ST-Segment Potentials and Mapping

Theory and Experiments

"You cannot believe in [electrophysiological] observations before they are confirmed by theory."

A. S. Eddington

As medical science has grown more complex in the last few decades, we have often found ourselves depending on experimental tools that are beyond our individual abilities to understand. A danger in our use of these tools is that through oversimplification we misinterpret the meaning of the results they give. ST-segment mapping is such a tool. Increasingly, experimental and clinical studies are made that depend on ST-segment changes as a monitor of potentially irreversible ischemic injury to heart muscle. However, there are major conceptual questions as to the independent reliability of ST-segment deviation as a measure of ischemia. It would be dangerous to accept a correlation between ST-segment changes and ischemia under particular experimental conditions in animals as proof that the technique is reliable under clinical circumstances.

A large body of electrophysiological knowledge has been gathered over many decades, and it is appropriate to consider if the use of ST-segment measurement for sizing of ischemic regions is consistent with this electrophysiological theory. We would like to emphasize that this electrophysiological theory of the origin of the ECG is not a "flight of fancy" by one individual, an improper use of the word theory, but it is the intellectual framework that has developed over decades through the work of hundreds of investigators.

This editorial draws from this theory to interpret ST-segment potentials and to identify the sorts of problems that we can expect to encounter with ST mapping. Specifically, we can argue that the ST segments are dependent on the shape and location of the ischemic area within the ventricular wall in relation to location of the electrodes. Under some circumstances ischemia could become more severe or more extensive with no change in ST-segments or with a return toward the isoelectric level. Since the ST-segment level is determined by interaction between the normal area and the ischemic area, interventions that alter resting or action potentials in the normal muscle could either accentuate or reduce ST-segment elevation without altering the size or intensity of ischemia. Therefore we conclude that ST-segment mapping should be considered a reliable tool only in a controlled laboratory environment. Its use to guide the physician in patient care is premature and is likely to be misleading.

Origin of the Cardiac Electrogram

As pointed out by Schaefer and Haas, study of the ECG is simultaneously highly theoretic and relatively straightforward. It is theoretic, in that we do not know the exact potential change of each cell in time or space, nor can we predict exactly the electric fields generated by potential differences in the heart from recordings at the body surface because of the complex and variable anatomy of the thorax. Considerable inference is therefore required in explaining extracardiac recordings. It is straightforward, in that we know the appropriate laws of electricity. No new concepts of physics or physiology are needed to understand the ECG. The justification for study of the ECG lies entirely in its clinical value.

The generator responsible for cardiac electricity is the membrane ion pump of the cardiac cell membrane. The cell membrane separates ions so that they are not distributed in an equilibrium fashion. The role of ionic gradients, along with changes in membrane conductances, in generating the cardiac action potential is widely appreciated by cardiac scientists and cardiologists (e.g., reference 2), and further discussion of this is not required. Further, each cell is normally connected electrically to other cardiac cells through gap junctions, so that its electrical behavior is closely coupled to that of its neighbors. Given time, a neighborhood of cells will tend toward the same potential by current flow through the junctions. The resting potential is uniform in normal ventricular cells, so that no potential gradients exist during the T-Q period. The action potential is propagated by current flow between cells, and this current generates the QRS. The ST-segment is usually isoelectric because the ventricular cells come to nearly the same depolarized potential, and current does not flow (fig. 1). As some areas repolarize before others, current again flows between cells to produce the T wave.

At the cellular level the repolarization process includes the action potential plateau and the more rapid later phase, so that the ST period and the T wave are reflections of different parts of the same repolarization process. Factors controlling the membrane events during repolarization are multiple and complex, including not only sodium and potassium currents, but also probably calcium and chloride currents, each with their dependencies on voltage, time, and temperature. It is widely appreciated that the T wave can be altered by a great number of normal and pathologic conditions such as changes in ion concentrations, temperature, heart rate, and autonomic activity. Indeed, almost every change in environmental condition may alter the T wave, so that it is surprising that any useful clinical information can be obtained from it. ST-segment changes have more precise clinical interpretations, but the origin of these ST changes is less widely understood.

The ST Segment

Normally, all of ventricular muscle depolarizes to about the same level during the plateau phase of the action potential. If an abnormal area of heart muscle repolarizes more quickly than normal, or does not depolarize at all because it

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*This quotation of Prof. A. S. Eddington was obtained from an article by S. Chandrasekhar (Nature 252: 15, 1974), and modified from "astronomical" observations to "electrophysiological" ones.
is inexcitable, then the interior becomes negative relative to adjacent normal muscle (fig. 2). Consequently, current would flow between the normal depolarized area and the abnormal polarized area, as long as the cells remain electrically coupled. The convention for describing current flow is to give it the direction that positive charges would move. Therefore, current is described as flowing intracellularly from the normal area to the abnormally polarized area through the gap junctions. The electrical circuit would be completed by current flow in the opposite direction in the extracellular space. A unipolar electrode (where potential is compared to a reference electrode that is uninfluenced by the cardiac electromotive force) would record positivity or negativity during the ST period, depending on whether it was closer to the polarized area or to the depolarized area (fig. 3). This is consistent with the clinical description of ST depression as a reflection of endocardial injury and ST elevation of epicardial injury. After the muscle repolarizes to its resting level, the current flow would cease, but only if both areas had the same resting potential.

If the abnormal area was depolarized in the resting state, current would continue to flow during this time. Such
depolarization could be the result of a fall in intracellular K or an increase in extracellular K, of arrest of an electrogenic Na pump, or of a change in resting membrane permeability. (Most evidence points to extracellular K accumulation as the factor of importance immediately after occlusion of a coronary artery.) With the abnormal area depolarized, current would flow from it to the normal relatively polarized area, opposite in direction to the current flow during the action potential (fig. 2). This current would produce deviation of the T-Q segment opposite to that of the ST segment. Since clinical electrocardiograms are obtained using a-c amplifiers, absolute zero potential cannot be determined, and what is usually called ST-segment deviation is actually the potential difference between the T-Q period and the ST period. In this discussion we refer to the TQ-ST difference as ST deviation for simplicity. The important physiological differences between local depolarization of the resting potential (true TQ deviation) and abnormal local repolarization (true ST deviation) should be clearly recognized, but we choose not to discuss them further in this editorial.

Realization of the origin of these “currents of injury” perhaps began with observations of Burdon-Sanderson and Page in 1879, supported by work of Eyster et al.6 in 1938. A review of this field leads to the work of almost every electrophysiologist and electrocardiographer of the last century (e.g. see Katz et al., reference 7). Direct recording of the appropriate cellular potential differences was finally made by Samson and Scher6 in 1960, after capillary microprobes became available for intracellular potential recording. They showed that shifts of the ST and T-Q segments were correlated with depolarization of the resting potentials and shortening of the action potentials in an ischemic region. Their work has been confirmed and extended by Prinzmetal et al.9 and others, and no effective challenges to their view have emerged in the subsequent 15 years. It was recently reinforced by measurements of d-c magnetic fields in experimental myocardial infarction,10 a valuable observation because magnetic field recording is subject to quite different sources of error from those associated with the ECG.

Inferences from the Physiologic Mechanisms of ST-T Changes

From this discussion of the origin of ST-segment potentials we can extract two important principles that help us to interpret ST-segment maps.

**Principle 1.** The current flow that causes ST-segment and T-Q-segment changes results from a potential difference at the boundary between normal muscle and an adjacent abnormal region, where resting and/or action potentials are different.

**Corollary 1A.** If the normal and abnormal areas become disconnected from each other (by disruption of the gap junctions between cells), the current will be abolished, even if cells in the abnormal area remain alive. This might occur during the “evolution” of an acute myocardial infarction, with the healthy cells disconnecting from the ischemic ones. The ability of heart cells to “heal over” after direct injury was recognized in 187711; it is a rather poorly understood phenomenon, which probably results from a change in the cellular Ca concentration.12, 13 This “healing over” may be the mechanism of ST-segment decline with time, indicating progression of the injury rather than its reduction. Substantial reduction in ST-segment elevation in patients over the first 24 hours following acute myocardial infarction has been reported by Madias et al.14 as part of the natural history of myocardial infarction. Consequently, in clinical studies one must wonder if an intervention has influenced the ST segment or if it has followed its natural history.

**Corollary 1B.** If a local lead (epicardial unipolar recording) is positioned over the abnormal area at a far distance from the normal tissue, current density in the vicinity of the electrode will be reduced and its deflection will be less than that of an electrode near the junction between the two areas. This may be the mechanism of normalization of the ST segment in an epicardial electrode overlying the center of a large infarct, reported by Kirk,15 Muller et al.,16 and Holland and Brooks.17 Consequently, mapping is useful in locating the approximate boundaries of the injured area rather than in estimating the magnitude of the injury.

**Corollary 1C.** Since the potential recorded by any given ECG lead is determined by the sum of currents from all contributing areas, cancellation may occur. For example, if endocardial injury lowers the ST segment, extension to the epicardial region can bring it to normal or raise it. If epicardial injury raises it, adjacent increased endocardial injury can normalize the ST segment. An ischemic region completely surrounded by normal tissue on all sides (buried within the wall) could be effectively silent, the vector sum of all currents being zero. Experimentally this requires consideration of the behavior of collateral coronary circulation (which varies with species), since that plays a large role in the location of the ischemia within the ventricular wall. One must wonder if ST-segment changes seen in the clinical setting can properly reflect the extent of damage in the middle and endocardial regions.

**Corollary 1D.** The farther an electrode is located from the boundary between the normal and abnormal tissue, the smaller the potential and the harder it is to distinguish changes. This summarizes the problem of **precordial** ST mapping.18 The problem is not only one of distance, but also of the inhomogeneous conducting medium between the heart and the body surface. Both factors combine to make mapping less applicable to inferior infarctions, and more difficult to interpret when precordial ST-segment changes are small.

**Principle 2.** Any factor altering the resting potential or the repolarization of heart cells can alter current flow between normal and abnormal areas.

**Corollary 2A.** An abnormal sequence of depolarization results in an abnormal sequence of repolarization, as seen in bundle branch block. If the conduction pathway is changed for any reason in the abnormal area or in the adjacent normal muscle, both the QRS and the ST segment will be altered.18, 19 This QRS change may itself be a useful indicator of
ischemic injury, but it interferes with ST-segment mapping in many patients.

Corollary 2B. Interventions that modify the resting or action potentials of the abnormal area would change current flow, and this could be completely independent of oxygen balance. Since depolarization of the resting potential and shortening of the action potential are largely due to $K^+$ accumulation extracellularly, we would expect that if the hypoxic region of muscle were perfused with solutions normal in $K^+$, the ST elevation might return to normal. This prediction was confirmed experimentally by Prinzmetal et al. The nature of drug and hormone actions on ischemic muscle is almost entirely unexplored, but there are clues that they may well be different from effects on normal tissue. An example of this sort of effect is influence of insulin on $K^+$ efflux, so that an intervention may alter electrical events without altering coronary flow or metabolism of the ischemic region.

Corollary 2C. Interventions that affect the normal tissue would change current flow. For example, increased extracellular $K$ in the normal area would depolarize it, shorten its action potential, and minimize the potential differences between it and an ischemic region. This has recently been shown experimentally by Holland and Brooks. Changes in heart rate might have similar effects because the dependence of action potential duration on rate. Once again, interventions may change electrical properties without modifying ischemia.

Reflections on These Criticisms

The cautions implied by the discussion above should not be accepted as proof that ST mapping is invalid as a tool to monitor ischemia and to predict cell death. Under the specific laboratory conditions used by Maroko and his associates, there has been good correlation between the area projecting epicardial ST changes and subsequent depletion of CPK enzyme and histologic evidence of cell death in the dog. Polarographic monitoring of local oxygen tensions shows a geographic correlation with overlying ST changes during coronary occlusion. Finally, the cumulative clinical experience of 55 years (since Pardee's original description) also shows rough correlation of severity of acute myocardial infarction with ST changes.

Even if normalization of electrical changes does not necessarily mean improved blood flow or reduced oxygen demand in an ischemic region, the patient may still have been helped. We remain ignorant of the biological process at the "point of no return," after which the cell eventually dies. Factors that alter pH, stabilize lysosomes, etc., may prove to be useful to the patient, regardless of their effects on the ST segments in the overlying electrogram.

Agents that promote electrical uncoupling of cells, or that make the action potentials of the normal or ischemic areas more alike, might reduce the current responsible for ST deviation, and might be beneficial to the patient in a fashion that is independent of death or survival of a single cell. The currents generating the ST segment changes may be the basis for producing arrhythmias that could compromise cardiac function or kill the patient, and interruption of these currents could help the patient, regardless of infarct size. If cell death is related to diffusible particles in the cytoplasm such as $H^+$ ion, these particles could invade an otherwise salvageable cell via gap junctions and propagate cell death. Therefore, pharmacological agents that promote uncoupling of the cells could thereby be of direct benefit in protecting cells that are in the environs of death.

Treatment to Reduce Infarct Size — A Double-Edged Sword

If treatments carried no risk of potential harm, then interventions could be made in acute myocardial infarction on the basis of inferential evidence. However, most of the therapeutic measures that have promise of significant reduction in infarct size are also capable of significant harm. An example of this is modification of arterial blood pressure. We are aware that experimental studies indicate that lowering of blood pressure, and consequent lowering of coronary perfusion pressure in diastole, increases the sum of ST-segment elevations and the number of leads with ST elevation and presumably indicates increase in infarct size. As such, reduction of mean arterial blood pressure may be considered to be detrimental to a clinician's effort to preserve myocardial mechanical function and pump integrity. However, in clinical practice and from evidence accumulating in the literature, it is evident that reducing the afterload in certain situations after acute myocardial ischemia may actually improve cardiac output and allow the heart to function better, relieving intracavitary pressure and wall tension. Even normotensive patients with acute left ventricular dysfunction may be improved by vasodilator therapy through reduction of the afterload, reducing the work of the injured heart. Here the clinician may well choose to settle for a somewhat diminished mean arterial blood pressure and welcome the benefits of vasodilator therapy for their overall contributions to the patient's welfare, even if experimental studies with ST-segment mapping are difficult to interpret.

We would like to emphasize that such clinical observations do not invalidate experimental data demonstrating that diminished mean aortic pressure can reduce coronary flow. Our endeavor is to bring into focus the dilemma a clinician may face in making critical therapeutic decisions on the basis of insufficient information.

From a review of the theoretical and experimental bases for ST-segment deviation, we suggest that ST-segment mapping is not a reliable measure of myocardial ischemia. It may be misleading as an indicator of response to treatment, and its use in clinical care at this time is unwise.

Conclusions

There are perhaps several points worth remembering from this discussion.

1) The physiological mechanism of ST-segment deviation is complex, but the laws of electricity and electrophysiological theory permit some understanding of the underlying cellular events. The value of understanding the basic mechanism in interpreting ST-segment mapping and other clinical measurements should not be underestimated.

2) No exact correlation of ST-segment change with ischemia should be expected, because the mechanisms in-
volve interaction between normal and abnormal tissue. Any factor influencing membrane properties in either area will alter the ST segments, regardless of its influence on ischemia.

3) Consequently, inferences from the extent or magnitude of ST changes overlying an area of ischemia may be misleading and ST-segment mapping should not be used as an independent measure of ischemia.

4) Since ST-segment deviation indicates abnormal current flow in the heart, it may be an important factor for other reasons, for example, in producing lethal arrhythmias. We feel that further studies of this possibility may be helpful in understanding or treating these important complications of ischemia.

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