Effects of Cardiac Glycosides upon the Electrical Activity of Single Ventricular Fibers of the Frog Heart, and Their Relation to the Digitalis Effect of the Electrocardiogram

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Using microelectrodes having an external diameter of less than 1 μ, potential variations of single cardiac fibers were obtained from frog ventricular muscle in situ. The normal membrane potential consists of a rapid depolarization and slow recovery, the latter occurring in three distinct phases. Digitalis glycosides alter profoundly the slopes of these various phases and drastically shorten the entire period of recovery. The characteristic cardiac action potential is thus converted into a spike which resembles the electrical events recorded for skeletal muscle or nerve. These changes occur independently of mechanical systole which remains essentially unaltered. The deformation of the action potential occurs uniformly throughout the ventricular muscle. They are related to the RS-T segment depression of the surface electrocardiogram which in this instance cannot be explained as being caused by a failure of the diastolic repolarization of the endocardial surface but must be an expression of uniform shortening of the entire process of recovery.

Certain inferences may be drawn from these experimental findings concerning the effect of digitalis on the ventricular complex of the surface electrocardiogram, which consists of a depression of the RS-T segment and a shortening of the Q-T interval. The significance of these changes has remained obscure, and the superficial resemblance to the electrocardiogram in myocardial disease has led to the statement that the effect of digitalis on the heart muscle is essentially a harmful one. Macleod has measured the duration of the excitatory state of the frog heart during administration of digitalis glycosides and has demonstrated a shortening of the electrical systole together with a decrease in the length of the refractory period similar in many respects to that obtained by the administration of acetylcholine. When a monophasic record was produced by injuring the surface of the ventricular musculature, again a striking decrease in the duration of the electrical systole occurred, giving the monophasic record a spike-like appearance. A similar loss of plateau of the monophasic record of injury with shortening of Q-T was also noted by Schellong and Stetzer using Schütz’s technic for inducing monophasic action currents. There exists a

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relationship between records obtained from freshly injured regions yielding a monophasic response and those obtained by ultramicro-electrodes from the cell interior. Therefore, these observations are of interest and offer information on the basic significance of the digitalis effect of the electrocardiogram not generally yielded by a discussion of the superficial resemblances of electrocardiographic surface patterns.

METHODS

The technic and the experimental methods used have been described previously15 and reference should be made to that paper for details. Summer stage leopard frogs were used as experimental animals. The frogs were pithed, the chest opened and the animals placed in a plastic chamber through which Howell's frog heart Ringer's solution was circulating. A nearly constant temperature for any particular experiment was maintained but various experiments were run at different temperatures.

A series of normal control records was obtained from each preparation. Digitoxin or one of the other cardiac glycosides was then administered and tracings were recorded thereafter every few minutes up to five hours.

The various compounds were usually injected into the aorta or directly into the lumen of the ventricle. Since the digitoxin had been dissolved in 40 per cent alcohol it was diluted 10 times with frog Ringer's immediately before injection. Control injections of 4 per cent and 10 per cent alcohol up to a dose of 0.5 ml. failed to cause any observable changes. The dose of the glycosides varied. The maximum amount administered did not exceed 3.0 mg. per kilogram of the active substance. The maximum volume injected was about 0.5 ml., although the usual volume generally approximated 0.3 ml.

It seemed desirable to correlate the mechanical and the electrical events of the cardiac cycle, but since the usual methods of recording mechanical events of the heart do not work well with the intact heart connected to the circulation it was necessary to devise another method. The system finally used employed a special electromechanical transducer tube (RCA 5734) which has the property of converting extremely small mechanical movements into voltage changes. The tube has a movable anode connected to an external lever. A change in anode-cathode spacing results in a change in plate current and therefore in output voltage. A small plastic L-shaped foot with a small (0.4 mm.) hole in the center of the foot was fastened to a stiff piece of spring brass. The anode lever on the transducer tube was coupled to the stiff spring by a piece of weak spring. The tube is so sensitive that a reduction in amplitude was necessary. The plastic foot was lowered over the frog heart so that a light but firm contact was made. The contractions of the heart raised and lowered the foot slightly so that a movement was transmitted to the anode lever of the transducer tube which produced an output voltage proportional to the amplitude of movement of the frog heart. The microelectrode was inserted through the hole in the foot. In this way simultaneous records could be made of the electrical activity of a single fiber and of the movement of the heart.

The experiments were carried out with five different glycosides known to have digitalis-like actions. Digitoxin* was used most frequently with varying doses and under various conditions. The results obtained with digitoxin constitute the main body of this report. A limited number of observations were carried out with ouabain, s-illaren B., lanatoside C, and K-strophantoside.

RESULTS

When a microelectrode, connected to a suitable recording system, is inserted into a single muscle fiber of a beating frog ventricle, a regular sequence of events is obtained.16 With the microelectrode on the outside of the fiber an isoelectric base line is traced on the recording. When the needle penetrates the cell membrane during diastole a sudden voltage, negative with respect to the outside of the fiber, appears. This is the membrane resting potential (MRP). When electrical systole occurs this membrane potential rapidly falls to zero, and then reverses itself as the inside of the cell becomes positive with respect to the outside (overshoot). The sequence of disappearance and then reversal of the membrane voltage constitutes depolarization and corresponds to excitation of the cell. Following depolarization a slow period of repolarization or recovery ensues which returns the membrane voltage to its resting state. The sequence of depolarization and repolarization is known as the membrane action potential (MAP) to distinguish it from action potentials taken from the outside of the cell. When the microelectrode is withdrawn from the cell, whatever voltage is present disappears and an isoelectric base line is again recorded.

The period of excitation or depolarization is quite rapid and is an inverse function of the

* Digitoxin-Lilly.
temperature; the higher the temperature, the shorter the time required for depolarization.

We have pointed out previously that the period of repolarization or recovery of the heart fiber is composed of at least three separate phases differing from each other in rate, duration and response to changes in environmental temperature. The three phases of recovery and the other components of the membrane action potential are illustrated in figure 1.

![Figure 1](image)

**Fig. 1.** Membrane action potentials of single ventricular fibers of the frog heart at different stages of digitoxin intoxication. Control: no digitoxin administered. A: early digitoxin effect. B: strong digitoxin effect. C: very strong effect, just before complete asystole.

P1-S, P2-S, P3-S, slope or rate of recovery of phase one, two and three respectively; P1-d, P2-d, P3-d, duration of phase 1, 2 and 3 respectively. OS: overshoot; US: undershoot or failure of complete repolarization. MP: membrane potential.

The duration of the normal action potential is an inverse function of the temperature, increasing in length as the temperature decreases. However, for any given temperature the action potential durations are quite constant. The rate of the heart beat increases with temperature, and in pithed frogs (vagal-parasympathetic control removed) the logarithm of the rate is directly proportional to the logarithm of the reciprocal of the duration. This relationship affords a means of evaluating changes in duration of the action potential when the heart rate changes.

**Effects of Digitoxin**

**Duration of the Membrane Action Potential and its Components.** When digitoxin is administered to the frog, the action potential duration as a whole may at first lengthen and then shorten or may shorten directly. In figure 2A are shown the changes of the total action potential duration with time in three experiments, exhibiting a mild, moderate and severe effect of digitoxin. In figure 2A transient lengthening followed by shortening is shown, in figure 2B there is a gradual but severe shortening, while in figure 2C a rapid extreme shortening ends in asystole. The net result of the digitoxin is to decrease the duration of the action potential.

The membrane action potential (MAP) consists of four components, the period of depolarization and the three phases of repolarization or recovery. The effect of digitoxin was studied upon the duration of these four components with the following results:

1. **Depolarization:** The period of depolarization is short compared with the period of repolarization. It ranges from about 29 milliseconds at 10 C. to about 14 milliseconds at 20 C. Since the deflection time of the string galvanometer used was about 5 milliseconds, measurements made at 20 C. or higher are in error. Preliminary studies indicated that there

![Figure 2](image)

**Fig. 2.** Action potential duration (APd) as a function of time after administration of digitoxin. A: mild effect with recovery; B: marked effect, but no asystole; C: strong effect with rapid asystole. APd in seconds.
were no effects of digitoxin upon the duration of depolarization that could be detected with the equipment used.

2. Repolarization: The primary effect of digitoxin is upon the duration of the repolarization process. Since repolarization is composed of three separate phases\textsuperscript{14, 15} it was necessary to establish the normal pattern before a detailed analysis could be made.

At all temperatures, phase 2 (the “plateau” of the monophasic curve) had the longest duration, phase 1 the next longest and phase 3 the shortest. At any given temperature the relation between the durations of the three phases in a normal heart is quite constant. Digitoxin modifies this relation profoundly. With large doses phases 2 and 3 apparently disappear completely; with moderate doses the relations among duration of the phases change. If the relations among the various phases remained constant during digitoxin the correlations between the phases would be positive and of moderately high value. A low correlation or a high negative correlation would indicate a change in the relation of the various phases to each other. Table 1 shows the correlations obtained among the various phases during the time course of a small dose of digitoxin. As may be seen from the correlations there was a dissociation between phase 1 and 2 and between phase 2 and phase 3. The high negative correlation between phase 1 and phase 3 indicates that under the influence of digitoxin the duration of these two phases changes in opposite directions.

Figure 3 illustrates the changes in the duration of the action potential and the various phases following a small dose of digitoxin. As may be readily seen the changes in phase duration do not parallel each other. The parallelism of phase 2 and the total action potential durations is explained on the basis that phase 2 constitutes a large portion of the total.

In summary it may be noted that under the influence of moderate doses of digitoxin the action potential shortens markedly. The major part of the shortening takes place in phase 2. Phase 3, however, lengthens and phase 1 shortens. With recovery these processes reverse.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Duration of the action potential (APd) and the various phases of recovery as a function of time after the administration of digitoxin.

### Changes in Rate of Recovery (Slope) of the Three Phases

Under ordinary conditions the three phases of recovery have different slopes. Under the influence of digitoxin the rate of recovery of the first phase becomes greater (the slope becomes steeper) while the rate of the third phase becomes slower (the slope becomes flatter) (fig. 1). The slope of phase 2 remains relatively unchanged.

With comparatively large single doses of digitoxin (1 to 2 mg. per kilogram) the effects are more striking. The slope of the first phase becomes steeper and those of the second and third phase become flatter. Eventually the second and third phase disappear and re-
recovery is apparently taken over by the first phase. Figure 1 illustrates these gradual changes from a normal action potential to the stage at which apparently only the first phase remains.

Under the influence of digitoxin there is a strong negative correlation ($r = -0.818$, $p < 0.001$) between the duration of the action potential and the rate of recovery of the first phase, that is, as the action potential duration shortens the slope of the first phase steepens. Whether either of these is a function of the other or whether both are dependent upon some other factor could not be determined.

Changes in Membrane Voltage. The amplitude of the membrane resting and the membrane action potentials of single fibers of the frog heart vary from fiber to fiber and from frog to frog. Within the limits of detectability there is no significant change with temperature or time under normal conditions. Moderate and large doses of digitoxin, however, produce alterations in the amplitude of the membrane action potential while leaving the membrane resting potential comparatively unaffected. The changes in amplitude of the membrane action potential appear somewhat later and recover earlier than the changes in duration. The general pattern of change in voltage due to digitoxin is shown in figure 4. The action potential is plotted as a percentage of the amplitude of the membrane potential against time after a dose of digitoxin. Three curves are shown, illustrating mild, moderate and severe effects of digitoxin. As can be seen from the curves the general pattern consists in a disappearance of the overshoot followed by undershoot or failure of the cell to depolarize completely. With mild doses recovery ensues. With large doses the effect continues until the action potential disappears; the cell is then in asystole but the membrane potential is still present.

Treating the difference between the membrane action potential and the membrane resting potential as overshoot and assigning an appropriate sign to it (positive or negative), we calculated correlations among the overshoot (as a percentage of the membrane potential), action potential duration, and the rate of recovery of phase 1. There was a moderate correlation ($0.568; p < 0.02$) between the per cent overshoot and the duration of the action potential. There was a high negative correlation ($-0.818, p = 0.02$) between the action potential duration and the rate of recovery (slope) of phase 1 and a nonsignificant correlation ($-0.321, p > 0.1$) between per cent overshoot and the rate of recovery of phase 1. Partial correlations by eliminating each of the variables in turn did not change the direct correlations significantly.

The correlation between per cent overshoot and action potential duration under the influence of digitoxin is noteworthy. For another group of experiments the correlations between action potential duration and per cent overshoot are illustrated in table 2. There is a progressive increase in magnitude of the correlation between these two variables as the digitoxin effect becomes greater. The correlation probably indicates that both changes are consequent upon some hitherto undisclosed mechanism.
Relation of Mechanical and Electrical Events.  
By use of the apparatus described above, the mechanical movement of the heart was recorded simultaneously with the membrane action potential of single fibers from the middle area of the ventricle. A record showing simultaneous recordings of the action potential and the mechanical events of the heart is shown in figure 5. The ordinate of the mechanical event sequence is essentially the change in diameter of the ventricle caused by contraction. The first peak is the change in ventricular diameter caused by the inflow from the auricle and is called the auricular peak. The second peak is that caused by the contraction of the ventricle. Occasionally a third peak caused by contraction of the conus is seen.

<table>
<thead>
<tr>
<th>Table 2.—Correlations between Per Cent Overshoot and Action Potential Duration for Various Effects of Digitoxin.</th>
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<td>Item</td>
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Figure 5 shows that the ventricular contraction commences shortly after the depolarization of the fiber. The peak of ventricular contraction is reached at a time depending on the temperature. It averages 0.11 second at 26 C. Following the peak of contraction the muscle relaxes and returns to its resting stage. Relaxation is completed just after the end of the action potential. Duration of the ventricular contraction is defined here as the time from the onset of depolarization of the fiber to the end of the relaxation of the muscle. This definition was adopted because the actual time at which the ventricle starts to contract is obscured by the inflow of blood from the auricles. When it was possible to determine with some certainty the onset of ventricular contraction it was found that this followed the depolarization by about 10 to 20 milliseconds, a time lag which is negligible compared to the normal duration of contraction which varies from 500 to 2500 milliseconds, depending on temperature.

Records of ventricular contraction were made simultaneously with single fiber recordings at temperatures ranging from 12 to 26 C. When the ventricular contraction duration

![Fig. 5. Mechanical events of the whole heart and electrical events of single ventricular fibers. Upper line mechanical record, lower line electrical record. In the mechanical record, the large peak is the result of ventricular contraction. The preceding elevation represents the change in ventricular diameter caused by inflow from the auricle.

A: Control record, no digitoxin. B, C, D: progressive changes following administration of 1.2 mg. per kilogram of digitoxin. Note that the duration of the action potential shortens markedly with little change in the duration of the mechanical events.

(VCd) was plotted against the action potential duration (APd), for normal control records a straight line was obtained as shown in figure 6. The equation was (VCd) = 1.195 (APd) -0.054. The intercept of -0.054 is significantly different from zero and the slope of 1.195 is significantly different from 1.
When effective doses of digitoxin are given there is a shortening of action potential duration (APd) but only a small, if any, change in ventricular contraction duration (VCd). The net result is that the ratio between these two events (VCd/APd) increases. In figure 7 the change of this ratio as a function of time after digitoxin is shown for two dose levels. At the 1.2 mg. per kilogram dose level (B) only minor fluctuations of the ratio occurred. At the 2 mg. per kilogram level (A) there was a sudden change in the ratio indicating an extreme decrease in the duration of the action potential compared to the ventricular contraction duration. Figure 5 shows typical records of the 2.0 mg. per kilogram dose experiment. As may be seen, the effective duration of the action potential shortens markedly, but the ventricular contraction remains about the same in duration. The changes in the amplitude of the ventricular contraction shown in figure 5 are real but are not necessarily proportional to the force of the contraction.

Under the influence of digitoxin, the ends of the mechanical and electrical events become dissociated. The ventricular contraction stays about the same in duration but the action potential shortens markedly. The action potential serves to initiate the contraction but does not, apparently, play an absolutely necessary part in the rest of the contractile process. In figure 5C the action potential has recovered to the extent of 80 to 90 per cent by the time the contraction has reached its peak, so that it...
is clear that the action potential need not be integrally concerned in the heart’s contractile process other than to initiate it.

**Surface Electrocardiogram.** Figure 8 shows simultaneous recordings of membrane action potentials from a single fiber and surface electrocardiograms taken within a millimeter or less of the single fiber. The figure shows the parallel change caused by digoxin in the membrane action potential and in the surface electrocardiogram. The auricular and the conus components of the whole heart electrocardiogram are not visibly present because of the small size of the electrode and its closeness to the ventricular surface.

The QRS complex corresponds to the depolarization of the fiber and the remainder of the electrocardiogram to the recovery part of the action potential of the fiber. Since the monophasic record is that of a single fiber and the surface electrocardiogram that of many fibers, a close time correspondence is not to be expected.

Measurements of the rate of recovery, after digoxin took effect, and the magnitude of the RS-T depression were correlated. The correlation was 0.91 ($p < 0.001$) and was highly significant.

**Effects of Other Cardiac Glycosides**

The other cardiac glycosides tested were ouabain, scillaren B, lanatoside C and K-strophantoside. Four experiments were performed using ouabain, two using lanatoside C,* one using scillaren B, and one using K-strophantoside. The results may be summarized by saying that, within the limits of variation of the data, their effects were indistinguishable from those of digoxin. Small quantitative differences may exist but were not found in these experiments.

**Discussion**

The impalement of a single fiber by an ultramicroelectrode permits the recording of the electrical events of a single fiber. We have demonstrated by this technic a peculiar but perhaps not entirely specific action of digitalis compounds on the rate of recovery from excitation which is drastically shortened, and on the various phases of repolarization, which are changed in a predictable fashion (figs. 1, 5, 8).

A fundamental difference between skeletal muscle and cardiac muscle is the long duration of the recovery process of the cardiac muscle. In skeletal muscle the action potential lasts only a few milliseconds; in cardiac muscle it may last for 0.4 to 6.0 seconds depending on the temperature. In skeletal muscle the action potential serves only to initiate contraction. In cardiac muscle the action potential not only initiates contraction but endures for almost the whole period of contraction.

One effect of digoxin in the normal frog heart in situ is to shorten profoundly the duration of the action potential without greatly affecting the duration of the contractile process. This results in a dissociation of the terminal electrical and mechanical events. With toxic doses of digoxin the action duration may become merely a spike and, except for the time scale, the picture of the action potential and the muscular contraction resembles those of striated muscle.

The long duration of the action potential is paralleled by a long refractory period. McLennan has shown that for the frog heart the refractory period is just slightly shorter than the action potential and that as the action potential duration shortens under the influence of cymarin (a cardiac glycoside) the refractory period shortens in a parallel fashion ($r = 0.983, p < 0.001$). The shortening of the action potential and the concomitant decrease in the refractory period would suggest that the heart could be thrown into tetanus at this stage.

It is interesting that digoxin had a different effect upon each of the three phases of recovery. The rate of repolarization (slope) of phase 1 was increased, that of phase 3 was decreased and that of phase 2 was comparatively unaffected. With increasing doses of digoxin, however, the slopes of phase 2 and 3 become zero and phase 1 takes over all of the recovery process. The reason for these various changes is obscure. We have suggested that the three phases of recovery

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* Cedilanid (Sandoz).
depend upon different metabolic processes, and it may be that digitoxin interferes with each of these processes in a different manner.

The gradual disappearance of the action potential, with loss of overshoot and later failure of the fiber to depolarize, but with the membrane potential comparatively unaffected, are reminiscent of other substances than digitoxin. Toman, Woodbury and Woodbury have shown that both di-isopropyl fluorophosphate (DFP) and eserine caused the surface action potential of a frog sciatic nerve to decrease and eventually to disappear while the demarcation potential remained relatively unchanged. The same effect has been shown for procaine on frog nerve by Bennet and Chimberg.

Potassium chloride, on the other hand, will abolish the action potential and the overshoot, but at the same time cause a decrease in the membrane potential, both in frog sciatic nerve and in single fibers of the frog heart (personal observation).

Daly and Clark pointed to a remarkable similarity of the effect of strophanthin on the intact heart to that of lack of sodium. On isolated frog sartorius muscle, on a single nerve preparation and on isolated Purkinje tissue, a decrease in concentration of sodium resulted in loss of overshoot roughly proportional to the logarithm of the extracellular sodium concentration. In the latter preparation, a shortening of the duration of the action potential was likewise present. No consistent changes in resting membrane potentials were noted in any of these experiments.

Surface electrocardiograms taken from the ventricular surface showed changes that could be correlated with simultaneously recorded ventricular single fiber records. As the duration of the action potential decreased the Q-T interval decreased. As the slope of the first phase of recovery increased the RS-T segment became depressed. The correlation between the slope of the first phase and the magnitude of the RS-T depression was 0.91 (p < 0.001). In the advanced toxic stages of digitoxin action extreme shortening of Q-T results in RS-T changes of a peculiarly exaggerated kind.

The origin of the surface electrocardiogram

is a complex subject involving, as it does, volume conduction effects, time and space summation of the activities of thousands of fibers and the derivatives of the membrane action potential. It is interesting to note that the correlation of the rate of recovery of phase 1 and the RS-T depression is extremely high. The implication is that the RS-T depression in digitoxin intoxication in the frog is merely a reflection of the increased rate of recovery of the heart.

For the mammalian heart, differences in the length of the excitatory state are known to be responsible for deviation of the R-T junction and for the shape of the T wave of the surface electrocardiogram. A delay of repolarization with localized lengthening of the excitatory state occasionally, for instance, by injury of subendocardial or of subepicardial regions of the heart is known to result in displacement of the RS-T segment and in T-wave changes. A similar explanation has been advanced for the digitalis effect of the human electrocardiogram. Our observations on the electrical events of single heart muscle fibers recorded simultaneously with surface electrocardiograms have, however, demonstrated that the RS-T segment changes of the electrocardiogram of the frog following digitalis medication are an expression of a uniform shortening of the excitatory process throughout cardiac musculature. It appears then that a more or less uniform shortening of repolarization following digitalis therapy results in RS-T segment depression in surface records which, except for the Q-T interval, resemble those apparently caused by localized lengthening of repolarization characteristic of myocardial disease.

Biphasic records of single fibers resembling the surface electrocardiogram may be obtained by plotting the rate of rise and fall of the monophasic action potential. The surface action current may be considered the first derivative of the membrane action potential. Generally speaking, the cell potential measured by the technic here used is defined as stored energy (charge). The current flowing over the cell (the surface action current) is a measure of the rate at which the charge is changing. Therefore, a change in the rate of recovery of the
action potential should be roughly proportional to the depth of the R-T junction depression. The peculiar superficial resemblance of the electrocardiogram of severe myocardial disease to that induced by digitalis therapy at a time when cardiac function is usually improved resolves itself nicely when it is considered that the surface electrocardiogram may be altered if (a) the length of the excitatory state is made to differ significantly in various parts of the heart, or if (b) the rate of the repolarization is uniformly shortened throughout the heart. Combined effects are likely to occur, but the over-all length of the excitatory state, the Q-T interval, long in (a), short in (b), may separate one from the other.

**SUMMARY**

1. The changes in membrane resting and action potentials of single cardiac muscle fibers of the frog heart in situ were examined before and after the administration of digitoxin, ouabain, scillaren B, lanatoside C and K-strophantoside. No obvious differences in response were noted for any of the compounds studied.

2. The major effects noted may be summarized as follows: The duration of depolarization is not affected but repolarization is profoundly altered so that the duration of the membrane action potential is markedly shortened. After toxic doses of digitoxin, the record assumes a spike like appearance.

3. The three separate phases of recovery, previously described by us, are altered and the rate of recovery of the three phases is changed in a characteristic manner: the slope of the first phase becomes steeper, that of the second and third flatter. Eventually, the second and third phases disappear and recovery is apparently accomplished by the first phase alone.

4. Recovery may commence before depolarization has been completed and the depolarization deflection appears prematurely arrested (undershoot).

5. These changes are independent of mechanical events. Mechanical movements simultaneously recorded with the membrane action potential remained relatively unchanged in the face of pronounced alterations of the membrane action potential.

6. The steepening of the first phase shows a high correlation \( r = 0.91 \) with the magnitude of the RS-T depression in simultaneously recorded surface electrocardiograms. It is assumed that the uniform shortening of the repolarization process caused by cardiac glycosides results in RS-T segment depression which, except for the Q-T interval, resembles the changes apparently caused by localized lengthening of repolarization characteristic of myocardial disease.

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