Mechanism of S-T Segment Alteration During Acute Myocardial Injury

By Werner E. Samson, M.D., and Allen M. Scher, Ph.D.

Electrocardiographic changes after myocardial injury were first described exactly half a century ago when Eppinger and Rothberger, using an esophageal-rectal lead, noted the "disappearance of the valley between the R and T waves" in dogs which had received injections of 20 per cent silver nitrate solution into the left ventricle. Pardee, in 1920, was the first to note S-T segment changes in a patient with coronary artery disease. The genesis of these electrical changes has since been a subject for disagreement.

First, there is controversy regarding the exact nature of the "S-T segment shift." Since the usual electrocardiographic recorders are capacitor-coupled and will compensate for the introduced injury current, differentiation between an apparent S-T shift caused by baseline changes at rest (T-Q segment) and a true S-T deviation from the iso-electric level caused by changes during activity is impossible. True displacement of either the T-Q or the S-T segment can be observed only when continuous records are taken while the injury is occurring, so that the changes can be related to the previous iso-electric line. Nahum and associates thought that T-Q displacement was the only significant change with myocardial injury, and Donoso et al. have reaffirmed this belief. Eyster et al., Hellerstein and Katz, and Sodi-Pallares, on the other hand, have observed a combination of T-Q and S-T segment changes. In the present experiments, a direct-coupled recorder was used to clarify this point.

A second disputed point is what changes in the heart cells produce the electrical changes associated with myocardial injury. There is little argument that the changes in the electrocardiographic baseline result from alterations in the polarization of the injured regions. The questions that arise are: (1) If there is a true S-T segment shift, is it caused by an observable alteration of myocardial conduction or by a change in the shape of the intracellular action potential in the injured region? (2) If there is T-Q displacement, is partial depolarization of the injured area during electrical diastole (T-Q interval) the source of the "injury current?" Intramyocardial recording was used to determine whether myocardial conduction is indeed altered. To learn if changes in the shape of the intracellular action potential is responsible for the changes seen on injury, measurements were made with intracellular microelectrodes.

Methods

Twenty-two dogs weighing between 9.8 and 17.5 Kg. were anesthetized with intravenously administered pentobarital (36 mg./Kg.) and maintained by artificial respiration. Wide exposure of the heart was obtained by removing the anterior chest wall. The opened pericardial sac, fastened to the margins of the incision, provided a cradle for the heart unless the experiments involved the use of intracellular electrodes. If intracellular recording was to be performed, windows approximately 1 cm. square were cut in the pericardium to prevent excessive drying. Warm physiologic saline or mammalian Ringer's solution was applied to the epicardium throughout the experiment. A ligature which could be tightened or loosened at will was placed around the anterior descending branch of the left coronary artery. It was thus possible to record before, during, and after injury of a portion of the myocardium and to repeat the observations a number of times on a single animal.
ACUTE MYOCARDIAL INJURY

Figure 1

Direct coupled electrocardiogram with the electrode over the area of injury. A. Progressive true S-T followed by T-Q segment changes after the ligature is tightened. Return of tracing towards normal after ligature is released. B. Same as A; however, T-Q changes precede true S-T shift.

In all experiments, electrocardiograms* were recorded with unipolar direct leads, the indifferent electrode being placed beneath the skin of the left lower hind leg. The exploring saline wick electrode, generally located in the center of the injured area, was connected to an Offner direct-coupled amplifier recorder in such a manner that positivity of the exploring electrode caused an upward deflection of the pen.†

Intramyocardial potentials were recorded with multipolar electrodes connected with a 16-channel oscilloscope. The face of this instrument was photographed with a Grass camera. Time pips at 5-msec. intervals were fed simultaneously into all channels from a master oscillator. The electrodes consisted of 15 or 29 fine insulated wires, staggered along a central shaft, with their bare tips exposed at 1 mm. intervals. The electrodes were inserted into the myocardium in most of the areas nourished by the ligated artery. Colored threads identified electrode paths for anatomic-physiologic correlation. A switch permitted taking of unipolar (potential between each terminal and an indifferent surface point) or bipolar (difference between adjacent terminals) records. Bipolar potentials were first related to a fixed time reference potential. This was recorded by the fifteenth oscilloscope usually from the lateral aspect of the right ventricle. Then, by a fixed time correction, they were related to the beginning of the epicardial QRS complex, recorded on the sixteenth oscilloscope. To measure changes in the velocity of depolarization, the time differences between the recorded potentials and the fixed time reference potential were compared before and after ligation.

Intracellular potentials were recorded from the center of the injured area with a Ling-Gerard ultramicroelectrode mounted on a fine (0.001 in.) tungsten wire as described by Woodbury and Brady. An electrometer tube input was utilized with a Sanborn amplifier, and the potentials were recorded by the Offner recorder simultaneously with the electrocardiogram.

Results

Electrocardiographic Changes

Figure 1 shows the most typical electrocardiographic changes produced by tightening a ligature around the anterior descending branch of the left coronary artery. The first change (fig. 1A) is a true elevation of the S-T
Intramyocardial Changes

Figure 2 shows bipolar intramyocardial potentials (difference between adjacent electrode tips 1 mm. apart) before and after coronary artery ligation. Time pips are 5 msec. apart. Electrode path indicated in sketch. A, control; B, four minutes after ligation; C, 40 minutes after ligation. Complexes are arranged vertically with dotted lines projected from control potentials. Complexes falling to left of line indicate earlier depolarization, those to right of line later depolarization. Discussion in text.

Segment starting within 40 seconds after ligation. Some 60 to 80 seconds later the T-Q segment is depressed, and the summation of these changes accounts for the progressive increase in the apparent S-T shifts. Figure 1B shows opposite changes. Here T-Q segment depression precedes the true S-T elevation. This occurs less frequently. The ratio of the magnitude of initial S-T changes to initial T-Q changes in the surface electrocardiogram was approximately 3:2. Both tracings show the return of the S-T and T-Q segments to the iso-electric line after circulation was re-established. The return to normal usually started within 10 seconds after the ligature was released and was complete in some 30 seconds.

Intracellular Potential Changes

Figure 3A1 depicts a normal intracellular action potential from the anterior wall of the left ventricle and a simultaneous electrocardiographic complex. Figure 3A2 shows a record from the same cell 4 minutes after impairment of the blood supply to that region. The electrocardiogram shows true S-T segment elevation. At the same time, the second phase of repolarization (the plateau) of the intracellular action potential is of shorter duration than in the control. In figure 3A3, 2 minutes later, the electrocardiogram shows a T-Q segment shift as well, while the intracellular potential from the same cell reveals a decreased resting potential in addition to the shortened action potential. Figure 3B shows true S-T segment changes associated with a decreased duration of the second phase of repolarization of the intracellular action potential. The decreased voltage during plateau ligation. The myocardium around the electrodes always showed gross ischemic changes after ligation. In figure 2B the configurations of some intramural complexes are altered. The polarity of one complex has reversed, an event indicating a local change in the depolarization pathway. In addition, the voltage of most of the complexes is somewhat reduced. There is no significant conduction delay. Changes such as these were usually seen 2 to 4 minutes after ligation, although the change during the early period of injury varied from experiment to experiment.

When ligation was maintained for longer periods (i.e., more than 15 to 20 minutes), these changes were greater. Figure 2C shows complexes recorded 40 minutes after ligation. Further decrease in voltage and prolongation of the bipolar complex, as well as a change in polarity, were often observed. The conduction delay was not pronounced in any experiment. The average conduction delay 5 minutes after interruption was 1.5 msec. Even as long as 50 minutes after the onset of myocardial ischemia, the average conduction delay was no more than 2 msec. (maximum, 18 msec.). At all times the simultaneous electrocardiogram showed S-T and T-Q segment shifts.
ACUTE MYOCARDIAL INJURY

A. EKG

Intra-cellular potential

1+2 Superimposed

6 Minutes 1+2 Superimposed

8 Minutes 1+3 Superimposed

1,2, + 3 Superimposed

Figure 3

A and B. Intracellular action potential and simultaneous direct coupled electrocardiogram before and after coronary artery ligation. Discussion in text. C. Return of intracellular action potential and EKG towards normal after release of ligature (not continuous record with A or B).
of repolarization occurs sufficiently early to account for the observed S-T segment shift. Electrocardiographic changes were observed whenever the coronary artery was ligated; however, simultaneous intracellular potential changes could not be recorded from all impaled cells. Apparently, acute ischemia does not equally affect the electrical properties of all cells within the injured region. In the 79 instances of initial true S-T segment changes, we were able to record simultaneous shortening of the second phase of repolarization of the intracellular action potential 41 times (51 per cent). Simultaneous action potential changes were also recorded in 22 of the 30 instances (73.4 per cent) where the true S-T changes followed T-Q changes. On 47 occasions, T-Q changes were observed first and in 31 instances (66 per cent), these were associated with a decrease in resting potential. Also, when T-Q changes followed true S-T changes (44 episodes), a simultaneous resting potential decrease could be recorded in 20 instances (45.5 per cent). In order to test the significance of the association of true S-T segment changes with action potential changes, a correlation test was performed on the following data:

- S-T changes with action potential changes ........................................... 63 instances
- S-T changes without action potential changes .............................. 25 instances
- No S-T changes with action potential changes ............................... 1 instance
- No S-T changes without action potential changes ....................... 15 instances

This gives a highly significant $\phi$ value (fourfold point coefficient) of .488.

In testing the significance of the association of T-Q changes with resting potential changes, the same test was carried out using the following:

- T-Q changes with resting potential changes ........................................... 51 instances
- T-Q changes without resting potential changes .............................. 19 instances
- No T-Q changes with resting potential changes ............................... 6 instances
- No T-Q changes without resting potential changes ....................... 30 instances

The $\phi$ value for this is .534.

Finally, a fourfold correlation test was performed on the following data:

- S-T changes with action potential changes ........................................... 63 instances
- S-T changes without action potential changes .............................. 9 instances
- T-Q changes with action potential changes ........................................... 3 instances
- T-Q changes without action potential changes ............................... 51 instances

This gives a highly significant $\phi$ value of .814.

Figure 3C shows the return of the intracellular action potential to normal after release of the ligature around the branch of the coronary artery. The normal configuration of the intracellular potential usually returned within 10 to 30 seconds after re-establishment of the circulation.

Discussion

A common theory regarding the nature of the injury currents is that the injured area is partially or completely depolarized at rest. A boundary would thus exist between the uninjured and the injured part of the cell, with the negative charges facing the injured and the positive charges facing the uninjured area of the cell. A current of injury would flow from the uninjured to the injured part of the cell at rest, the so-called "diastolic current of injury." Electrocardiographically this current would produce a displacement of the isoelectric line at rest, i.e., a T-Q segment shift without S-T segment shift (fig. 4A1). According to this theory, when the entire heart becomes completely depolarized the injury current disappears. As mentioned earlier, this is the hypothesis advanced by Nahum et al. and supported by Donoso et al.

Others have felt that regional depolarization at rest is not the only change accompanying myocardial injury, but that in addition during activity the injured area becomes positive with respect to the adjacent area, changes that have already been observed some 80 years ago by Burdon-Sanderson and Page using the capillary electrometer. In this case, one would also record a shift in the S-T segment (fig. 4A3). This theory finds further support in the work of Eyster and associates.
A. CURRENTLY ACCEPTED THEORIES OF ST SEGMENT PRODUCTION

1. TQ DISPLACEMENT
   - Injured area completely depolarized
   - Baseline
   - Injury deflection

2. TRUE ST DISPLACEMENT
   - Injured area unresponsive to excitation wave
   - Injury deflection

3. COMBINED TQ+ST DISPLACEMENT
   - Injured area partially depolarized
   - Baseline
   - Injury deflection

B. THEORY ON THE BASIS OF EXPERIMENTAL DATA

Figure 4

A. Currently accepted theories of S-T segment production: (1) depolarization of injured area at rest causing T-Q segment displacement; (2) failure of normally polarized injured area to depolarize with activity causing true S-T displacement; (3) combination of (1) and (2).

B. Theory of S-T segment production on basis of presented experimental data. Partial depolarization at rest and earlier repolarization of injured area causing T-Q as well as true S-T displacement.

Pallares,7 Sugarman et al.,12 Hellerstein and Katz,6 Alzamora-Castro et al.,33 and is the one most generally accepted. Hellerstein and Katz6 have also shown that at times only a true S-T segment is recorded. They accept the interpretation that the injured area is normally polarized but fails to depolarize with the rest of the myocardium (fig. 4A2).

In our experiments, the direct-coupled recorder showed that both S-T segment changes and T-Q shifts occurred after ligation of a coronary artery branch.14 When the exploring electrode was on the injured region, the changes were S-T elevation and T-Q depression, usually in that sequence. Our results differ from those of Katcher et al.15 In one instance in which the exploring electrode was inside the left ventricular cavity, reciprocal changes were observed.

The mechanisms underlying the S-T and T-Q segment changes remain to be explained. If failure of the injured area to depolarize...
normally produces the true S-T segment shift, the intramural excitation pattern should be abnormal with a reduced propagation velocity in the injured areas. In the early stages of myocardial injury, i.e., up to approximately 20 minutes after ligation of the artery, conduction was not significantly slowed. The lack of change in velocity soon after ligation has also been observed by Durrer (personal communication); however, Conrad et al. re- cently reported that some points in the wall were depolarized 27 msec later than normally—about 5 minutes after coronary artery occlusion. In our experiments, even after 1 hour the delay in depolarization was minimal (average 2.5 msec.); these findings vary from those of Formijne and Durrer who reported greater delay 30 minutes after ligation. The duration of the S-T segment in the dog is approximately 150 msec. If conduction delay causes the S-T segment shift, the delay must be this long in some of the injured areas. The maximum delay was nowhere of this magnitude, and it would thus seem that the injured area responds nearly normally to the excitation wave.

Since lack of depolarization was not found to account for some S-T segment changes in the early stages of injury, it appeared most reasonable to look for changes in the electrical behavior of the myocardial cells in the injured areas. The most common sequence of alteration of intracellular potentials observed after ligation of a branch of the coronary artery was that reported by Trautwein, who studied the effects of oxygen lack using the papillary muscles of the cat, and by Kardesch et al., who studied complete ischemia in perfused hearts. These results and ours are contrary to what would be predicted from the experiments of Katcher et al. As pointed out in the results, the shortening of the plateau of repolarization coincided with true S-T segment changes and generally with later changes in the resting potential with T-Q changes.

Since the injured area produces nearly normal potentials during depolarization, changes in the S-T segment cannot be ascribed to failure of all cells to depolarize. However, since there was a progressive decrease in the magnitude of bipolar intramyocardial complexes as well as an increase in their duration and some reversals of polarity, failure of some myocardial cells to depolarize cannot be excluded. Even so, the simultaneous electrocardiograms and intracellular recordings show that the true shift in the S-T segment is a manifestation of earlier repolarization of myocardial cells in the injured area. As a result, a potential gradient exists between the injured and uninjured areas during the latter part of electrical systole; current flows from the relatively positive (earlier repolarized) injured to the relatively negative uninjured regions (fig. 4B). An epicardial electrode over the injured area faces an area of positivity, and an S-T elevation is recorded.

The T-Q segment change results from an injury current at rest. The membrane potential is lower in the injured area during electrical diastole. Consequently, current flows from the uninjured to the injured area. An epicardial electrode over the injured area faces a region of negativity during electrical diastole and the electrocardiographic iso-electric line is depressed (T-Q segment shift).

Summary

Electrocardiograms recorded with a direct-coupled amplifier and recordings of intramyocardial and intracellular potentials were used to determine the nature of the S-T segment shift after myocardial injury. Immediately after coronary artery ligation in the dog, both true S-T and T-Q changes are produced. Lack of responsiveness to the activation wave in the injured area does not account for the initial change in the S-T segment. Changes in the intracellular action potential can be correlated with the electrocardiographic changes. Immediately after injury, cells in the injured area usually repolarize more rapidly than normal cells and this change is significantly correlated with S-T segment shifts. A decrease in resting potential, generally occurring later
ACUTE MYOCARDIAL INJURY

than the action potential changes, is similarly correlated with T-Q segment changes.

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References

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WERNER E. SAMSON and ALLEN M. SCHER

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