

Mechanism for ST Depression Associated with Contiguous Subendocardial Ischemia

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Mechanism for ST Depression. Introduction: A mechanism for ST depression arising on the epicardial surface over the border between normal and ischemic tissue is proposed. Depression is caused by current flowing in a transmural loop that begins and ends at the lateral boundary between healthy and ischemic tissue and passes through the transmural boundary between healthy and ischemic tissue. The result is ST depression at the epicardium over the lateral boundary. The size and direction of current flow are dictated by differences in the magnitude and orientation of anisotropic conductivity between those boundaries.

Methods and Results: Computer simulations verified and quantified the relationship between ST depression and conductivity differences. We used computer simulations based on an anatomically accurate, anisotropic model of canine ventricles and a bidomain representation of the effects of ischemia to verify the biophysical basis of this mechanism.

Conclusion: ST depression at the epicardium appears over a lateral boundary between healthy and ischemic tissue. (*J Cardiovasc Electrophysiol*, Vol. 15, pp. 1200-1206, October 2004)

ischemia, ST depression, conductivity, computer model

Introduction

The diagnostic meaning of the location and extent of ST segment depression on the body surface ECG remains controversial. According to standard clinical practice, in the absence of ST elevation recorded by one of the standard 12 lead electrodes, ST depression may indicate the presence of subendocardial ischemia at an undetermined location within the heart.¹ However, researchers have come to different conclusions regarding the prognostic significance of the location of ST depression, with² or without³ concomitant ST elevation. ST depression in the case of multivessel coronary artery disease is particularly complicated due to the interplay between voltage patterns caused by two or more ischemic regions.⁴

Most theories on the mechanism of ST depression rely on correlations between depression and coronary artery disease observed in patient studies. Given the many factors that can influence the nature of ST depression, the disparate conclusions of these studies are not surprising.

To avoid these complicating factors and more clearly isolate the relationship between ST segment changes and the underlying ischemia, Li et al.⁵ and Guyton et al.⁶ measured epicardial potential patterns in sheep and dogs, respectively, at various degrees of transmural ischemia. Li et al. also implemented a computer model of ischemia based on a heart with

isotropic conductivity. According to the experimental and modeling study of Li et al., ST depression occurs on the epicardium over one of the lateral boundaries, or border zones, between the ischemic and healthy tissue. The depression occurs with or without ST elevation directly over the ischemic region. In the case of ischemia caused by occlusions of the left anterior descending artery (LAD) and left circumflex artery (LCX), respectively, the boundaries of ischemic zones overlap so that the site of depression cannot distinguish between inferior and anterior ischemia, at least in the absence of ST elevation. Li et al.⁵ found that ST elevation occurred, and ST depression intensified, as the ischemia became increasingly transmural.

Regardless of the presence or absence of the primary ST elevation, Li et al. posited that ST depression occurs over the lateral healthy/ischemic boundary because the primary "injury" currents causing ST depression flow across this boundary.

Because of limited computational resources at the time, Li et al. were unable to compute a full anisotropic model of the heart. However, work by Johnston et al.⁷ suggests that anisotropy plays an important role in determining the pattern of epicardial surface potentials (ESPs) resulting from subendocardial ischemia.

We provide here computer simulations, based on a fully anisotropic whole heart model, and theoretical considerations that lend additional support for the theory of Li et al.⁵ The anisotropic model allows us to support the basic finding of lateral boundary ST depression by Li et al. and to examine more fully the underlying mechanisms of ST depression. One result is a fundamentally different explanation than that posited by Li et al. for the distribution of extracellular source currents producing ST depression. Specifically, our simulation results show that both the magnitude and location of ST depression are sensitive to changes in the values of anisotropic conductivity of cardiac tissue. Finally, we discuss some possible clinical implications of our findings.

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Methods

Ischemia was simulated using a geometric model based on the anatomic and fiber structure data of the Auckland canine heart.⁸ The computer model solves the equation governing the passive flow of current in the heart, according to the bidomain theory (Equation 1), given a distribution of transmembrane potentials (TMPs). To represent the electrical consequences of localized ischemia, we assigned to a patch of tissue in the left ventricle transmembrane potentials that were 30mV smaller than in the remaining healthy cells, as shown in Figure 1 in the case of 70% transmural ischemia. The size of the ischemic patch was altered in the transmural direction to simulate various degrees of transmural ischemia.

In most simulations, the border zone between healthy and ischemic tissue was a few millimeters wide. However, because the transmural ischemic border zone may be wider than the lateral border zones,^{5,9,10} some simulations tested the effect of changing the width of the transmural ischemic border. Specifically, some simulations were run at 40% ischemia with a transmural border zone 2 to 3 times as wide as that shown in Figure 1, subject to the constraint that the border zone did not extend to the epicardium. Within the ischemic border zone, the TMP varied smoothly from -30 to 0 mV according to an exponential function.¹¹

The anatomy of the Auckland heart, including ventricles filled with blood, was represented by a hexahedral mesh defined by a number of nested, concentric layers. The heart consisted of 60 layers that were weighted averages of the epicardial and endocardial surfaces. For example, the 30th layer was approximately equal to $0.5 \cdot \text{Epi} + 0.5 \cdot \text{Endo}$, where Epi and Endo are the cartesian coordinates defining the epicardial and endocardial surfaces, respectively. The degree of ischemia was defined with respect to the 60 layers. For example, 40% ischemia means that the ischemia extended from the endocardium to the 24th layer.

The generated mesh was used to solve the bidomain passive current flow equation:

$$\nabla \cdot (\sigma_{ie} + \bar{\sigma}_e) \nabla V_e = -\nabla \cdot \bar{\sigma}_i \nabla V_m \quad (1)$$

where V_e is the extracellular potential, $\bar{\sigma}_i$ is the intracellular conductivity tensor, $\bar{\sigma}_e$ is the extracellular conductivity tensor, and V_m is the transmembrane potential.

With regard to boundary conditions, the heart was assumed to be surrounded by a perfect insulator so that no current could flow out of the heart. At any interface between ventricular blood and heart muscle, the extracellular potential V_e was continuous, the normal component of the extracellular current was continuous, and no intracellular current could flow across the interface.

Equation 1 was solved according to a Galerkin-based finite element method with trilinear basis functions. Gauss quadrature was used to integrate the resulting equations. The conductivity tensor at each quadrature point was based on the fiber orientation, which was computed by forming a weighted average of the fiber orientation data corresponding to the eight nearest points from the Auckland data. Conductivity values were chosen based on results from our model of cardiac tissue,¹² normalized to the value of the extracellular longitudinal conductivity¹¹: $\sigma_{el} = 1$, $\sigma_{et} = 1/3$, $\sigma_{il} = 1$, $\sigma_{it} = 1/20$, where σ_{el} and σ_{et} are the extracellular longitudinal and transverse conductivities, respectively, and σ_{il} and σ_{it} are the intracellular longitudinal and transverse conductivity, respectively.

The ischemic conductivity values were chosen to correspond to two different stages of ischemia: (1) the time between 5 and 10 minutes after the onset of ischemia, after the extracellular space has shrunk but before a substantial number of gap junctions have closed ($\sigma_{el}^i = 1/2$ and $\sigma_{et}^i = 1/4$) with the intracellular conductivities for the ischemic tissue unchanged¹²; and (2) some time between 15 and 30 minutes of ischemia, after a substantial number of gap junctions have closed ($\sigma_{el}^i = 1/2$, $\sigma_{et}^i = 1/4$, $\sigma_{il}^i = 1/10$, and $\sigma_{it}^i = 1/1000$).¹² Normalizing all conductivities to an extracellular longitudinal conductivity of 1 is acceptable because extracellular potentials do not depend on the absolute values of the bidomain and blood conductivities but only on the conductivity ratios. The reference potential was chosen such that the sum of the epicardial potentials was zero.

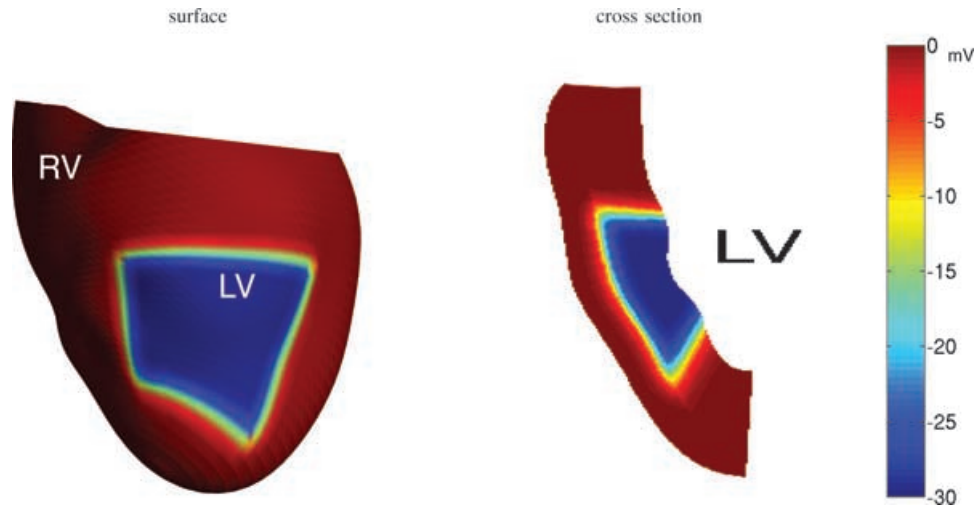


Figure 1. Transmembrane potential distribution over a midmyocardial layer and a sagittal slice showing an anterior, subendocardial ischemic zone. The transmembrane potential of the ischemic patch was negative with respect to the transmembrane potential of the healthy tissue, as indicated by the color bar. The region of changing color indicates the boundary, or border, zone.

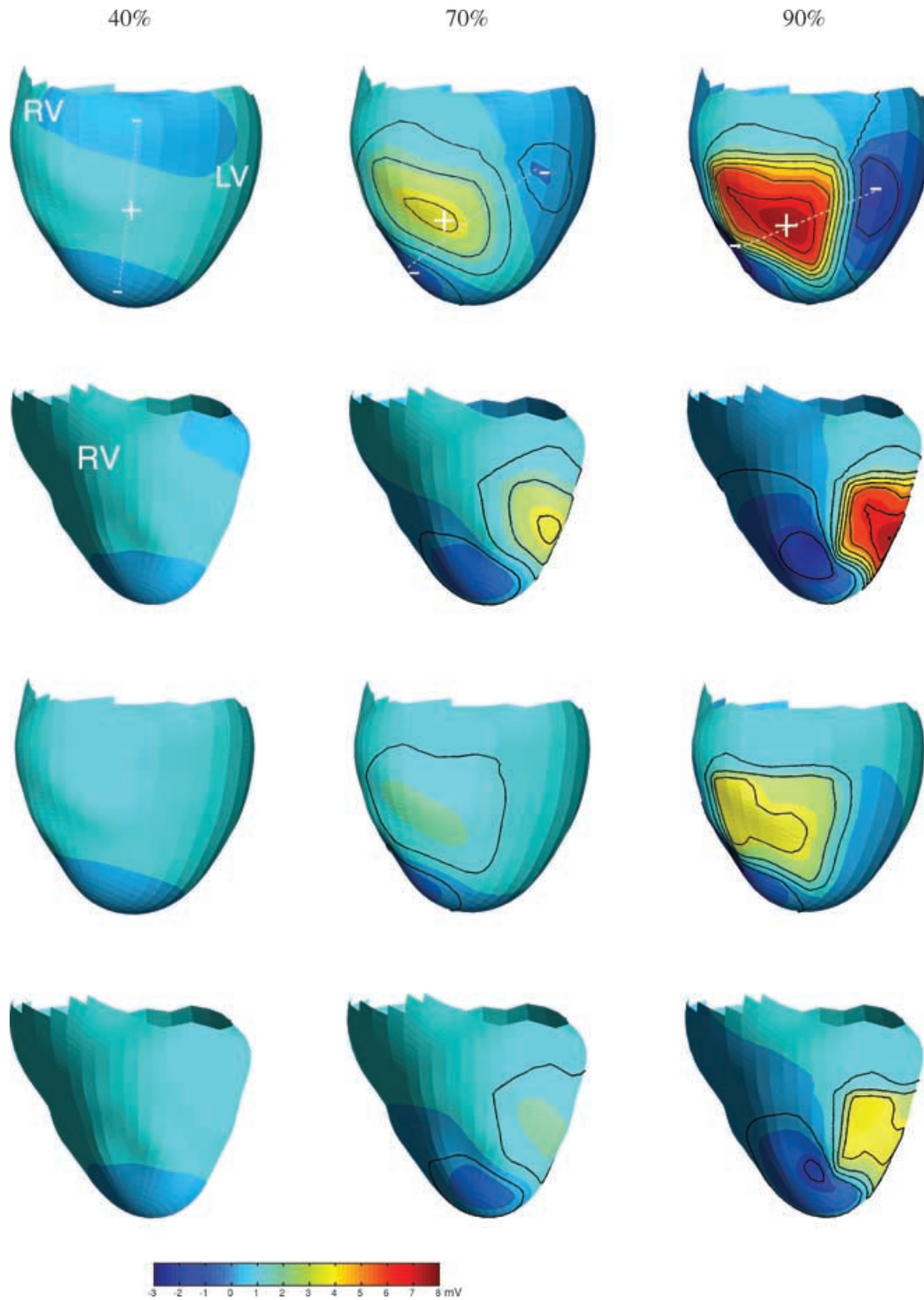


Figure 2. Epicardial distributions resulting from various degrees of transmural ischemia. The percentage transmural ischemia is shown at the top of each figure. The top two rows and bottom two rows show simulation results of stage 2 and stage 3 ischemia, respectively. The first and third rows show anterior views; the second and fourth rows show right anterior views. In the first row, the lines that roughly connect the relative extrema show the rotation of the minima as the degree of transmural ischemia increases.

Results

The top two rows in Figure 2 show the computed ESPs that result from 40%, 70%, and 90% transmural ischemia of the type that would occur between 5 and 10 minutes after the onset of ischemia, before gap junction closure. The

bottom two rows in Figure 2 show corresponding ESPs after gap junction closure. As shown, ST depression along at least one side of the ischemic patch increased with the degree of transmural ischemia. ST elevation centered over the ischemic region arose for ischemic zones of between 40% and 70% thickness. The ESPs were smaller

in the cases where the gap junctions were closed, consistent with experimental findings.¹³ For the case of 40% ischemia before gap junction closure, simulations were run with a wider transmural border zone than that shown in Figure 1. The resulting ESP patterns (not shown) were similar to the corresponding ESPs in Figure 2.

To isolate the effects of fiber orientation on voltage drops across the ischemic boundary, in one set of simulations ischemia was restricted to a very thin transmural section, between 65% and 70% of the ventricular wall. Figure 3 shows the resulting voltage distribution on an interior heart layer within the thin ischemic region. The figure shows a consistent finding that the voltage drop across the ischemic boundary tended to be greatest along the direction of the fibers.

Discussion

Overview

The top rows of Figure 2 show ESPs mirroring the general pattern of lateral boundary ST depression that intensifies as the degree of transmural ischemia increases. Maximal ST depression of approximately -3 mV was smaller than the -12 mV measured by Li et al.⁵ in sheep studies but was within a millivolt of maximal ST depression reported by Guyton et al.⁶ in canine studies. In our simulations, as in the studies of Li et al. and Guyton et al., ST depression occurred at lower degrees of transmural ischemia than ST elevation. Also, in the two animal studies and in our simulations, the magnitude of ST depression increased modestly with increasing transmural ischemia, whereas the magnitude of ST elevation increased rather abruptly, after it first occurred, as ischemia progressed transmurally. Finally, as in the studies by Guyton et al., endocardial ST elevation (not shown): (1) was centered on the ischemic region, at all degrees of transmural ischemia, as was found by Li et al.; (2) had a magnitude (e.g., approximately 4 mV during the first stage of ischemia at 70% thick-

ness ischemia) larger than the magnitude of the maximum epicardial ST depression but smaller than the magnitude of maximal epicardial ST elevation at high degrees of transmural ischemia; and (3) increased in magnitude more gradually with increasing transmural ischemia than did the epicardial ST elevation (after epicardial elevation first occurred).

The ESP patterns shown in the top rows of Figure 2 are consistent with computer simulations of propagation by Colli Franzone et al.¹⁴ Specifically, Figure 2 shows two potential minima roughly aligned with a potential maximum along a line that rotates with transmural fiber orientation. Colli Franzone et al. observed a similar alignment of potential extrema, two maxima separated by a minimum, and a similar rotation of the line connecting the extrema. In addition, Figure 2 shows that the maximum voltage drop occurs along the fiber direction, as was noted by Colli Franzone et al.

The concordance between propagation and ischemia is reasonable because an ischemic patch of heart tissue is similar to an activated patch of heart tissue during propagation but before epicardial breakthrough. The polarities of the extrema in results presented by Colli Franzone et al.¹⁴ were opposite to those in the present study because the TMP gradient between activated and resting tissue during propagation is opposite in polarity to the TMP gradient between ischemic and healthy tissue.

The ESP patterns shown in the top rows of Figure 2 are somewhat similar to those in the bottom rows. However, the amplitudes of the ESPs are markedly different, suggesting that ESP amplitudes are sensitive to the values of the bidomain conductivities. An important aspect of the relationship between the bidomain conductivities and ESPs is discussed in the following.

Biophysical Theory

A relatively simple model of ischemia can explain the depression over the boundary between the ischemic patch and healthy tissue. For purposes of discussion, we assume that the ischemic patch is reasonably homogenous with TMPs that are negative compared to healthy cells, a condition that occurs during the ST segment. Unless otherwise stated, all references to currents and voltages mean extracellular currents and voltages, respectively. The extracellular voltage on the epicardium is the quantity of interest because it is directly measurable with electrodes on the heart surface or indirectly measurable on the body surface.

The negative TMP of the ischemic cells with respect to healthy cells creates a current source/sink system at the boundary between healthy and ischemic cells, as shown in Figure 4. The current source is on the ischemic side and the current sink is on the healthy side. The result is a flow of current out of the ischemic patch directly across the boundary, as indicated by the straight arrows in the figure. If the voltage drop across the lateral boundary is greater than the voltage drop across the transmural boundary, as is the case in Figure 4 (indicated by the size of the $+/-$ symbols), a small amount of extracellular current will flow in a loop from the ischemic side of the lateral boundary, through the ischemic tissue, across the transmural boundary, through the healthy tissue, and then to the healthy side of the lateral boundary.

This extracellular current loop is responsible for both ST segment elevation and depression on the epicardium. Specifically, because one arm of the current flows from the

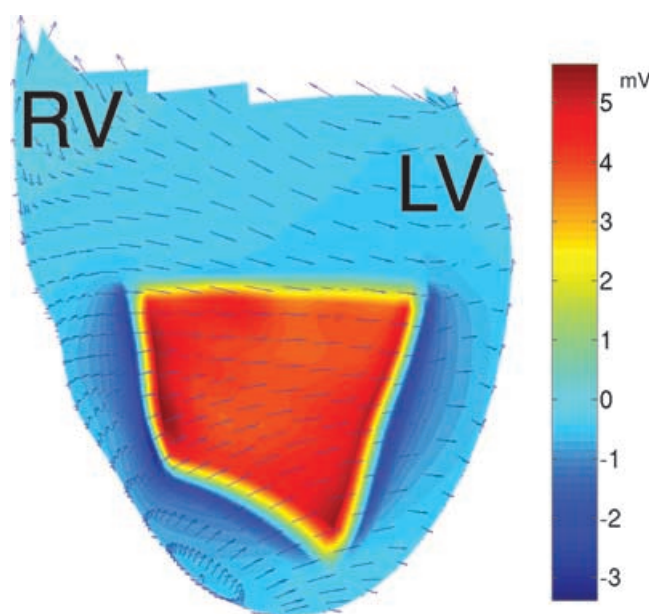


Figure 3. Extracellular potential distribution on an internal heart layer showing the effect of fiber orientation on the voltage drop across the ischemic boundary (indicated by the positive potential values).

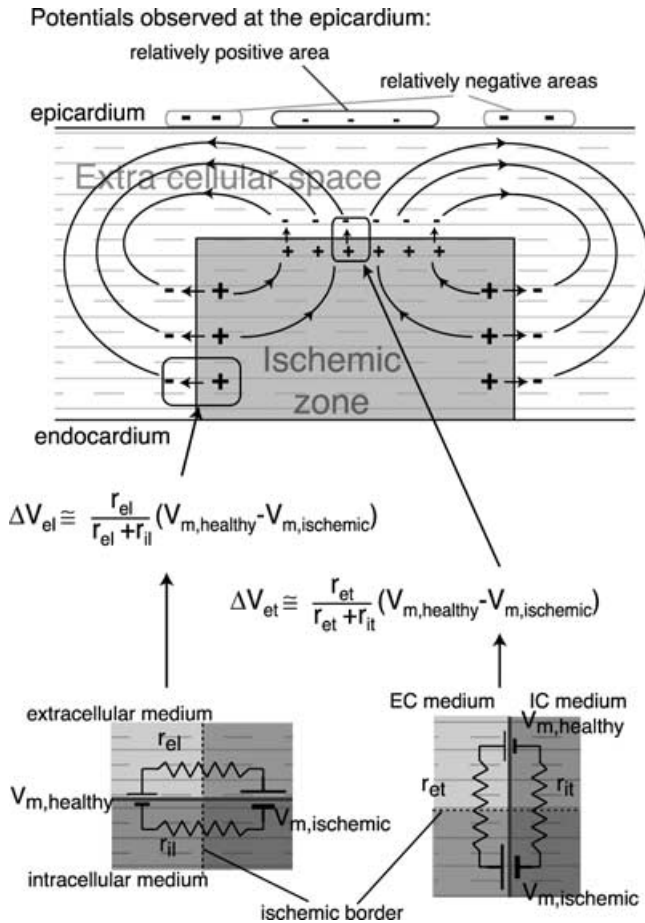


Figure 4. Current flow and voltage drops in an ischemic heart. The voltage drop across the lateral ischemic boundary is greater than the voltage drop across the transmural boundary, as indicated by the size of the + and – symbols. Most current flows directly across the ischemic boundary, as indicated by the thick arrows. However, a small amount of current flows in a loop from the lateral ischemic boundary, through the ischemic tissue, across the transmural boundary and then to the healthy tissue on the lateral boundary. The voltage drop ΔV_e is greater across the lateral boundary than the transmural boundary due to the difference in resistances of the two boundaries. The voltage drop is a function of the intracellular-to-extracellular resistance ratio, as indicated by the circuit diagrams in the lower panels of the figure. The resistors in the circuit diagrams represent the components through which current crossing the boundary must flow and are oriented with respect to fiber orientation. At the lateral boundary, the resistors are parallel to the fiber direction and thus are displayed horizontally. Resistors at the transmural boundary are transverse to the fiber direction and are displayed vertically. In consequence, the extracellular space is placed above the intracellular space in the left circuit diagram, whereas these two spaces are side to side in the right circuit diagram. The relative placement of the extracellular space with respect to the intracellular space is an artifact of the resistor orientation and does not have any independent significance.

transmural boundary toward and then along the epicardium to the lateral boundary, the area of the epicardium centered over the ischemic region shows a positive potential with respect to the area of the epicardium over the lateral boundary of the ischemic region. The resulting epicardial potential distribution is positive (ST segment elevation) over the ischemic region and negative (ST segment depression) over its edges. To recapitulate, the voltage drop across the lateral ischemic boundary is greater than the drop across the transmural ischemic boundary. This difference in voltage drops results in

ST depression on the epicardial region over the lateral ischemic boundary.

The reason why the voltage drop across the lateral boundary tends to be greater than the corresponding drop across the transmural boundary is the difference in tissue resistance between these sites. The lower panels of Figure 4 show the situation schematically in which the potential differences between the intracellular and extracellular spaces, $V_{m,healthy}$ and $V_{m,ischemic}$, are coupled by the intracellular and extracellular resistances r_i and r_e . The important difference between the lateral and transmural boundaries is the alignment of fiber direction—and the associated longitudinal or transverse resistance—with the ischemic boundary. In both cases, one can express the change in extracellular potential across the ischemic boundary as follows:

$$\Delta V_e = (V_{m,healthy} - V_{m,ischemic}) * 1/(1 + r_i/r_e), \quad (2)$$

where r_i and r_e are intracellular and extracellular resistors (the reciprocals of the intracellular and extracellular conductivities in Equation 1) and $V_{m,healthy}$ and $V_{m,ischemic}$ are the respective TMPs of cells across the ischemic boundary. Thus, as the ratio of intracellular to extracellular resistance r_i/r_e (IC/EC resistance ratio) decreases, the extracellular voltage drop across the boundary increases.

The IC/EC resistance ratio typically is smaller throughout the lateral boundary than the transmural boundary due to the anisotropic nature of cardiac tissue conductivity. This difference arises from the tendency of tissue fibers to align in a circumferential direction and thus be generally orthogonal to the lateral border of the ischemic zone and tangential to its transmural border. It is well known that both intracellular and extracellular resistances are greater across fibers (transverse) than along fibers (longitudinal), i.e., $r_{it} > r_{il}$ and $r_{et} > r_{el}$. Moreover, we and other investigators have shown that intracellular resistance is far more anisotropic than extracellular resistance,¹² i.e., $r_{it}/r_{il} > r_{et}/r_{el}$. A simple rearrangement of this inequality also shows that the IC/EC resistance ratio is smaller along fibers than transverse to fibers, i.e., $r_{il}/r_{el} < r_{it}/r_{et}$. Thus, the IC/EC resistance ratio is also smaller at the lateral edges of the ischemic zone—where current flows along fibers—than at the transmural edges—where current crosses the fibers. As a consequence, the extracellular potential drop is generally larger at the lateral boundary than at the transmural boundary.

The dependence of the IC/EC resistance ratio on fiber orientation results in a different voltage pattern compared with the case of a constant IC/EC resistance ratio, which is the underlying assumption of the uniform double layer theory (UDL). Assuming no current can flow through ventricular blood and further assuming ischemia is not transmural, according to the UDL there will be no ESP gradient. There is no ESP gradient because there is no loop current flow. The uniform IC/EC resistance ratio means that the voltage drop across the entire ischemic boundary is constant, so there is no potential difference to drive loop current. If current can flow through ventricular blood, according to the UDL, ST depression will be centered over the subendocardial ischemic region rather than over the lateral border zones because current will flow in a loop from the ischemic transmural boundary to the healthy transmural boundary through the ventricular blood. Similarly, in a heart characterized by ventricular isotropic

conductivity, solid angle theory predicts that ST depression will occur over the subendocardial ischemic region.¹⁵

In sum, ST depression tends to occur over the lateral boundary of the ischemic region because the voltage drop across the lateral boundary is greater than the voltage drop across the transmural boundary. The difference in voltage drop arises from the difference in the IC/EC resistance ratio, which varies with fiber orientation.

Volume Conductor Effects

The properties of the heart and blood as a volume conductor affect the magnitude and pattern of ESPs. However, we have run simulations suggesting that the voltage drops across the ischemic boundary largely determine ESPs and that volume conductor effects are of secondary importance.

In our simulations, the epicardium was insulated, whereas in normal physiologic conditions, the epicardium is electrically loaded by a torso, which can be expected to affect ESPs. Li et al.⁵ found that electrical insulation of the epicardium increased the magnitude of ESPs but did not significantly alter ESP patterns. Thus, we believe that torso loading effects would not have substantially altered the ESP patterns resulting from our simulations.

Variation with Stage of Ischemia

The relation between conductivity and extracellular potential, as described earlier, may explain the difference in potential distributions between the top and bottom two rows of Figure 2, which correspond to the second and third stages of ischemia, respectively. In the simulations corresponding to stage 3, closure of a substantial number of gap junctions within the ischemic tissue greatly increased the IC/EC resistance ratio compared with stage 2 ischemia, during which only a few gap junctions have closed. Hence, the voltage drop across the ischemic boundary in stage 3 ischemia tended to be smaller than stage 2 ischemia, which in turn resulted in smaller ESP gradients. A decrease in ESP gradients as a probable result of gap junction closure has been observed experimentally.¹³

The stage 3 simulations showed a greater sensitivity to fiber orientation than the stage 2 simulations. In the stage 3 simulations, the IC/EC resistance ratio transverse to fibers was very large. In particular, the ratio transverse to fibers was 250:1, compared with a corresponding ratio of 5:1 in the stage 2 simulations. Thus, in the stage 3 simulations, there was a very small extracellular voltage drop transverse to fiber direction. As a consequence, the resulting ESP depression was concentrated over the region where fibers throughout the ischemic region, from endocardium toward the epicardium, tended to be aligned with the TMP gradient (i.e., fibers were mostly parallel to the TMP gradient). In the computer heart model we used, fibers toward the apex of the heart, where the depression occurred in the stage 3 simulations, tended to be aligned with the TMP gradient throughout the ischemic zone because the fibers did not rotate much throughout that zone. However, fibers toward the base tended to rotate transmurally so that only a small portion were aligned with the TMP gradient. Thus, the net voltage drop across the lateral boundary toward the base tended to be small, such that there was a relatively smaller ESP depression at the lateral boundary towards the base.

By contrast, in the stage 2 simulations, ESP depression over the lateral boundary toward the base was relatively large. In this case, the IC/EC resistance ratio transverse to fiber direction was sufficiently small to allow a significant voltage drop across the ischemic boundary, even where the fibers were not exactly aligned with the TMP gradient across the boundary.

As discussed, the exact magnitude and location of ST depression depend on various conductivity values, fiber orientation, and the transmural geometry of ischemia. In reality, the nature of the depression also depends on the TMP distribution within healthy and ischemic tissue during the ST segment, which is generally more complicated than the simple patch described here. In particular, there is possibly a transmural TMP gradient in the ischemic zone due to transmural repolarization differences, which are caused by transmurally varying degrees of potassium channel activation.¹⁶ In addition, fiber orientation during systole, which includes the ST segment, is different from fiber orientation at rest.¹⁷ The fiber orientation data incorporated into the present computer model were based on measurements of an excised dog heart in diastole.⁸ Despite these limitations, the simple model described here generally accords with the experimental findings of Li et al. and Guyton et al.

We also have studied the relationship between ESPs and some of the earlier mentioned parameters, specifically the bidomain conductivities and the location and geometry of the ischemic boundary. We are in the process of drafting a paper describing these findings.

Possible Clinical Implications

We did not simulate body surface potentials. Therefore, we cannot quantify the extent to which lateral boundary ST depression manifests itself on the body surface. Nonetheless, based upon the biophysical theory described earlier, we hypothesize the following.

1. The reciprocal theory of ST depression is correct to the extent that, as measured by ECGs, ST depression tends to occur in leads that are not located "over" an ischemic region.
2. In the absence of ST elevation, the location of ST depression tends to occur in electrodes that are somewhere over a lateral boundary between ischemic and healthy tissue. In other words, if the ischemia is not sufficiently transmural, ST depression will not necessarily be observed in electrodes over healthy heart tissue away from the ischemic boundary.
3. In the case of multivessel coronary artery disease, in which two different ischemic regions are close together, the lateral TMP gradient may be small near the boundary between the ischemic regions, thereby tending to decrease the magnitude of both ST depression and ST elevation. In addition, even if a strong lateral TMP gradient exists for both ischemic regions, an electrode placed over one of the ischemic regions may remain isoelectric because the tendency toward ST elevation over that region may be canceled by reciprocal ST depression from the other region.⁴ Conversely, if a recording electrode is placed over the boundary between the two regions, ST depression as measured by that electrode may be relatively enhanced because both ischemic regions may contribute to the depression.⁴

4. As suggested by Smith et al.,¹³ the magnitude of ST depression may decrease as ischemia progresses in time, due to gap junction closure.
5. The voltage gradient on the body surface may be a sensitive indicator of ischemia. In body surface mapping studies, Menown et al.¹⁸ found that the body surface voltage gradient serves as a marker of ischemia. Moreover, the direction of the gradient may localize the ischemic tissue.

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