numerous areas of most hearts, portions of the muscle contracted comparatively late, continuing to shorten well into the diastolic period.

Ischemic control periods were provided after coronary occlusion or critical narrowing by waiting until the fall in myocardial oxygen had given way to a steady low level and muscle contraction abnormality was fully developed.

*With the collaboration of Drs. William B. West and Santiago Guzman, Department of Pharmacology.
Figure 1
Effects of levarterenol on the epicardial electrocardiogram and polarographic myocardial oxygen.

A. Small Dose. The first electrocardiographic change is a depression of the RS-T segment at about 15 sec., just after the extrasystole. T-wave change begins at about 25 sec. The only QRS complex change is a slight deepening of the S-wave.

B. Moderate Dose. The first electrocardiographic change (RS-T segment depression) is measurable at about 17 sec., just before the slowing of rate, which is preceded by a transient sinus tachycardia. Nodal extrasystoles and tachycardia are followed by runs of ventricular extrasystoles and multifocal tachycardia during the second half-minute following injection. During the second and third minutes levarterenol effects are still seen in the normal complexes, but a return toward the control pattern has begun.

Myocardial oxygen percentages are selected from the complete series of semi-continuous readings, plotted in Figure 2. Paper speed of all electrocardiograms in these figures: 25 mm./sec.
Nonischemic Hearts

Following an intravenous injection of levarterenol (0.5 to 1.0 μg./Kg. or more) negative RS-T segment displacement occurred in epicardial leads within 15 to 35 sec., and after reaching a maximum within less than one minute, disappeared slowly during the next few minutes (fig. 1A). Diminution of T-wave amplitude was measurable 5 to 12 sec. after the first RS-T segment change. In the next few seconds the direction of the T-wave changed rapidly from negative to less negative or diphasic or positive, with increasing dosage. When limb leads showed RS-T segment changes due to levarterenol these were best seen in lead II or III but often they were absent or inconspicuous. However, precordial leads displayed the changes satisfactorily. In DC amplifier epicardial records the earliest electrocardiographic effect of levarterenol was RS-T depression, rather than a shift in baseline. Maximal RS-T depression was found after the compensatory pauses that followed ventricular extrasystoles.

Within 15 to 30 sec. of the intravenous administration of levarterenol and within a few seconds after the first electrocardiographic change it could be seen that the left ventricular surface was contracting earlier and more rapidly. Its muscle contraction amplitude had become greater and more of the ventricular surface showed obvious contraction. The visibly expanding areas in the vicinity of the apex tended to shorten in systole, so that there was greater synchronism of ventricular contraction. When slowing of the heart rate occurred, the diastolic length increased but the systolic length remained as short as, or shorter than the control.

Intravenous levarterenol increased polarographic myocardial oxygen at 4/5 of electrode insertion sites when the dosage was 0.5 to 1.0 μg./Kg. and at all sites when doses larger than 2.0 μg./Kg. were administered.

Regional Ischemia

Critical Ischemia

Injections of small amounts of levarterenol produced effects on the RS-T segment of regionally ischemic muscle closely resembling those described for nonischemic hearts (fig. 4). When the electrocardiogram was unchanged during ischemia the response to levarterenol resembled nonischemic situations. When the pattern had been made abnormal by the ischemia, the result of lowering the elevated RS-T segment was to return the pattern in AC amplifier records toward or to that of the preischemic control. Muscle in

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*Rarely there was a transient increase of T-wave negativity, contemporaneously with the start of RS-T depression. Elevation of the T-J junction or a small positive U-wave commonly appeared within 20 to 30 sec. (fig. 3).

† Muscle in

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Circulation Research, Volume VIII, January 1960
Responses of nonischemic hearts to small intravenous injections of levaterenol: myocardial oxygen, RS-T segment and T-wave of epicardial electrocardiogram, and heart rate.

(Continued on bottom of opposite page)
the ischemic area rapidly underwent the same sort of change as nonischemic muscle although to a lesser degree. It began to shorten earlier in systole and bulge less; and diastolic lengths tended to decrease, so that there was an apparent shrinkage in size of the whole ischemic area. There was no resemblance to either spontaneous recovery or release-recovery because the levarterenol-induced systolic shortening was prompt and early, and also because the systolic bulge of the ischemic area returned as the influence of injected levarterenol diminished. Rises of oxygen occurred at most of the central areas. Border electrodes generally showed rises. These were more likely to occur when the oxygen fall at the particular border electrode had been comparatively profound than when it had been shallow.

Levarterenol infusions (0.1 to 0.2 μg./Kg./min.) caused prolonged decreases of systolic bulging, reddening of local veins and flushing of the borders of the ischemic areas so that they became less sharply defined. The result was to make the area appear smaller and the localized bulging difficult to discern at all. Electrocardiographic patterns returned toward control configuration. Rises of myocardial oxygen occurred at the centers of the ischemic areas and at most of the border electrodes, although some fall might occur at high-reading border electrodes (fig. 5, electrode no. 3). It was only after cessation of the infusion that the full extent of the ischemic area again became obvious.

**Maximal Ischemia**

In medium-sized ischemic areas the levarterenol effects frequently produced only a transient delay in development or an incomplete reversal of severe ischemic patterns. However, some alteration of the electrocardiographic picture was measurable in every animal studied. Even when oxygen remained immovably at low levels and there was progressive electrocardiographic abnormality this progression was transiently reversed or slowed by levarterenol. Muscle contraction did not change at the centers of maximal ischemia areas. Increasing the rates of infusion so as to deliver more than 0.2 μg./Kg./min. or raise mean blood pressure more than 20 mm. Hg regularly produced extrasystoles and sometimes paroxysmal nodal or ventricular tachycardia but never hypotension or ventricular fibrillation.

Figure 4 and table 1 illustrate and summarize the response of ischemic areas to levarterenol.

**Administration of Oxygen**

During levarterenol infusions, the inhalation of pure oxygen further increased any myocardial oxygen rises. In the case of certain medium-sized ischemic areas which had not shown a favorable oxygen response to levarterenol there was some rise only when oxygen inhalation was added. There was no tendency to production of additional extrasystoles by oxygen. We had observed previously that pure oxygen inhalation did not protect against ventricular fibrillation during ischemic episodes (or just after release). In contrast to this we have not seen fibrillation during ischemia with oxygen and levarterenol together, or with levarterenol alone.

**Hypoxia and Asphyxia**

Administration of 10 per cent oxygen lowered myocardial oxygen by 15 to 50 per cent as in previous experiments but did not grossly change contractility. Electrocardiographic changes did not occur. Heart rate and blood pressure increased slightly. Levar-
Effects of levarterenol on nonischemic hearts: muscle contraction, myocardial oxygen and electrocardiogram. The boxes indicate the range of variation of onset time; the dotted lines, the interval between onset and maximum effect. In the animals with epicardial electrocardiograms a downward shift of the RS-T segment was the earliest consistent evidence of levarterenol effect. However, all the other changes tended to start almost as promptly, with the exception of extrasystoles (inconstant and very variable), bradycardia (sometimes early, sometimes later) and T-wave change (later than the RS-T segment change by several seconds in every instance). Blood pressure determinations in these animals were not precisely timed, but some rise occurred promptly and invariably. In addition to the episodes graphed in figure 2, muscle contraction data are plotted here for 4 other dogs in which epicardial electrocardiograms were not recorded and limb leads failed to show significant changes.

Intracoronary Injections

In 2 dogs intracoronary injections of 0.2 to 0.5 μg. of levarterenol were made, the dose of drug being mixed with 0.5 ml. of freshly aspirated blood. Both animals showed evidence of ischemia in the distribution of the injected arterial branch in the form of systolic muscle bulging of greater extent than we had seen in any nonischemic situation. However, the local electrocardiograms and myocardial oxygen levels were within the limits of normal variation.

*During aspiration local oxygen levels were slightly lowered. Normal saline injections of equal volume did not alter any of our indices of function.
Table 1

Electrocardiographic and Myocardial Oxygen Responses to Levarterenol Injections in Regional Ischemia

<table>
<thead>
<tr>
<th>RS-T segment deviation (mm.)</th>
<th>Polarographic oxygen (%)</th>
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<tbody>
<tr>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>Isch. control minus non-ischemic</td>
<td>Further increase of RS-T response</td>
</tr>
<tr>
<td>Ranges</td>
<td>Means</td>
</tr>
<tr>
<td>Small Ischemic Areas (3 dogs, 10 injections, 16 oxygen electrodes)</td>
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<tr>
<td>Ranges</td>
<td>Means</td>
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<tr>
<td>Small Ischemic Areas (3 dogs, 10 injections, 16 oxygen electrodes)</td>
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</tr>
<tr>
<td>Medium-sized Ischemic Areas (2 dogs, 6 injections, 14 oxygen electrodes)</td>
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</table>

*In column 1 the change of RS-T segment level is compared with the control before coronary obstruction. Column 2 records any further change between the time of injection and the beginning of the rapid downward RS-T segment shift in response to levarterenol. The maximal amount of this RS-T depression is recorded in column 3. Column 4 gives the pre-levarterenol myocardial oxygen level at central or border electrodes in per cent of the control. In column 5 the maximum change following the levarterenol injection is indicated.

The effect of intracoronary injection of levarterenol on the RS-T segment of slightly or severely ischemic muscle was discernible in 2 to 5 sec. (fig. 6). A reddening of the local veins could be detected within 3 to 10 sec., and myocardial oxygen rose promptly and consistently. Early systolic muscle shortening began within 5 sec. so abruptly that contraction could be seen to change within 1 or 2 heart beats. The early shortening was maintained throughout systole for several seconds. Contraction then began to fail in late systole. The changes in local muscle contraction after the first few seconds of levarterenol action were attributable in part to recirculation effects of the drug on the myocardium throughout the left ventricle (perhaps with a lessened incremental effect on the muscle in the partially obstructed coronary branch's distribution). L-epinephrine produced effects similar to those of levarterenol but required slightly larger dosage to increase the myocardial oxygen (fig. 6).

Constriction of the coronary branch around the catheter produced falls of myocardial oxygen, RS-T segment elevation in the electrocardiogram, and holosystolic muscle bulging. Injection of levarterenol via the catheter distal to the obstruction caused changes similar in direction but briefer and of lesser degree as compared with the effects of injections into an incompletely obstructed artery.

Discussion

The salient findings of these studies may be epitomized as (1) the occurrence of primary negative RS-T segment displacement in local and precordial electrocardiograms following levarterenol injection, together with increased muscle contraction; (2) the concomitant increases of myocardial oxygen (except in the case of very small doses) and the indefinite maintenance of the effects by infusions of levarterenol; (3) the occurrence of qualitatively similar levarterenol effects following larger doses, in association with a visibly narrowed coronary arteriovenous oxygen difference; and (4) the similarity in behavior of regionally ischemic muscle and nonischemic muscle in the levarterenol response. In com-
The effect of levarterenol injections on locally ischemic myocardium: RS-T segment, myocardial oxygen and heart rate. In the upper band, changes of RS-T segment are graphed against time after the injection. The solid portion of the lines indicates the period of significant downward shift of RS-T segment level which occurred within 15 to 50 sec. in all the small ischemic areas and all but one of the medium-sized areas. The medium-sized ischemic areas show increases of RS-T segment level prior to levarterenol as compared with their preischemic controls (taken as zero), whereas the small ischemic area electrocardiograms show little or no RS-T segment elevation at this time. In one run a relative negativity of the RS-T segment has persisted from a previous injection.

The middle band shows the response of myocardial oxygen at electrodes within the ischemic area. 

(Continued at bottom of opposite page)
menting on our results we shall review the recent literature on levarterenol and epinephrine. A full review of the general literature through 1955 has been provided by von Euler.11

Electrocardiographic Effects

The stability of epicardial electrocardiographic patterns in the face of changes in rate and blood pressure should be borne in mind in considering the response to levarterenol. We did not think that any of the levarterenol effects were the consequence of rate or rhythm alterations except perhaps for the increase of RS-T segment depression occurring after the compensatory pauses of extrasystoles which is an exaggeration of the normal response. There appears to have been little or no QRS complex change induced by levarterenol except in severely ischemic muscle when the QRS form had been considerably distorted by the ischemia. In this latter circumstance levarterenol appeared to return the QRS complex toward normal. However, our apparatus (low frequency response) was not suitable for determining whether this represents a true reversal of the change or the superimposition of a different effect.

Epinephrine and levarterenol have been found to cause similar electrocardiographic changes in animals, but in general the dosages employed by other investigators have been higher than the smallest doses reported in this communication. Attention has been given mainly to the T-wave changes, but RS-T segment shifts have regularly been present whenever looked for and measured, although the direction of the shift varies with the electrode positions and lead systems used. Essentially similar changes have been described for ventricular muscle strip preparations,12,13 and for the hearts of frogs,14 guinea pigs,15 rabbits,16 cats,16 and dogs.17 The combination of experimental localized ischemia and levarterenol or epinephrine electrocardiographic effects has not been studied by other investigative groups to our knowledge.

From our findings in dogs and the similar behavior of other species and types of experimental preparation described by others we conclude that the earliest and the most consistent electrocardiographic effect of levarterenol and epinephrine in animals is a primary shift of the RS-T segment. The direction of the shift is always constant for any particular type of preparation, lead system and electrode site. It is generally negative in leads with the exploring electrode on the ventricular surface and the reference electrode remote from the heart, such negativity being greater over the left ventricle. The response of the surface of ischemic muscle is similar to that of nonischemic muscle, if the ischemic area be not so extensive as to preclude any measurable local drug effect at all.

Possible explanations for the RS-T segment shifts associated with levarterenol (or epinephrine) include (1) primary change in the characteristics of the myocardial cell membrane, (2) altered concentration of the intracellular (lower?) and extracellular (higher?) potassium, (3) an altered type of metabolism (glycolysis?) or (4) a combination of 2 or more of these mechanisms. Whatever their origin and significance may be, the shifts of the RS-T segment would seem to represent differences in the levels and/or the slopes of the plateaus of the action potentials of some myocardial cells as compared to others: and not diastolic ‘current of injury’ phenomena.8

The only inference one must certainly make

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\text{ischemic area to levarterenol injections given at zero time. Zero on the ordinate represents the pre-levarterenol ischemic control value. At most electrodes this was less than 25 per cent of the preischemic control value and it was less than 50 per cent in all.}
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The\text{ lower band shows the response of rate. One hundred per cent (on the ordinate) is taken as the pre-levarterenol ischemic control. The responses of medium-sized and small ischemic area hearts to the levarterenol injections are similar. A bradycardia was the rule, occasionally preceded by brief tachycardia.}
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from the T-wave changes is that they indicate an alteration of the control patterns of differences in repolarization time from some parts of the ventricles as compared with other parts. Since serum potassium and temperature effects occurring in response to levarterenol or epinephrine must greatly complicate T-wave behavior, we believe that neither the T-wave data of our experiments nor of the pertinent literature can be usefully analyzed.

**Muscle Contractility**

With levarterenol (and epinephrine) the alterations of muscle contraction that the eye sees at the experiment or in motion pictures consist of a quickening of the onset of contraction, an earlier shortening by portions of the surface that had been delayed or slow in shortening, and a consequently greater synchronousness of contraction. The changes occur rapidly, reach a maximum within less than 70 sec. and then slowly subside. There is
The effect of intracoronary epinephrine and levarterenol on myocardial oxygen and the electrocardiogram. The control RS-T segment levels taken as zero are plotted in millimeters. We have not attempted to indicate diphasic T-wave changes in the plot but have taken the largest deviation (in mm.) from the baseline for each point plotted.

The RS-T segments and the T-waves show a diphasic response. The first T-wave change is an augmentation (in contrast to the effect of intravenous injections). This increased negativity occurs roughly at the same time as the early negative RS-T segment shift but is followed at 10 to 15 sec. by a rapid diminution of negativity resulting in partial or complete reversal of the T-waves within 30 sec. The second period of segment depression and the T-wave reversal are comparable with those for intravenous injection, suggesting that this portion of the record may reflect the effects of recirculation. The oxygen responses do not have a diphasic character. Reddening and constriction of the local veins could be easily seen in the movies at 5 to 10 sec. for all injections. A sharp increase of local muscle contraction was regularly seen within a few heartbeats of each injection.
also a more synchronous and perhaps slightly earlier lengthening of the muscle so that diastole tends to be slightly longer in proportion to systole (even in the absence of rate change). These changes also occur in ischemic muscle—the earlier shortening being specially well seen with intracoronary injections. The levarterenol effects contrast strikingly, both in their promptness and their effect on early systole, with muscle behavior during spontaneous improvement or release-recovery, for in these latter situations contraction changes begin gradually with a late systolic and early diastolic shortening that suggests prolongation of the contractile process. The visual impressions can be confirmed, refined and measured in cinematographic plots.\footnote{Failure\textsuperscript{5} produced by stenosis of the left common coronary artery (diminished increments of stroke work per increment of filling pressure with progressive decreases of work at higher pressures) can be reversed by levarterenol as well as metaraminol,\textsuperscript{30} and in shock produced by widespread lycopodium spore blockage of small myocardial vessels there is improved muscle contraction (strain gage) after levarterenol.\textsuperscript{31}}

The experimental literature is in close agreement with our own findings as to contraction. Both levarterenol and epinephrine have comparably powerful positive inotropic effects on isolated ventricular muscle strips\textsuperscript{15-20} and on the hearts of rats,\textsuperscript{21} frogs,\textsuperscript{22} rabbits,\textsuperscript{23} cats\textsuperscript{24} and dogs.\textsuperscript{25,26} Tension increases in systole and is developed more rapidly; contraction is earlier, more rapid and more synchronous.\textsuperscript{10} There is more rapid diastolic relaxation.\textsuperscript{27} Systolic volume is decreased by decreasing systolic fiber length, the diastolic length tending to increase with reflex bradycardia.\textsuperscript{28} Greater external stroke work can be accomplished per increment of homolateral atrial filling pressure.\textsuperscript{29} However, the effect of levarterenol on localized ischemia due to coronary occlusion has not been studied.\footnote{Central vagal stimulation itself has been shown to produce a brief, early arterialization of coronary sinus blood, associated with a smaller coronary flow. Artificial increases of heart rate have been shown not to increase oxygen consumption per beat or alter the coronary arteriovenous oxygen difference, although oxygen consumption per minute, of course, increases.\textsuperscript{38}}

Myocardial Oxygen, Coronary Venous Oxygen and Coronary Flow Responses

The most striking finding of the experiments reported above was the association of increased myocardial oxygen with the electrocardiographic and muscle contraction changes. The trend toward a greater degree and consistency of oxygen increase with larger dosages; the similar responses of accessible ischemic muscle; the confirmation of polarographic changes by visible vein color changes and measurable coronary sinus saturation increases; the indefinite continuance of the increased oxygen availability with infusions of levarterenol; the independence of effect from that of oxygen inhalation—all set the repolarization and contraction changes in a new light. We know of only one other study concerned with polarographic myocardial oxygen that has aims somewhat similar to ours, and its findings resemble our own insofar as the experimental situations could have been expected to be similar.\textsuperscript{32} Measurement of coronary sinus oxygen, coronary flow or myocardial metabolism after levarterenol have been the subject of many other studies. The consistency of the findings is not apparent unless cognizance is taken of the experimental circumstances in each instance. There has furthermore been a certain amount of unfamiliarity of the investigative groups with each others' work insofar as this can be judged from their bibliographical cross references. Two general experimental study situations may be distinguished (table 2).

It has been regularly found (table 2, upper portion) that Adrenalin, levarterenol and epinephrine increase coronary sinus oxygen content in innervated heart lung preparations (vagal and sympathetic supply to heart preserved) and in intact or semi-intact animals.\textsuperscript{33-38} There is some difference of opinion as to how necessary vagal slowing is to this response, although clearly the occurrence of a bradycardia makes the coronary venous oxygen rises larger.\footnote{Failure produced by stenosis of the left common coronary artery (diminished increments of stroke work per increment of filling pressure with progressive decreases of work at higher pressures) can be reversed by levarterenol as well as metaraminol, and in shock produced by widespread lycopodium spore blockage of small myocardial vessels there is improved muscle contraction (strain gage) after levarterenol.}

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The most striking finding of the experiments reported above was the association of increased myocardial oxygen with the electrocardiographic and muscle contraction changes. The trend toward a greater degree and consistency of oxygen increase with larger dosages; the similar responses of accessible ischemic muscle; the confirmation of polarographic changes by visible vein color changes and measurable coronary sinus saturation increases; the indefinite continuance of the increased oxygen availability with infusions of levarterenol; the independence of effect from that of oxygen inhalation—all set the repolarization and contraction changes in a new light. We know of only one other study concerned with polarographic myocardial oxygen that has aims somewhat similar to ours, and its findings resemble our own insofar as the experimental situations could have been expected to be similar.\textsuperscript{32} Measurement of coronary sinus oxygen, coronary flow or myocardial metabolism after levarterenol have been the subject of many other studies. The consistency of the findings is not apparent unless cognizance is taken of the experimental circumstances in each instance. There has furthermore been a certain amount of unfamiliarity of the investigative groups with each others' work insofar as this can be judged from their bibliographical cross references. Two general experimental study situations may be distinguished (table 2).

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Table 2
Responses of Myocardial Oxygen, Coronary Venous Oxygen and Coronary Flow to Levarterenol and Epinephrine: Summary of Pertinent Literature

<table>
<thead>
<tr>
<th>Dog preparation</th>
<th>Oxygen</th>
<th>Coronary flow</th>
<th>Other observations or investigators' inferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innervated heart lung and open-chest: Adren. and levart.</td>
<td>up</td>
<td>rise</td>
<td>Believed to require reflex bradycardia (Entlastungsreflex). Slowing might precede BP rise for levarterenol.</td>
</tr>
<tr>
<td>Open-chest: Adren.</td>
<td>up</td>
<td>rise</td>
<td>100% O₂ effects independent and additive.</td>
</tr>
<tr>
<td>Epineph. &amp; levart.</td>
<td>up</td>
<td>up</td>
<td>Nonischemic hearts. Large doses. Reddened coronary veins.</td>
</tr>
<tr>
<td>Levart. &amp; epineph.</td>
<td>up</td>
<td></td>
<td>Ischemic areas; small doses. Slowing of rate considered important. Improved muscle contraction.</td>
</tr>
<tr>
<td>Closed-chest: epineph. &amp; levarterenol.</td>
<td>up</td>
<td>rise</td>
<td>Atropine or vagotomy did not abolish epinephrine effects.</td>
</tr>
<tr>
<td>Open-chest: epineph. &amp; levarterenol.</td>
<td>up</td>
<td></td>
<td>Response not abolished by strangulation, vagotomy, or carotid sinus denervation.</td>
</tr>
<tr>
<td>Control cardiac output: epinephrine &amp; levart.</td>
<td>up (usually)</td>
<td>rise</td>
<td>No correlation with increasing dosage found.</td>
</tr>
<tr>
<td>Denervated heart-lung: Adren.</td>
<td>down</td>
<td></td>
<td>Repeated doses maintained effects. Control A-V O₂ differences small.</td>
</tr>
<tr>
<td>Denervated heart-lung: Adren.</td>
<td>down</td>
<td>rise</td>
<td>Control A-V O₂ differences small.</td>
</tr>
<tr>
<td>Fibrillating or open-chest, constant coronary perfusion pressure: epin. &amp; levart.</td>
<td>down</td>
<td>fall then rise</td>
<td>Greater oxygen tension falls with larger doses. Increased &quot;vigor&quot; of contraction. Flow changes attributed to initial coronary vaso-constriction then dilatation due to anoxia.</td>
</tr>
</tbody>
</table>

*Upper Portion. Findings of investigative groups employing intact or semi-intact preparations: uniformly increased coronary venous oxygen and (when determined) increases of polarographic myocardial oxygen and coronary flow. Lower Portion. Results of studies in which either the nerve supply of the heart was interrupted, the control coronary arteriovenous differences were narrow, or the coronary perfusion pressure was not free to vary. | Unpublished experiments with Kuo, P. T., Foltz, E. L., and West, J. W. |

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do not abolish either the epinephrine or levarterenol effects on coronary sinus oxygen. Epinephrine in doses too small to produce hypertension has been found to increase coronary sinus oxygen, but there has always been at least a transient systemic blood pressure increase with levarterenol. Increases of coronary flow have been found in all animals given levarterenol or epinephrine under these circumstances, beginning at the time of, or slightly earlier than the rise of coronary sinus oxygen. 1,26, 27
Regarding the mechanisms for coronary flow increase, in addition to increased perfusion pressure from systemic hypertension, it has been proposed that the increased coronary flow consequent on levarterenol administration is mainly due to a comparative lengthening of diastole, produced by the prompter relaxation of the ventricular muscle which is characteristic of the positive inotropic effects of epinephrine and levarterenol; but perhaps also to a more complete emptying of the venous and capillary beds by the more rapid and forceful systole.

For locally ischemic muscle an increased systemic pressure would tend to increase flow through even a severe narrowing, though not an occlusion. In either event, collateral circulation effects should be important. Lengthening of diastole for the nonischemic muscle would improve the perfusion of any collateral channels supplying the ischemic zone. Increased contraction of the ischemic muscle should help empty its own deep venous and capillary channels in systole, while earlier relaxation might further reduce the resistance to flow into the area from collaterals in diastole. Our experimental results throw no direct light on such mechanisms except that the character of initial ischemic muscle contraction improvement favors direct action of levarterenol rather than improvement in blood supply as the earliest mechanism of favorable effects.

In contrast to the experimental situation just described, denervated heart-lung preparations, or hearts perfused by constant-pressure coronary reservoir systems (table 2, lower portion) do not show increases of coronary sinus oxygen content; rather, there is a fall of both oxygen content and tension. There may also be an initial coronary flow decrease followed by a prolonged increase.

There seem to be no important inconsistencies among the results of the published investigations with which we are familiar when these relationships are taken into consideration. It may be concluded that, given a relatively normal ability to regulate coronary perfusion pressures, the effect of all but the smallest doses of intravenous or intracoronary injections of levarterenol and epinephrine is to increase coronary venous oxygen content and polarographic ventricular myocardial oxygen levels consistently, in association with increases of coronary flow. If levarterenol is administered by intravenous infusion, the narrowed coronary arteriovenous differences and increases of myocardial oxygen can be maintained throughout prolonged infusions. The myocardial oxygen increases can be produced during hypoxia or even asphyxia. Under all these circumstances they can be detected almost as early as the electrocardiographic and contractility changes, and they persist almost as long. To what extent a shift to anaerobic metabolism or the opening of arteriovenous shunts may contribute these oxygen responses is uncertain.

Disturbances of Rhythm

For nonischemic hearts, our findings of occasional extrasystoles following small doses of levarterenol are similar to those of others under comparable circumstances. The anesthesia we used somewhat enhances vagal tone, which should at least slightly increase the frequency of extrasystoles and the likelihood of ventricular fibrillation, but we have no instances of fibrillation. That blood pressure was always well maintained or somewhat increased during arrhythmias may account for the absence of any adverse consequences. Perhaps because our ischemic episodes were of not more than a few hours duration—so that our animals did not enter the period of ventricular arrhythmia described as beginning 4 to 6 hours after coronary ligation—we found no increase of arrhythmias after levarterenol as compared with nonischemic hearts.

General Considerations

Our experience, like that of others, has been that the systemic circulatory (blood pressure,
rate and rhythm) responses to either levarterenol or epinephrine vary considerably from animal to animal, with the order in which the drugs are given, and from one part of an experiment to another. Such variations in circulatory response contrast with the regularity of electrocardiographic changes and contractility increases and with the myocardial oxygen increases that are constant with slightly higher dosages. We have, however, regularly found slight mean blood pressure rises following levarterenol and not infrequently slight falls of pressure following epinephrine, the latter drug having a greater tendency to produce extrasystoles. In ischemic situations these characteristics of $l$-epinephrine have seemed disadvantageous.

The potentiation or attenuation of some or all of the circulatory effects of levarterenol by sensitization, by tissue levarterenol concentration alterations, and by synergistic or antagonistic mechanisms or agents do not appear to be factors pertinent to the directional responses we have described for nonischemic hearts; except for a tendency toward respiratory alkalosis consequent on slight hyperventilation which might have increased sensitivity to levarterenol in some of our animals. In ischemic areas there was presumably a low pH from lactic acid and perhaps accumulation of carbon dioxide. The latter has been reported to diminish sensitivity to levarterenol, but the indices of such change in sensitivity in the intact animal have either been changes in ectopic rhythm frequency, pressor effect and rate response, or else contractile force alterations (strain gage). The behavior of the parameters of direct myocardial action which are our main concern in this report have not been evaluated.

The considerable differences in circulatory response to levarterenol and $l$-epinephrine between man and the dog will not be discussed here. However, there would seem to be at least 4 implications of our experimental findings and the pertinent literature for studies in man. (1) The electrocardiogram (precordial leads) should be a valuable index of ventricular action for levarterenol, $l$-epinephrine and/or Adrenalin. (2) The RS-T segment shifts do not signify ischemia in animals but are closely associated with positive inotropic effects and an increased myocardial oxygen supply/demand ratio not only for ischemic muscle but for critical ischemia situations, hence certain common clinical assumptions require reconsideration. (3) Atropinization alters the response to both levarterenol and $l$-epinephrine in dogs so as to reduce the frequency of arrhythmias and increase the electrocardiographic and contractility effects in association with a greater pressor response but the persistence (in part, at least) of the favorable ventricular oxygen supply-demand ratio, hence this combination of drugs should be experimented with more widely. (4) The combination of levarterenol and high concentrations of oxygen may bring out the best effects of both agents.

Summary

In open-chest dogs levarterenol has been found to produce a primary RS-T segment shift in the surface electrocardiogram in association with its strong positive inotropic action. These effects are constant and are accompanied by an increase of polarographic myocardial oxygen and cardiac venous oxygen (except with the smallest doses).

The increased contractility and RS-T segment shifts tend to occur together and are produced by doses that cause no other measurable effects except transient rises of mean blood pressure. They can be maintained by slow infusions. The effects of levarterenol on myocardial oxygen can occur in nonischemic muscle, during anoxia, asphyxia, or with direct injections distal to a coronary occlusion. They increase following larger dosage of levarterenol or $l$-epinephrine, despite multiple ectopic beats and large blood pressure rises. Pure oxygen inhalation enhances the levarterenol effects on ischemic muscle. Ventricular fibrillation does not occur.

The effects of levarterenol are thought to be associated with both an increase of relative blood supply and a shift to anaerobic-
type metabolism. Our experimental findings are consistent with those of others who have studied one or more of the parameters of myocardial function we have used. They do not fit in with a number of current convictions or assumptions about levarterenol action. In particular, no "anoxiating effects" for ischemic or nonischemic muscle have been demonstrated and the favorable effects of levarterenol on regionally ischemic muscle have been confirmed.

**Summary of Literature**

Essere constatate in canes a thoraces apertes che levarterenol produce un dispercentamento primari del segmento RS-T di elettrocardiogrammas superficiali in association con sua forte action inotropic positiva. Le effectos es constant e es accompagnate de un augmento del oxygeno myocardial e del oxygeno in le venas del corde, excepte quando le droga es usate in le plus ultra doses.

Le augmentate contractilitate e le dispercentamentos del segmento RS-T tende a occurrer concomitante e es produite per doses que causi nulla altere measurabile effecto, excepte un transient augmento del tension sanguine media. Illos pote esser mantene per lente infusiones. Le effectos de levarterenol super le oxygeno del myocardio pote occurrer in muscolo nonischeiuic e in musculo ischemic, durante anoxia, durante asphyxia, o in consequentia de directe injectiones distal a un occlusion coronari. Illos deveni plus marcate post plus grande doses de levarterenol o lepinephrina, in despecto de multe pulsos ectopics e de grande augmentos del tension de sanguine. Le injectiones di oxygeno per promove le effectos de levarterenol super le musculo ischemic. Fibrillation ventricular non occurre.

Es opinato che le effectos de levarterenol es associate con un augmento del provision relative di sanguine e ctiam con un transition a un typo measurabile di metabolismo. Nostre constatationes experimental es de acordo con le constatationes de alteres qui ha studiato un o plurres del aspectos di function myocardial con que nos esiste preoccupate. Del altere latere, nostre constatationes non concorda con un numere di currente convictions o suppositiones relative al action di levarterenol. In particular, nulla effectos "anoxiante in musculo ischemic o nonischein" ha essite demonstrate e le effectos favorible de levarterenol super regionalemente ischemic musculos ha essite confermate.

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LEVARTERENOL ON HEART


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The Effect of Levarterenol on Polarographic Myocardial Oxygen, the Epicardial Electrocardiogram and Contraction: in Nonischemic Dog Hearts and Experimental Acute Regional Ischemia

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Circ Res. 1960;8:109-128
doi: 10.1161/01.RES.8.1.109

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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