Source of Electrocardiographic ST Changes in Subendocardial Ischemia

Danshi Li, Chuan Yong Li, Ah Chot Yong, David Kilpatrick

Abstract—To clarify the source of electrocardiographic ST depression associated with ischemia, a sheep model of subendocardial ischemia was developed in which simultaneous epicardial and endocardial ST potentials were mapped, and a computer model using the bidomain technique was developed to explain the results. To produce ischemia in different territories of the myocardium in the same animal, the left anterior descending coronary artery and left circumflex coronary artery were partially constricted in sequence. Results from 36 sheep and the computer simulation are reported. The distributions of epicardial potentials from either ischemic source were very similar ($r=0.77\pm0.14$, $P<0.0001$), with both showing ST depression on the free wall of the left ventricle and no association between the ST depression and the ischemic region. However, endocardial potentials showed that ST elevation was directly associated with the region of reduced blood flow. Insulating the heart from the surrounding tissue with plastic increased the magnitude of epicardial ST potentials, which was consistent with an intramyocardial source. Increasing the percent stenosis of a coronary artery increased epicardial ST depression at the lateral boundary and resulted in ST elevation starting from the ischemic center as ischemia became transmural. Computer simulation using the bidomain model reproduced the epicardial ST patterns and suggested that the ST depression was generated at the lateral boundary between ischemic and normal territories. ST depression on the epicardium reflected the position of this lateral boundary. The boundaries of ischemic territories are shared, and only those appearing on the free wall contribute to external ST potential fields. These effects explain why body surface ST depression does not localize cardiac ischemia in humans. (Circ Res. 1998;82;957-970.)

Key Words: ST depression, potential mapping, bidomain model, subendocardial ischemia, regional myocardial blood flow.

Electrocardiographic ST-segment depression has long been recognized as a sign of ischemia, but the explanations of the responsible mechanisms have been controversial. Much of the current opinion regarding the genesis of ST-segment depression is derived from interpretations based on certain theoretical considerations and indirect evidence from animal experiments. Ischemic muscle generates intracellular currents, which effectively cause TQ depression and ST elevation over the ischemic area and which conventional electrocardiography with AC-coupled amplifiers reflects as ST elevation. ST-segment depression recorded at the epicardium has been considered to be secondary to an injury current in the underlying subendocardium.

In conventional stress testing, as myocardial demand exceeds the ability of the narrowed coronary arterial bed to increase blood flow, the ischemic threshold is exceeded, and reversible ST-segment depression is produced. However, the location of this ST depression does not enable us to localize the ischemic region. The difficulty in localizing myocardial ischemia from ST depression cannot be explained by the classic theories, which all suggest that ST depression should provide the means for localizing ischemia. Studies of computer-derived epicardial maps in patients with inferior infarction and patients having ST depression without infarction have hypothesized that ST depression on the ECG originates from current flow from a region of endocardial ischemia and progresses back to the outside of the heart through the great vessels and atria. To test this hypothesis, we measured the epicardial and endocardial potential distributions in the in vivo sheep heart after generating regional subendocardial ischemia, which was confirmed by fluorescent microspheres. A computer bidomain model was developed to explain the experimental results.

Materials and Methods

Experimental Studies

Experimental Animals
A total of 36 Polworth/Comeback cross sheep (30 to 45 kg) of both sexes were used in this study. Table 1 shows the groups of animals subjected to different experimental procedures.

Group 1: Control
In group 1 (control, $n=5$), the epicardial ST potential fields were recorded before and during pacing at a rate of 120, 140, 160, 180,
Group 2: Partial Occlusion of Either LCX or LAD in Different Animals With Interventions

In group 2, either the LAD or the LCX was partial occluded (LAD occlusion, n=3; LCX occlusion, n=14). The epicardial ST potential distributions were recorded before and after 2, 5, 10, 15, and 20 minutes of ischemia. The endocardial electrograms were simultaneously recorded by a quadripolar electrode catheter. The following tests were performed to investigate the nature of the ischemic source after the production of subendocardial ischemia:

(1) Insulating the Heart From Surrounding Tissues (n=8). A thin plastic bag was placed onto the heart, covering the right and left ventricles and portions of both atria, to insulate the heart from the surrounding tissues during ischemia. The epicardial ST potential changes were recorded. The insulator was quickly removed, and the potentials were again recorded and compared with those during insulation. The time difference between the two recordings was ~10 seconds.

(2) Transforming Subendocardial Ischemia to Full-Thickness Ischemia (n=5). The percent stenosis of a coronary artery was increased by fully inflating the hydraulic occluder at 10 to 15 minutes of partial coronary occlusion to transform the subendocardial ischemia to full-thickness ischemia. In 2 animals, the potential changes were recorded before and 2, 30, 60, 90, and 120 seconds after the transition. In another 3 animals, the potential changes during the transition were recorded continuously for a period of 30 seconds (n=2) and 50 seconds (n=1).

Group 3: Alternate LAD and LCX Partial Occlusion in the Same Animal

In group 3 (n=6), posterior subendocardial ischemia and anterior subendocardial ischemia were produced in the same animal by alternate partial occlusion of the LAD and the LCX plus pacing. Each partial occlusion lasted for 20 minutes, followed by 30 minutes of rest before the next partial occlusion (the flow and pressure returned to the control level after 30 minutes of rest). The epicardial potential maps were constructed, and the epicardial potential distributions between these two types of ischemia were compared.

<table>
<thead>
<tr>
<th>TABLE 1. Animal Groups and Treatments</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>-------</td>
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<tr>
<td>1</td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
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</table>

Group 4: Epicardial and Endocardial Potential Mapping in Relation to RMBF

In group 4 (n=8), the subendocardial ischemia production was similar to that in group 3; ie, there was alternate LAD and LCX occlusion in the same animal. Both the epicardial and the endocardial ST potentials were then recorded and compared. The RMBF was measured before and during ischemia, and the flow maps were constructed.

Surgical Procedures

Anesthesia was induced intravenously with sodium pentobarbital (30 mg/kg) and then maintained at 3 to 8 mg/kg per hour throughout the experiment. The animals were artificially ventilated at a rate of 18 to 20 breaths/min with room air. The animals were heparinized before instrumentation. A left thoracotomy was performed in the fourth intercostal space, and the heart was suspended in a pericardial cradle. The left ventricular pressure was measured by a 7F side-hole catheter introduced into the left ventricular cavity retrogradely from a femoral artery approach. The LCX and the LAD were each isolated proximally near their origin for the electromagnetic flow transducer (NARCO, Carolina Medical Inc) for blood flow measurement and, again, 10 to 20 mm distally for the hydraulic occluder (In Vivo Metric) for inducing arterial stenosis. Another cannula (PE-90) was inserted through the left atrial appendage into the left atrium for microsphere injection. Two pacing wires were sutured to the left atrial appendage for left atrial pacing.

Subendocardial Ischemia

The subendocardial ischemic sheep model, combining pacing with partial occlusion of an artery, was previously validated in our laboratory by fluorescent microspheres. The percent stenosis was achieved by inflating the hydraulic occluder, causing a reduction in flow to ~50% of the control level, and then the left atrium was paced by a stimulator (SRI, Scientific and Research Instruments Ltd). The pacing started with a rate of 120 bpm and increased gradually by 10 bpm every 2 minutes until it reached 180 bpm.

Perfusion Beds and RMBF Measurement

RMBF was measured before ischemia and at 20 minutes of ischemia by using fluorescent microspheres (Molecular Probes, Inc) as previously described. The fluorescent microsphere suspension was mixed with 10 mL of warm blood, and the mixture was administered over 10 seconds via the implanted left atrial cannula. The cannula was then flushed with 10 mL of saline. The reference flow was established using an in-line electromagnetic flow transducer. After completion of the experiment, 10 mL of 0.1% methylene blue dye (Sigma) was injected into the LAD, and 10 mL of normal saline was simultaneously injected into the LCX to delineate the nonischemic and the ischemic areas, depending on which coronary artery was stenosed. These data were used to support the measurement of regional myocardial blood flow as displayed in Figures 2 and 5. The ischemic boundary was expected to be well defined in the absence of functionally significant collateral blood vessels. The left ventricle was divided into three to five circumferential rings from the base to the apex. The circumferential rings were then cut into sections of epicardial arc (length, 12 mm per piece). Sections of the myocardium were divided into endocardial, middle, and epicardial thirds. The anatomic location of each myocardial piece was recorded on the tracing of the left ventricle wall and related to the positions of the electrodes, so that potential and flow mapping could be made (see below). The dimensions of each piece were roughly 12×10×3 mm³. The LCX- and the LAD-supplied areas were cut into 30 pieces on average. The average weight of each piece was 1.1 g (0.5 to 1.5 g). Each sample was placed into a screw-cap polystyrene tube to which 2 mL of 4 mol/L KOH was added, and the tube was placed in a 37°C water bath for 12 hours. After digestion, 3 mL of ethyl acetate was added, and the tube was vortexed for 1 minute and then centrifuged for 2 minutes at 2500 rpm. The upper layer of solvent was transferred to a quartz cuvette, where fluorescence intensity was read at the appropriate wavelengths by a Perkin-Elmer 650-10S fluorescence spectrophotometer (Hitachi Ltd).
RMBF in each sample was expressed both in absolute terms (as milliliters per minute per gram of myocardium) and in relative terms (as a percentage of the control flow obtained before ischemia). The endo/epi flow ratio was obtained by dividing the flow to the endocardial third by the flow to the epicardial third. After the flow for each sample was calculated, maps of the left ventricular blood flow were constructed from both the absolute flow and the relative flow. The flow maps were combined with the endocardial contour potential maps.

**Epicardial and Endocardial Potential Recording**

The epicardial potentials were recorded using an epicardial sock containing 64 electrodes (Cardiovascular Research and Training Institute, University of Utah, Salt Lake City). Each electrode was constructed of fine silver wire mounted in a nylon sock. The arrangement of the 64 electrodes provided extensive coverage of the epicardial surface of the left and right ventricles (Figure 1). Endocardial electrograms were recorded using a home-made 40-electrode basket mapping apparatus. The apparatus was oval-shaped and constructed with spring steel wire (diameter, 0.25 mm) as the skeleton and polyethylene tube (outer diameter, 1.27 mm) as the outer covering, on which 40 silver electrodes were mounted. The steel skeleton consisted of eight arms. Each arm was insulated with a polyethylene tube and mounted with five unipolar silver electrodes (0.15\(\times\)4 mm). To avoid injury current, the electrodes were mounted on the inside of the cage in such a manner that they were not in direct contact with the endocardium. The eight arms were at equal distance and were connected to each other at both ends, so that when the apparatus was expanded, a uniform distribution of electrodes resulted. Two arms were marked with different colors for orientation. The apparatus was 50 mm long and 32 mm across when fully opened. Placement of the apparatus was accomplished by using thin-wall tubing (inserter) with an outer diameter of 8 mm via the apex. The closed apparatus was placed inside the inserter, and a left apical ventriculotomy of \(\sim 10\) mm was performed. The inserter was introduced into the apex, and the apparatus was placed into the left ventricle while the inserter was withdrawn. The apparatus was secured by a purse-string suture around the point of insertion. The time for positioning the apparatus was a matter of seconds. Once inside the left ventricle, the apparatus deploys, placing the eight arms into position, with each maintaining constant contact with the endocardium. The electrodes were not in direct contact with the endocardium, but they detected the potential changes from the nearest endocardium. At the end of each experiment, the sheep was killed, and the heart was opened to verify the positions of the electrodes. The electrode positions corresponded to the tissue samples subsequently taken for measurement of RMBF, so that the ST-segment changes after coronary artery occlusion could be correlated with the blood flow of each sample. From the postmortem examination, the distance between the electrodes and the endocardium ranged from 1.3 to 3.0 mm.

Initial experiments comparing the noncontact electrodes with contact electrodes showed barely detectable differences in QRS amplitude between the two but no ST-segment shifts in the noncontact electrodes. From the computed intracavity potential fields, one would expect the only significant change over 3 mm to occur at the boundary where a powerful dipole exists. The apparatus enabled the authors to record the signal from a working heart and to map the whole endocardial surface at one time, although at a moderate spatial resolution. The apparatus removes the difficulties of conventional methods and makes it possible to record the potential while ischemia has been induced with the heart in situ.

Hemodynamic measurements of LV pressure and heart rate in our experiments confirmed that the insertion of the 40-pole intracavity...
electrodes into the left ventricle did not cause significant hemodynamic deterioration (Table 2). The electrodes did not provoke arrhythmias or injury currents, and they remained in their positions throughout the experiments. The quality of all unipolar electrical signals remained satisfactory.

The potentials were sampled simultaneously at 1000 samples per second per channel by a 128-channel data acquisition system directly onto computer memory through an S110W (Engineering Design Team, Inc.) interface to a portable computer based on Shug (BriteLite RDI Computer Corp). All data were recorded with a 12-bit and a bandwidth of 0.1 to 500 Hz. Individual gains could be set for each channel, but for these experiments the gain was the same for all channels. All the potentials were recorded in reference to the left leg. An instant display of the sampled ECG signals enabled a check on the quality of the data. During data acquisition, the opening in the chest wall was covered by moisturized warm saline pads not touching the myocardium. To avoid the interference of injury currents, we obtained recordings at least 20 minutes after setting up, when the ST-T shifts had disappeared almost completely.

**Construction of Isopotential Maps and Map Display**

At the termination of each experiment, the sheep was killed, and the heart carefully removed from the chest cavity. After marking the epicardial electrode position with mapping pins, the heart was opened, and the endocardial electrode positions were verified and marked. The electrode positions corresponded to the tissue samples subsequently taken for measurement of RMBF, so that the ST-segment changes after the coronary artery occlusion could be correlated with the blood flow of each sample. By making an incision from the posterior edge to the apex, the ventricles could be opened flat (for epicardial mapping, the incision was made from the middle of the septum). The electrode positions, the epicardial vascular patterns, and the outlines of the ventricles were traced on transparent plastic and transferred to paper, where the coordinates of the whole picture were measured and reconstructed using our own statistical package. The picture was then combined with the ST potential contour map to give either an epicardial or an endocardial potential map as illustrated in Figure 1. For each sheep, detailed epicardial maps were built from both the left and right ventricular potentials. In 8 sheep, detailed endocardial maps were constructed from the endocardial potentials of the left ventricle recorded at 20 minutes of ischemia. The endocardial potential maps were then combined with the flow maps constructed from the simultaneously measured RMBF.

The electrograms were plotted, and their quality was evaluated. Missing or poor electrograms were discarded, with between 3% and 10% (average, 6%) being discarded as bad leads. These bad leads were picked out and replaced by interpolation from the surrounding leads. The onset of the QRS complex was chosen manually from the electrograms. The potentials were sampled simultaneously at 1000 samples per second per channel by a 128-channel data acquisition system directly onto computer memory through an S110W (Engineering Design Team, Inc.) interface to a portable computer based on Shug (BriteLite RDI Computer Corp). All data were recorded with a 12-bit and a bandwidth of 0.1 to 500 Hz. Individual gains could be set for each channel, but for these experiments the gain was the same for all channels. All the potentials were recorded in reference to the left leg. An instant display of the sampled ECG signals enabled a check on the quality of the data. During data acquisition, the opening in the chest wall was covered by moisturized warm saline pads not touching the myocardium. To avoid the interference of injury currents, we obtained recordings at least 20 minutes after setting up, when the ST-T shifts had disappeared almost completely.

**TABLE 2. Hemodynamic Responses to Pacing, Endocardial Electrodes, and Ischemia**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=5)</th>
<th>Pace (n=5)</th>
<th>Control 1 (n=31)</th>
<th>Control 2 (n=8)</th>
<th>Ischemia (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSP, mm Hg</td>
<td>85±9</td>
<td>89±8</td>
<td>86±10</td>
<td>85±15</td>
<td>74±11*</td>
</tr>
<tr>
<td>LVPD, mm Hg</td>
<td>2±1</td>
<td>3±1</td>
<td>2±2</td>
<td>3±3</td>
<td>5±2*</td>
</tr>
<tr>
<td>LAP, mm Hg</td>
<td>1±2</td>
<td>3±4</td>
<td>1±1</td>
<td>2±2</td>
<td>6±3*</td>
</tr>
<tr>
<td>LCX flow, mL/min</td>
<td>34±6</td>
<td>41±7†</td>
<td>35±5</td>
<td>34±8</td>
<td>20±4†</td>
</tr>
</tbody>
</table>

Control 1 indicates before ischemia without endocardial electrodes; control 2, before ischemia with endocardial electrodes; LVSP, left ventricular systolic pressure; LVPD, left ventricular diastolic pressure; LAP, mean left atrial pressure; and LCX flow, flow to left circumflex coronary artery by EM flow probe. Values are mean±SD.

*P<0.05 and †P<0.01 vs control.

Data Analysis and Statistics

Left ventricular pressure, left atrial pressure, and coronary flows were recorded on a multichannel recorder (Grass Instrument Co); they were also recorded by a Macintosh H II computer via an analog-to-digital converter (NB-DMA-8 and NI-488 for Mac-SN 3643 and Labview software, National Instruments Corp) at a sampling rate of 100 Hz. All data points were averaged over at least 40 cardiac cycles and were processed by a SUN workstation (SUN Microsystems, Inc).

Results were expressed as mean±SD. Hemodynamic data were analyzed by two-tailed Student paired t test with the 0.05 level of probability considered as being significant. The correlation coefficient (r) was used to analyze the similarity between two potential distributions. In all correlations, the recorded signals were used without interpolation, and it was assumed that the electrode arrays had not shifted throughout the procedure. Epicardial and endocardial arrays were tested separately. The resulting correlation coefficient is between −1 and 1, with the correlation coefficient approaching 1 if the data sets are identically shaped and a zero correlation coefficient if there is no association between the two data sets. This technique has been used previously for analyzing body surface map data.

Computer Simulations

Endocardial and epicardial potentials were simulated in a bidomain model of an isolated heart. The ischemic region was constructed from the measurements of RMBF during observed subendocardial ischemia.

**Bidomain Model and the Source**

The myocardium was represented by the bidomain model, in which intracellular and extracellular volumes occupy the same space and were separated everywhere by the membrane. According to previous studies, the intracellular potential (Φ) and the extracellular potential (Φ) are governed by the following equations:

(1) \( \nabla \cdot \sigma \nabla \Phi_i = -\nabla \cdot \sigma_i \nabla \Phi_m \)

(2) \( \nabla \cdot \sigma \nabla \Phi_e = -\nabla \cdot \sigma_i \nabla \Phi_m \)

where \( \sigma = \sigma_i + \sigma_e \) is the bulk conductivity of the heart muscle, and the subscripts i and e represent the intracellular and extracellular space, respectively. Both spaces are coupled through the transmembrane current, where outflow from one region must be equal to inflow to the other. \( \Phi_m \) indicates transmembrane potential. Equation 2 is the governing equation for the extracellular potentials. It includes two major components: the bioelectric source \( -\nabla \cdot \sigma_i \nabla \Phi_m \), which is a volume current density \( (A/m^2) \), and the volume conductor, which usually has several compartments with distinct conductivities (\( \sigma \)).

The ST segment corresponds to the plateau phase of the action potential. In the normal ECG, the ST segment remains isoelectric because of the zero source (no spatial gradient). When ischemia occurs, the transmembrane potential of injury cells changes, produc-
Subendocardial ischemia from two different arterial territories was induced by occluding either the LAD or the LCX, and the ischemic regions shared the same lateral ischemic boundaries (perpendicular to the epicardium). The lateral boundaries were defined by the transmural boundary (parallel to the epicardium) and the lateral supplied by the involved artery, the ischemic boundaries included the endocardial area and that supplied by the involved artery, respectively. Since the ischemic region incorporated only the endocardial area (from 1.19±0.28 to 1.12±0.17 mL·g⁻¹·min⁻¹, *P<0.05 vs control) and the ischemic boundary to normal cells remains at 10 mV, 9,30 in our model in which ischemic cells were defined as cells with intracellular potentials less than 10 mV for ischemic cells and between 10 and 30 mV for normal cells, and the potential changed linearly from 30 to 100 mV for myocardial cells in the transition zone. Since the transmembrane potential (during plateau phase) is reduced to 0.175 S/m; the myocardial bulk conductivity, \( s_2 \), was calculated from the width of the boundary, the given conductivity, \( s_1 \), and blood conductivity was 0.67 S/m.²⁸

**Action Potentials**

We simulated only the true ST-segment shift for which the reduction of transmembrane potentials during plateau phase is responsible. According to our experimental measurements of the RMBF, we assumed that the epicardial layer of the “ischemic” region is normal tissue, the middle layer is transition zone, and the endocardial layer is the ischemic zone. Since the transmembrane potential (during plateau phase) in early transmural ischemia is reduced to −40 mV while the normal cells remain at −10 mV,²⁸,³⁰ in our model in which ischemia was less severe, we assumed that the transmembrane potential during the plateau phase was −30 mV for ischemic cells and −10 mV for normal cells and that the potential changed linearly from −30 to −10 mV for myocardial cells in the transition zone.

It is currently accepted that there is a sharp interface (1 to 2 mm)³¹ between ischemic and nonischemic regions in the lateral boundary, whereas there is a gradual ischemic change in the transmural boundary.³² We ignored the difference between the transmural boundary and lateral boundary for the convenience of mathematical calculation. The boundary transitional zone was assumed to be 2 mm in both transmural and lateral boundaries in the simulations.

**Modeling Structure**

In this study, the geometry of the heart of a normal 58-year-old woman was constructed from a magnetic resonance imaging scan. It includes the atria, the ventricles, the myocardium, part of the inferior and superior vena cava, the pulmonary artery, and the aorta. Subendocardial ischemia from two different arterial territories was simulated. According to our RMBF measurement, for either the LAD or the LCX occlusion, almost half of the left ventricle was involved. Since the ischemic region incorporated only the endocardial area supplied by the involved artery, the ischemic boundaries included the transmural boundary (parallel to the epicardium) and the lateral boundaries (perpendicular to the epicardium). The lateral boundaries were in the central septum on one side, and the left free wall was on the other. Both ischemic regions share the same lateral ischemic boundaries.

**Results**

**Experimental Studies**

**RMBF and Hemodynamic Response**

The flow and the hemodynamic responses to pacing and ischemia are shown in Tables 2 and 3. Pacing alone to the rate of 180 bpm had no significant effect on the left ventricular pressures and the mean left atrial pressure but increased the anterograde coronary flow (Table 2). The RMBF to each third of the myocardium was also increased during pacing (Table 3). The increase to the epicardial third was slightly higher than that to the endocardial third, but the endo/epi flow ratio reduction was not significant (\( P>0.05 \)).

Stenosis with tachycardia caused a marked decrease in flow to the endocardial third of the ischemic area (from 1.19±0.28 to 0.64±0.22 mL·min⁻¹·g⁻¹, \( P<0.001 \); averaging of the LAD and the LCX occlusion values), whereas flow to the epicardial third had a less significant change (from 0.99±0.22 to 0.80±0.19 mL·min⁻¹·g⁻¹, \( P<0.05 \)) (Table 3). The endo/epi flow ratios (Table 3) in the ischemic area decreased from 1.23±0.21 to 0.80±0.17 (\( P<0.001 \)) at 20 minutes of ischemia. The ratio in the nonischemic region was unchanged (from 1.23±0.17 to 1.12±0.25, \( P=NS \)). The ischemia was accompanied by a marginal increase in the left ventricular end-diastolic pressure and a decrease in the left ventricular systolic pressure (both \( P=0.01 \), Table 2). In the nonischemic area, there was also a mild decrease in the RMBF in all the animals, but the change was not significant (Table 3).

Figure 2 displays the spatial flow distributions across the left ventricular wall before and during LAD occlusion. It was plotted with the RMBF data of one experiment from group 4. Before ischemia (control), there were marked variations of RMBF from piece to piece within a layer and from layer to...
layer across the ventricular wall. Generally speaking, flow to the inner layer was higher than flow to the outer layer. During ischemia, flow to the ischemic regions decreased, with the maximum reduction in the inner layer and the minimum reduction in the outer layer. This disproportionate flow reduction produced a gradual flow transition from the endocardium to the epicardium.

**Epicardial Potential Distributions**

During pacing alone, the magnitude of ST potentials and their spatial features did not change until a pacing rate of 240 bpm was reached. When the pacing rate reached 240 bpm, minor ST depression (with a peak magnitude of ~4 mV) occurred over the anterior region and the apex in 3 of the 5 sheep. In the rest of the sheep, ST potential did not change even when the heart was paced to 240 bpm.

From group 2, in which either the LAD or the LCX was partial occluded in different animals, we recorded general ST depression with maximum change in the anterolateral wall of the left ventricle, and the potential distribution was similar in various subendocardial ischemic locations. When alternate LAD and LCX partial occlusions were tested in the same animal (group 3), we obtained even more similar ST potential patterns during ischemia. Representative maps of epicardial ST potential distributions from three typical experiments are displayed in Figure 3. The epicardial ST potential change in each individual electrode position during the LAD occlusion was compared with that during the LCX occlusion. When such potential changes from the 64 electrode positions in each of 6 sheep of group 3 were tested, we obtained a correlation coefficient of 0.77±0.14 on average (ranging from 0.66 to 0.97, all P<0.0001). The correlations for each animal are shown in Table 4.

**Endocardial Potential Distributions**

The simultaneous epicardial and endocardial ST potential changes induced by ischemia are displayed in Figure 4. From the epicardium, general ST depression was recorded. The potential changes were independent of the partial occluded artery. From the endocardium, localized ST elevations were registered, and the ST elevations corresponded to the partial occluded artery.

**Epicardial and Endocardial Potential Distributions in Relation to RMBF**

Figure 5 displays the spatial relationship between endocardial RMBF and ST potential changes during ischemia. Figure 5A was constructed by combining the epicardial potential contour map with the endocardial RMBF image map. Figure 5B was constructed by combining the endocardial potential contour map with the endocardial RMBF image map. As demonstrated by these maps, the most negative epicardial ST depression did not coincide with the lowest flow region.
(Figure 5A); however, the positive endocardial ST potential was related to the low flow region (Figure 5B). Figure 5B also shows that the endocardial flow reduction in the ischemic region was relatively uniform from the ischemic center to the boundary (compared with the transmural flow distribution in Figure 2), producing a sharp lateral interface between ischemic and normal regions. The peak endocardial and epicardial ST potentials, based on the average of the peak three values, were of similar order, with endocardial control potentials being 1.2±0.83 mV and endocardial ischemic potentials being 6.8±2.56 mV (LCX), and 8.07±3.01 mV (LAD). Epicardial potentials were 1.71±0.85 mV (control), 7.57±2.69 mV (LCX ischemia), and 8.29±3.27 mV (LAD ischemia).

**Potential Changes by Insulation**

The magnitude of the epicardial ST depression was increased by insulation (from 9±2 to 12±4 mV), but the distribution patterns were not changed (Figure 6A). Routine ECG limb leads showed a significant decrease in the magnitude of QRS complex and T wave (Figure 6B). The effects of insulation in three animals are illustrated in Figure 6A, and surface ECGs from one animal are shown in Figure 6B. The values from all experiments are shown in Table 5.

**Transition of Subendocardial Ischemia to Transmural Ischemia**

To transform subendocardial ischemia into full-thickness ischemia, the percent stenosis of a coronary artery was increased by fully inflating the hydraulic occluder at 10 to 15 minutes of subendocardial ischemia in 5 sheep of group 2, and the instant potential changes were recorded. From 50 seconds of continuous recording, it was found that ST depression increased gradually as ischemia progressed, until ST elevation ensued at 30 to 35 seconds (Figure 7). The increase of the ST depression occurred at the lateral boundary in either the LCX or the LAD occlusion, whereas the ST elevation started from the posterior wall of the heart in LCX occlusion (Figure 7) and the anterior wall in LAD occlusion. The ST changes were not captured in the 30-second recording because the recording period was not long enough.

**TABLE 4. Correlation Coefficient of Epicardial Potentials Between LAD and LCX Ischemia**

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<th>Correlation Coefficient</th>
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<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>0.65</td>
</tr>
<tr>
<td>3</td>
<td>0.97</td>
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<tr>
<td>4</td>
<td>0.91</td>
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<tr>
<td>5</td>
<td>0.69</td>
</tr>
<tr>
<td>6</td>
<td>0.66</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.77±0.14</td>
</tr>
</tbody>
</table>

**Figure 4.** Simultaneous records of epicardial (upper) and endocardial (lower) potential distributions at 2 minutes of LCX (left) and LAD (right) occlusions (isopotential difference maps from the same sheep). The format of the contour maps is described in the Figure 1 legend. The colors are scaled from blue (ST depression) to red (ST elevation).
Computer Simulations

The simulated results are displayed in Figure 8, where either the LAD or the LCX ischemia shows a similar pattern on the epicardium, with ST depression mainly occurring on the lateral boundary. On the cross section of the heart, endocardial ST elevation appears over the ischemic region, whereas epicardial ST depression occurs on the lateral boundary, i.e., the left free wall for either the LCX or the LAD ischemia.

Discussion

Epicardial ST Depression Does Not Predict Ischemic Region

A major finding of the present study is that ischemic ST depression on the epicardium can not predict the location of an ischemic region. As shown in Figure 3, the distributions of epicardial ST depression are independent of the responsible ischemic location. Either LAD or LCX ischemia gave a similar epicardial ST distribution pattern, although the absolute values of the potentials varied. The bidomain model produced similar results when applied to the same regions of ischemia (Figure 8). Although epicardial ST depression is generated by subendocardial ischemia, the position of the ST change does not localize the responsible myocardium. Unlike body surface recording, epicardial potential recordings are free of the intervening structures, such as lungs, bone, and skeletal muscle, and therefore directly relate to the underlying myocardium. If epicardial ST depression cannot distinguish an ischemic region, neither will the body surface ST depression. These results explain the difficulty in localizing ischemia from body surface ST depression.15–19 However, they are not consistent with classic ECG theories,7,8,20 all of which suggest that ST depression should enable us to localize ischemia.

The Origin of Ischemic ST Depression

In transmural ischemia, epicardial ST elevation occurs when injury currents flow between the ischemic regions and the normal myocardium.9,10 The region of ST elevation is closely related to the region of ischemia.9 At a cellular level, two major mechanisms are considered to underlie ST-segment displacement: (1) a localized shortening of action potential duration and diminishing of the amplitude of the action potential and (2) a localized decrease in resting membrane potential. The former generates current only during the ST segment. The latter generates a steady injury current that is interrupted during the ST segment when all the cells are depolarized. The injury current produces a TQ-segment shift that cannot be directly detected on the ECG because the amplifiers are AC-coupled; however, the interruption of the injury current during the ST segment produces an apparent ST shift, which is equal and opposite the TQ-segment shift on the AC-coupled ECG.

With ST depression, there is no satisfactory explanation of the cardiac electrophysiological changes. Early work1,2,33 in isolated hearts suggested that the ST-segment response to myocardial injury was elevation and that the ST-segment depression recorded at the epicardium was the reciprocal of ST elevation in the underlying subendocardium. This amplified the dipole theory, which was developed by Wilson and coworkers in 1930s.20,33 The dipole model considered the active myocardial event as a single dipole source that contained both the maximum and the minimum potentials. Accordingly, an injured region of the myocardium acts in systole as the positive pole of a layer of dipoles situated on its boundary with normal myocardium, whereas the latter acts as
In the event of subendocardial ischemia, the ventricular surface and the precordium over the ischemic region faces the negative pole of the dipole; the cavity faces the positive pole. Thus, the electrodes over the ischemia should record depressed ST segments, and the cavity should yield elevated ST segments. However, this theory does not explain either the clinical difficulty in localizing ischemia by ST depression or our results. The limitations of the single dipole model have been demonstrated and discussed extensively.

Prinzmetal and coworkers proposed that ST depression was a primary effect of abnormal membrane polarization rather than a reciprocal effect of ST elevation. From their canine model, Prinzmetal and his coworkers recorded relative ST-segment depression (true TQ-segment elevation) from the epicardium of “mild” ischemic areas produced by severe hemorrhagic hypotension. The TQ-segment elevation coincided with the increase in membrane resting potential.

### Table 5. Maximal ST Depression in Ischemia With and Without Insulation

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Control</th>
<th>Ischemia</th>
<th>Ischemia and Insulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.23</td>
<td>9.83</td>
<td>17.83</td>
</tr>
<tr>
<td>2</td>
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</tr>
<tr>
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<td>1.23</td>
<td>6.39</td>
<td>9.4</td>
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<tr>
<td>5</td>
<td>2.75</td>
<td>8.75</td>
<td>12.75</td>
</tr>
<tr>
<td>6</td>
<td>1.55</td>
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<td>11.55</td>
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<td>2.03</td>
<td>10.03</td>
<td>10.35</td>
</tr>
<tr>
<td>8</td>
<td>1.11</td>
<td>9.11</td>
<td>11.21</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.65±0.62</td>
<td>8.86±2.23</td>
<td>11.56±3.69</td>
</tr>
</tbody>
</table>

### Figure 6. A, Epicardial potential distributions with and without insulation. During insulation, the magnitude of ST depression was increased, but the pattern of ST distribution remained unchanged (isopotential difference maps at 20 minutes of partial LCX occlusion). Results from three sheep are shown with the contour interval being 2 mV. B, Routine analog body surface ECG recordings with and without insulation. During insulation, the magnitudes of QRS and T waves were significantly reduced. The ECGs were recorded at a speed of 25 mm/s; a calibration of 10 mm = 1 mV. The format of the contour maps is described in the Figure 1 legend.

### Figure 7. Sequential epicardial potential distributions during the transition of subendocardial to full-thickness ischemia in the LCX occlusion (contour interval = 4 mV). The format of the contour maps is described in the Figure 1 legend.
The ECG reflects the potential difference between two when blood flow to the deeper myocardial layers decreases. A study (Figure 2) revealed that epicardial ST depression occurs. Furthermore, the RMBF measurement in the present (Figures 4 and 5) were also inconsistent with their point of view. Endocardial electrogram recordings from our experiments (Figure 8) along with Kleber’s work on intracellular recording have suggested that the source of the ischemic ECG is related to the endocardium. In the present study, the minimum potential was independent of the lowest flow region (Figure 5A), whereas the maximum potential was related to the low flow region (Figure 5B), suggesting that the ischemic source relates to the endocardial ST change but not the epicardial ST change. This finding cannot be interpreted by the solid angle theory.

The solid angle theory, a concept developed from a mathematical formula and applied to interpret ECGs by Wilson et al in 1933, was expanded to ECG theory by Holland and Arnsdorf. The theory, by taking into account the geometry of the ischemic boundaries, the degree of transmembrane or action potential duration differences, and alterations in intracellular and extracellular conductivities, has provided a geometrical ischemic heart model that quantitatively links changes in ST shifts to the distribution of transmembrane potential changes in the ischemic region. In this model, the ventricle is represented by a sphere of specified thickness, and a region of ischemia is represented by the intersection of the sphere with a cone, the apex of which lies at the center of the sphere. The ischemic boundary is defined as the annular shell that interfaces the cone and the sphere. The ischemic source is assumed to have a uniform potential gradient at the injury boundary. According to this model, the magnitude of ST depression (Φ) recorded at a surface electrode over the ischemic region is as follows:

\[ \Phi = \frac{\Omega}{4\pi} (\Delta V_m) K \]

where Ω is the solid angle subtended by the ischemic boundary at the electrode site, Ω is defined as the annular shell that interfaces the cone and the sphere. The ischemic source is assumed to have a uniform potential gradient at the injury boundary. According to this model, the magnitude of ST depression (Φ) recorded at a surface electrode over the ischemic region is as follows:

\[ \Phi = \frac{\Omega}{4\pi} (\Delta V_m) K \]

where Ω is the solid angle subtended by the ischemic boundary at the electrode site, ΔV denotes the transmembrane potential difference of the normal and ischemic regions, and K is a term correcting for differences in intracellular and extracellular conductivity and the occupancy of much of the heart muscle by interstitial tissue. This model predicts that endocardial ischemia would cause relative depression of the ST segment in the epicardium and precordium due to the reversed current flow at the boundary of the normal and the ischemic myocardium, and that this ST depression should provide the means for localizing ischemia. However, Holland and Brooks failed to produce subendocardial ischemia in the porcine model that they used and were unable to confirm their theoretical prediction of subendocardial ischemia. Furthermore, the solid-angle analysis is limited as is the classical dipole theory, by the fact that the thorax is neither a homogeneous nor an infinite volume conductor. Theoretically, the solid-angle model is a solution of Equation 2 in the particular case when the double layer is in an infinite, homogeneous, and isotropic conducting medium and the exploring point is far from the source. To be able to use the approximation that a potential gradient is proportional to the source strength for a dipole layer–type source, these
conditions must be met. Unfortunately, they are hardly met in reality; e.g., the source is surrounded by a bounded inhomogeneous medium, and the exploring point is very close to the source, especially when the point is on the epicardium. In a finite inhomogeneous volume conductor, the potential distribution around the source is greatly affected by its surrounding medium and is unlikely to have a uniform potential gradient at the injury boundary.

A bidomain model, which was developed by Miller and Geselowitz in 1978,45,46 has provided a good simulation of the body surface ECG for the normal heart and infarction. In this digital computer model, the ventricles of a human heart were represented in detail and were taken to be located in a torso with realistic surface boundaries.45 Ischemia and infarction were simulated by altering the shape of transmembrane action potentials assigned to the injured regions of the heart model.46 A simulation in which action potentials with decreased resting potentials were assigned to anterior subendocardial region has resulted in body surface ST depression in leads V2 to V5 and leads I and aVL. Unfortunately, ST depression was not fully evaluated in this model because neither the endocardial nor epicardial potential was simulated. In addition, the anisotropy and inhomogeneity of the body as a volume conductor were ignored in this model.45,46

On the basis of their studies using body surface mapping and an inverse transformation22,47,48 in 219 patients with acute inferior infarction and 93 patients with ST depression and no infarction, Kilpatrick et al22 postulated that ST depression on ECG originates from current flowing from an endocardial ischemic region to the outside of the heart through the great vessels and atria. This hypothesis explained the difficulty in localizing ischemia from body surface ST depression, but to be a valid explanation, the current paths from the heart would need to be demonstrated. In the present study, the paths have been interrupted by insulating the heart from the return current, resulting in an increase in the magnitude of ST depression when the epicardial surface was insulated, which is inconsistent with the hypothesis. Insulation increased the magnitude of epicardial ST depression by 2 to 8 mV (P<0.05) without altering the distribution patterns (Figure 6A), whereas the magnitudes of the QRS complex and T wave in the routine ECG limb leads showed a significant decrease (Figure 6B). Since the present study was carried out in an open-chest preparation with the anterior wall of the left ventricle not in contact with the thorax, insulating the heart would change the amount of the lateral and posterior wall of the left ventricle and the right ventricle in contact with the surrounding tissues. Being nearly fully encircled by the plastic bag, the ventricles were well insulated. The increase in ST depression strongly implies that the source of the ST depression is intramyocardial and does not involve external current paths.

A recent study has demonstrated that the amplitude of the epicardial QRS potentials from both intact and isolated hearts was markedly higher when the heart was surrounded by an insulating medium but that the QRS potential distribution patterns were less affected by the insulating medium.49 The introduction of the insulating material has the effect of reducing the net flow of current from the heart into the surrounding medium. Because of this effect, the magnitudes of the epicardial ST potential increased (Figure 6A), whereas the magnitudes of the limb QRS potentials decreased (Figure 6B). The excitation of the heart can be detected by the ECG primarily because of the existence of the potential difference between the activated cells and the resting cells during the propagation of the action potential in the ventricles. The similar increase in the magnitude of the epicardial ST potentials might represent the same behavior, suggesting that the current source is intramural. This contention was further tested by the transition of subendocardial ischemia to transmural ischemia.

From the transition of subendocardial ischemia to full-thickness ischemia, it was found that epicardial ST depression increased gradually over the boundary region as ischemia progressed and ST elevation ensued over the ischemic region as ischemia became transmural (Figure 7). The increase of ST depression before the occurrence of ST elevation was also observed in a study with a perfused canine heart by Guyton et al49 in 1977. The electrical transition from ST depression to ST elevation was consistent with the contention that the current path is in the myocardium.

In the normal ECG, the ST segment remains isoelectric because there are no great potential differences occurring in the myocardium during this period. In transmural ischemia, epicardial ST elevation occurs when injury currents flow at the boundary between the ischemic regions and the normal myocardium because of the potential difference between these two regions.9,10 Since the myocardial cells in subendocardial ischemia undergo changes qualitatively similar to those in transmural ischemia,51 it is likely that the injury currents in subendocardial ischemia also originate from the ischemic boundary. Since subendocardial ischemia involves only the inner layer of the ventricular wall, the boundary between the ischemic region and the normal myocardium should include the transmural boundary parallel to the endocardium and the lateral boundary perpendicular to the endocardium. However, the flow distribution during subendocardial ischemia demonstrated that transmurally there was a gradual flow transition from the endocardium to the epicardium (Figure 2) but that at the lateral boundary, flow changed sharply from the ischemic zone to the nonischemic zone, producing a sharp lateral interface between ischemic and normal regions (Figure 5B). Studies on transmural ischemia also found a sharp lateral interface between ischemic and normal cells with severely ischemic tissue lying adjacent to normal well-perfused tissue.31,52,53 In ischemic pig hearts, transmembrane action potential recordings using floating microelectrodes also demonstrated a sharp and distinct transition from electrophysiologically abnormal to normal cells.54 As shown in Equation 2, the injury current is directly associated with the spatial gradient of the transmembrane potentials. A greater potential gradient exists at the lateral boundary, which in turn produces a stronger current. Under such circumstances, the greater epicardial potential change should appear at the lateral boundary regions with less change in the ischemic center, where the transmural boundary is located and less injury current occurs. Accordingly, in the present study, the maximum epicardial potential change.
should be at the lateral wall and middle septum, where the LAD and the LCX share their borders, and this explains the experimental results. The transition of subendocardial ischemia to full-thickness ischemia showed that as ischemia progressed, ST depression increased gradually until ischemia became transmural and ST elevation ensued in the ischemic center (Figure 7). The increased ST depression occurred at the lateral border, whereas the ST elevation started at the ischemic center. ST elevation gradually progressed toward the ischemic border. These results support the postulate that the major source of electrical current in subendocardial ischemia is located at the lateral boundary of the ischemia. This postulate was verified by our computer simulation, which showed clearly that the current source was at the lateral boundary (Figure 8).

Our computer simulation, in which a bidomain model was used to represent the myocardium, took many factors into account. Those included the four chambers of the heart, parts of the big vessels, and the blood inside the heart. A distinguishing feature of our model was that we used volume current density for the source and a real injury boundary with both lateral and transmural boundaries. From our model, we obtained epicardial ST depression over the lateral region in either the LAD or the LCX partial occlusion and endocardial ST elevation over the ischemic region (Figure 8). These results correlated well with those from the experiments (Figures 3 and 6). We believe that the major source of epicardial ST depression is the lateral boundary of the ischemia in the free wall of the left ventricle. The boundary parallel to the endocardium has high currents normal to the boundary that are localized to a narrow region 3 to 4 mm in maximum dimension and that result in no observable field at the epicardium. At the endocardial side of the left lateral boundary, the injury current flows from the ischemic region to the normal region through the highly conductive intracavity blood. We observed a resulting depression of epicardial ST potential over the boundary. Since the LAD and the LCX share their boundary at the lateral wall, ST potentials showed a similar distribution pattern of lateral ST depression (Figures 3 and 8). The source at the lateral boundary in the septum is not seen on the epicardium because it is surrounded by the myocardium, which is fundamental in electrocardiography, is recognized to be complex. Source orientation and strength, volume-conductor characteristics of the body, and source location are all factors in the relationship. This multiplicity of factors makes it difficult to rigidly prove and quantitatively define the roles for each. Despite this, findings in the present study strongly suggest that epicardial potential patterns are not substantially affected by the cardiac locations of responsible subendocardial ischemia and that the ECG changes are generated by the lateral boundary on the free wall, where the LAD and the LCX share their borders.

### Evaluation of Experimental Method

The present study was based on the previously validated subendocardial ischemic sheep model produced by a combination of partial arterial stenosis coupled with left atrial pacing. The presence of the subendocardial ischemia was evidenced by the reduction in the endo/epi flow ratio in the ischemic area (Table 3). In the absence of a stenosis, the myocardial blood flow increased with a pacing rate of 180 bpm (Table 3). This was primarily due to a decrease in the coronary vascular resistance, which maintains uniform net transmural perfusion even if a marked reduction in diastolic perfusion time or higher heart rates are achieved.

In the presence of a coronary artery obstruction, pacing to a rate of 180 bpm caused a decrease in the subendocardial flow, with a less significant change in the subepicardial perfusion and thus a reduction in the endo/epi flow ratio in the ischemic area (Table 3). The susceptibility of the subendocardium to ischemia is due to its limited reserve for vasodilation, the extrinsic compression from the higher wall stress to which it is subjected, and the resultant high metabolic demands in this region. Atrial pacing was associated with a decrease in diastolic perfusion time, an increase in oxygen demand, and an increase in stenosis resistance. Therefore, partial coronary occlusion plus the added atrial pacing would produce a degree of subendocardial ischemia similar to that reported during the exercise, as indicated by the elevation of the ST segment in the endocardial recording and depression of the ST segment in the epicardial recording.

Sheep have few native coronary collateral anastomoses and are similar to humans, and the anatomy of the coronary arterial circulation is remarkably consistent. Thus, in sheep, the ischemic size is determined primarily by the size of the occluded vascular bed because of the lack of collateral connection. These coronary anatomic features in sheep permit predictable and reproducible myocardial ischemia with small standard deviations. The present study provides an alternative model for ischemic research.

The advantage of seeing an epicardial distribution is that the electrogram changes directly reflect the source. In the present study, we used the epicardial distribution during the ST segment to test the hypothesis of ST depression. The methods in the present study differed in certain aspects from those used by others. To avoid variables introduced by the isolated heart, the study was carried out with the heart in situ. The epicardial ST potentials were recorded from 64 electrodes spread over the whole surface of the heart. The endocardial ST was recorded by a 40-pole basket electrode. Previous studies have been performed in the isolated heart in which the epicardial ST changes after physical or chemical injury were only recorded in the injured region.
in the in situ heart, ST depression was either not produced, or the epicardial and the endocardial potential changes during subendocardial ischemia were not investigated.

**Limitations**

The first limitation occurs in the experimental work. Attempts at intramural recordings were not successful because of injury currents; thus, the definite current flow path was unable to be confirmed. The second limitation was in the computer simulation, in that the torso was not included in our model; therefore, the influence of the body as a volume conductor was not evaluated. However, according to the experimental results of insulation (Figure 6A) and one other study in this area, the torso would change (decrease) the magnitudes of only the ST shifts but not the distribution patterns.

**Clinical Implication**

The clinical significance of our results is that data are provided for further study of ST depression. Many workers have shown that although body surface ST elevation was highly related to the region of ischemia, body surface ST depression was poorly related, if at all. Our results explain this poor localization of ischemia by ST depression in humans and suggest that the source might be at the lateral boundary of endocardial ischemia. The present data support the following conclusions: (1) Epicardial potential patterns are not substantially affected by the cardiac location of the responsible subendocardial ischemia. (2) ST depression is not due to the endocardial current flow back on to the cardiac surface and is not fully explained by the current models of the ST depression. (3) Ischemic ST depression originates from the injury current, which flows at the lateral boundary of subendocardial ischemia.

**Acknowledgments**

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Danshi Li, Chuan Yong Li, Ah Chot Yong and David Kilpatrick

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