A Mechanism for ST Depression Associated with Contiguous Subendocardial Ischemia

Short title: Mechanism for ST Depression

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Abstract

Mechanism for ST Depression. *Introduction:* A mechanism is proposed for ST depression that arises on the epicardial surface above the border between normal and ischemic tissue. Depression is caused by current that flows in a transmural loop that begins and ends at the lateral boundary between healthy and ischemic tissue and that passes through the transmural boundary between healthy and ischemic tissue. The result is ST depression at the epicardium above the lateral boundary. The size and direction of current flow is dictated by differences in the magnitude and orientation of anisotropic conductivity between those boundaries. *Methods and Results:* Computer simulations verified and quantified the relationship of ST depression and these conductivity differences. We have 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 above a lateral boundary between healthy and ischemic tissue.

Index Terms

ischemia, ST depression, conductivity, computer model

I. Introduction

The diagnostic meaning of the location and extent of ST segment depression in 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, with [2] or without [3] concomitant ST elevation. ST depression in the case of multi-vessel coronary artery disease is particularly complicated due to the interplay between the voltage patterns caused by two or more ischemic regions [4].

Most of the theories regarding the meaning of ST depression rely on correlations between depression and coronary artery disease observed in patient studies. Given the large number of factors that can influence the nature of ST depression, the disparate conclusions of these studies is perhaps not surprising.

In an attempt 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 above one of the lateral boundaries, or border zones, between the ischemic and healthy tissue; this depression occurs with or without ST elevation directly above the ischemic region. In the case of ischemia caused by occlusions of the left anterior descending artery (LAD) and left circumflex (LCX), respectively, the boundaries of ischemic zones overlap so that the site of the 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 becomes increasingly transmural.

Regardless of the presence or absence of the primary ST elevation, Li et al. posited that ST depression occurs above the lateral healthy/ischemic boundary because the primary ”injury” currents that cause 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 and Kilpatrick [7] suggests that anisotropy plays an important role in determining the pattern of epicardial surface potentials (“ESPs”) that result 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 allowed us to support the basic finding of Li *et al.* of lateral boundary ST depression and also 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 that produce 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.

At the conclusion of this paper, we discuss some specific clinical implications of our findings.

II. METHODS

Ischemia was simulated using a geometric model based on the anatomical 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. To represent the electrical consequences of localized ischemia, we assigned to a patch of tissue 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 location and extent of the ischemic patch was chosen to match roughly the heart tissue that becomes ischemic due to a proximal occlusion of the left anterior descending artery [9]. The border zone between healthy and ischemic tissue was a few millimeters wide. Within this border zone, the transmembrane potential varied smoothly from -30mV to 0mV according to an exponential function [10]. The size of the ischemic patch was altered in the transmural direction to simulate various degrees of transmural ischemia.

The anatomy of the Auckland heart, including ventricles filled with blood, was represented with a hexahedral mesh defined by a number of nested, concentric layers. The heart consisted of 60 such layers that were weighted averages of the epicardial and endocardial surfaces. For example, the 30th layer was equal to 0.5*Epi + 0.5*Endo, where Epi and Endo are the cartesian coordinates that define 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:

$$\nabla \cdot (\bar{\sigma}_{ic} + \bar{\sigma}_e)\nabla V_e \quad = \quad -\nabla \cdot \bar{\sigma}_i \nabla V_m, \tag{1}$$

where

V_e is the extracellular potential

$\bar{\sigma}_i$ is the intracellular conductivity tensor

$\bar{\sigma}_e$ is the extracellular conductivity tensor

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. To set the conductivity values, we used results from our model of cardiac tissue [11], normalized to the value of the extracellular longitudinal conductivity[10]: $\sigma_{el} = 1, \sigma_{et} = 1/3, \sigma_{il} = 1, \sigma_{it} = 1/20$, 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 conductivities, respectively.

The ischemic conductivity values were chosen to correspond to two different stages of ischemia: (i) the time between 5–10 minutes after the onset of ischemia, after the extracellular space has shrunk but before a substantial number of gap junctions have closed ($\sigma^i_{el} = 1/2$ and $\sigma^i_{et} = 1/4$) with the intracellular conductivities for the ischemic tissue unchanged[11]; and (ii) some time between 15–30 minutes of ischemia, after a substantial number of gap junctions have closed ($\sigma^i_{el} = 1/2$ and $\sigma^i_{et} = 1/4$ and $\sigma^i_{il} = 1/10$ and $\sigma^i_{it} = 1/1000$) [11]. Normalizing all of the conductivities to an extracellular longitudinal conductivity of 1 is acceptable because the 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.

III. 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 5–10 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 case in which gap junctions have closed, consistent with experimental findings[12].

To isolate the effects of fiber orientation on the voltage drops across the ischemic boundary, in one set of simulations we restriced ischemia 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.

IV. Discussion

a) Overview: The top rows of Figure 2 show ESPs that mirror the general pattern of lateral boundary ST depression that intensifies as the degree of transmural ischemia increases. The maximal ST depression of approximately -3mV is smaller than the -12mV measured by Li *et al.* in sheep studies, but within a millivolt of the maximal ST depression found by Guyton *et al.* in canine studies [6]. 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 both the above mentioned animal studies and 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 the ischemia progressed transmurally. Finally, as in the Guyton *et al.* studies, we found endocardial ST elevation (not shown): (i) centered on the ischemic region, at all degrees of transmural ischemia, as was also found by Li *et al.*; (ii) having a magnitude (*e.g.* approximately 4 mV during the first stage of ischemia at 70% thickness 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 (iii) that 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 by Colli Franzone *et al.* of propagation[13]. 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[13]. In addition, Figure 3 shows that the maximum voltage drop occurs along the fiber direction, as was noted by Colli-Franzone et al. [13].

The concordance between propagation and ischemia is reasonable since an ischemic patch of heart tissue is similar to an activated patch of heart tissue, arising during propagation but before epicardial breakthrough. The polarities of the extrema in results presented by Colli Franzone *et al.* were opposite to those in the present study because the transmembrane potential ("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, which suggests that ESP amplitudes are sensitive to the values of the bidomain conductivitites. An important aspect of the relationship between the bidomain conductivities and ESPs will be discussed in the following paragraphs.

b) 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 which occurs during the ST segment. Unless otherwise stated, all references to currents and voltages will 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 measured 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 thence to the healthy side of the lateral boundary.

It is this extracellular current loop that is responsible for both ST-segment elevation and depression on the epicardium. Specificially, because one arm of the current flows from the transmural boundary toward and then along the epicardium to the lateral boundary, the area of the epicardium that is centered above the ischemic region will show a positive potential with respect to the area of the epicardium above the lateral boundary of the ischemic region. The resulting epicardial potential distribution will be 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 above the lateral ischemic boundary.

The reason that 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 extracallular potential across the ischemic boundary as:

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

where r_i and r_e are the 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 TMP's of the cells across the ischemic boundary. Thus, as the ratio of intracellular to extracellular resistance r_i/r_e (the IC/EC resistance ratio) decreases, the extracellular voltage drop across the boundary increases.

The IC/EC resistance ratio is typically 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 to 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) then along fibers (longitudinal), *i.e.* $r_{it} > r_{il}$ and $r_{et} > r_{el}$. Moreover, we and others have shown that the intracellular resistance is far more anisotropic than extracellular resistance [11], *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 in which the IC/EC resistance ratio is constant, which is the underlying assumption of the uniform double layer theory ("UDL"). Assuming that 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, there will tend to be ST depression centered above 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.

In sum, ST depression tends to occur above 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.

c) Volume conductor effects: The properties of the heart and blood as a volume conductor affect the magnitude and pattern of ESPs. However, simulations show that the voltage drops across the ischemic boundary largely determine ESPs and that volume conductor effects are of secondary importance.

d) Variation with the stage of ishcemia: The relation between conductivity and extracellular potential, as described above, 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, respectively, of ischemia. In the simulations corresponding to stage 3, the 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 [12].

Furthermore, 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 above 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 since these 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 towards 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, the ESP depression over the lateral boundary towards 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 TMP gradient across the boundary.

As discussed, the exact magnitude and location of ST depression depends on various conductivity values, fiber orientation, and the transmural geometry of the ischemia. In reality, the nature of the depression will also depend on the TMP distribution within healthy and ischemic tissue during the ST segment, which is generally more complicated than the simple patch described in this paper. Furthermore, fiber orientation during systole, which includes the ST segment, is different from fiber orientation at rest [14]; the fiber orientation data incorporated into the present computer model was based on measurements of an excised dog heart in diastole [8]. Despite these limitations, the

simple model described herein generally accords with the experimental findings of Li *et al.* and Guyton *et al.*

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

V. Conclusion

Our simulation results suggest the following:

1) The reciprocal theory of ST depression is correct to the extent that, as measured by ECGs, ST depression will tend to occur in leads that are not located ”over”an ischemic region.
2) In the absence of ST elevation, the location of ST depression will tend to occur in electrodes that are somewhere in front of 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 too far beyond the ischemic boundary.
3) In the case of multi-vessel CAD, in which two different ischemic regions are close to one another, 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 above one of the ischemic regions may remain isoelectric, since the tendency toward ST elevation above that region may be canceled by reciprocal ST depression from the other region [4]. Conversely, if a recording electrode is placed above the boundary between the two regions, ST depression as measured by that electrode may be relatively enhanced, since both ischemic regions may contribute to the depression [4].
4) As suggested by Smith *et al.* [12], 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.* [15] found that the body surface voltage gradient serves as a marker of ischemia. Moreover, the direction of the gradient may localize the ischemic tissue.

References

[1] Wagner GS. *Marriott’s practical electrocardiography*. Lippincott Williams & Wilkinstenth ed. 2001.

[2] Zoghi M, Gürgün C, Yavuzgil O, Türkoğlu I, Kültürsay H, Akilli A, Akin M, Türkoğlu C. The angiographic correlation between ST segment depression in noninfarcted leads and the extent of coronary artery disease in patients with acute inferior myocardial infarction: a clue for multivessel disease *Can J Cardiol.* 2003;19:67-71.

[3] Barrabés JA, Figueras J, Moure Cristina, Cortadellas J, Soler-Soler J. Prognostic Significance of ST Segment Depression in Lateral Leads I, aVL, V5 and V6 on the Admission Electrocardiogram in Patients With a First Acute Myocardial Infarction Without ST Segment Elevation *J Am Coll Cardiol.* 2000;35:1813-1819.

[4] Lew AS, Maddahi J, Shah PK, Weiss AT, Peter T, Berman DS, Ganz W. Factors that Determine the Direction and Magnitude of Precordial ST-Segment Deviations During Inferior Wall Acute Myocardial Infarction *Am J Cardiol.* 1985;55:883-888.

[5] Li D, Li CY, Yong AC, Kilpatrick D. Source of Electrocardiograhpic ST Changes in Subendocardial Ischemia *Circ Res.* 1998;82:957-990.

[6] Guyton RA, McClenathan JH, Newman GE, Michaelis LL. Significance of subendocardial S-T segment elevation caused by coronary stenosis in the dog. Epicardial S-T segment depression, local ischemia and subsequent necrosis *Am J Cardiol.* 1977;40:373-380.

[7] Johnston P, Kilpatrick D, Yong Li C. The importance of anisotropy in modeling ST segment shift in subendocardial ischaemia *IEEE Trans Biomed Eng.* 2001;48:1366-1376.

[8] Nielsen PMF, LeGrice IJ, Smaill BH, Hunter PJ. Mathematical model of geometry and fibrous structure of the heart *Am J Physiol.* 1991;260(4 Pt2):H1365:H1378.

[9] Kléber AG, Riegger CB. Electrical constants of arterially perfused rabbit papillary muscle *J Physiol.* 1987;385:307-324.

[10] Johnston P, Kilpatrick D. The effect of conductivity values on ST segment shift in subendocardial ischaemia *IEEE Trans Biomed Eng.* 2003;50:150-158.

[11] Stinstra JG, Hopenfeld B, MacLeod RS. A model for the passive cardiac conductivity *International Journal of Bioelectromagnetism.* 2003;5:185-186.

[12] Smith WT, Fleet WF, Johnson TA, Engle CL, Cascio WE. The Ib Phase of Ventricular Arrhythmias in Ischemic In Situ Porcine Heart Is Related to Changes in Cell-to-Cell Electrical Coupling *Circulation.* 1995;92:3051-3060.

[13] Colli Franzone P, Guerri L, Pennacchio M, Taccardi B. Spread of Excitation in 3-D Models of the Anisotropic Cardiac Tissue. III. Effects of Ventricular Geometry and fiber structure on the potential distribution *Math Biosci.* 1998;151:51-98.

[14] Streeter DD Jr, Spotnitz HM, Patel DP, Ross J Jr., Sonnenblick EH. Fiber orientation in the canine left ventricle during diastole and systole *Circ Res.* 1969;24:339-47.

[15] Menown IB, Patterson RS, MacKenzie G, Adgey AA. Body-surface map models for early diagnosis of acute myocardial infarction *J Electrocardiol.* 1998;31 Suppl.:180-188.

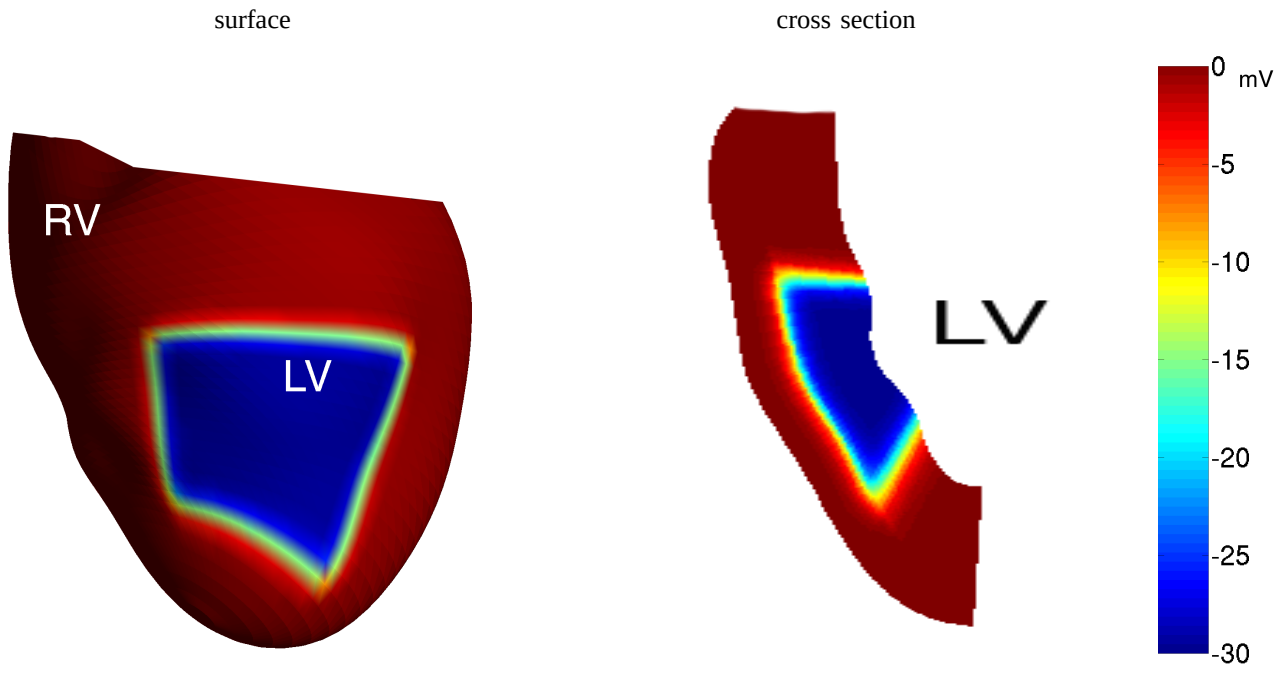

Fig. 1. Transmembrane potential distribution over a midmyocardial layer and a sagittal slice showing an anterior, subendocardial ischemic zone. The transmembrane potential of the ischemic patch was negative with respect to the transmembrane potential of the healthy tissue, as indicated by the colorbar.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

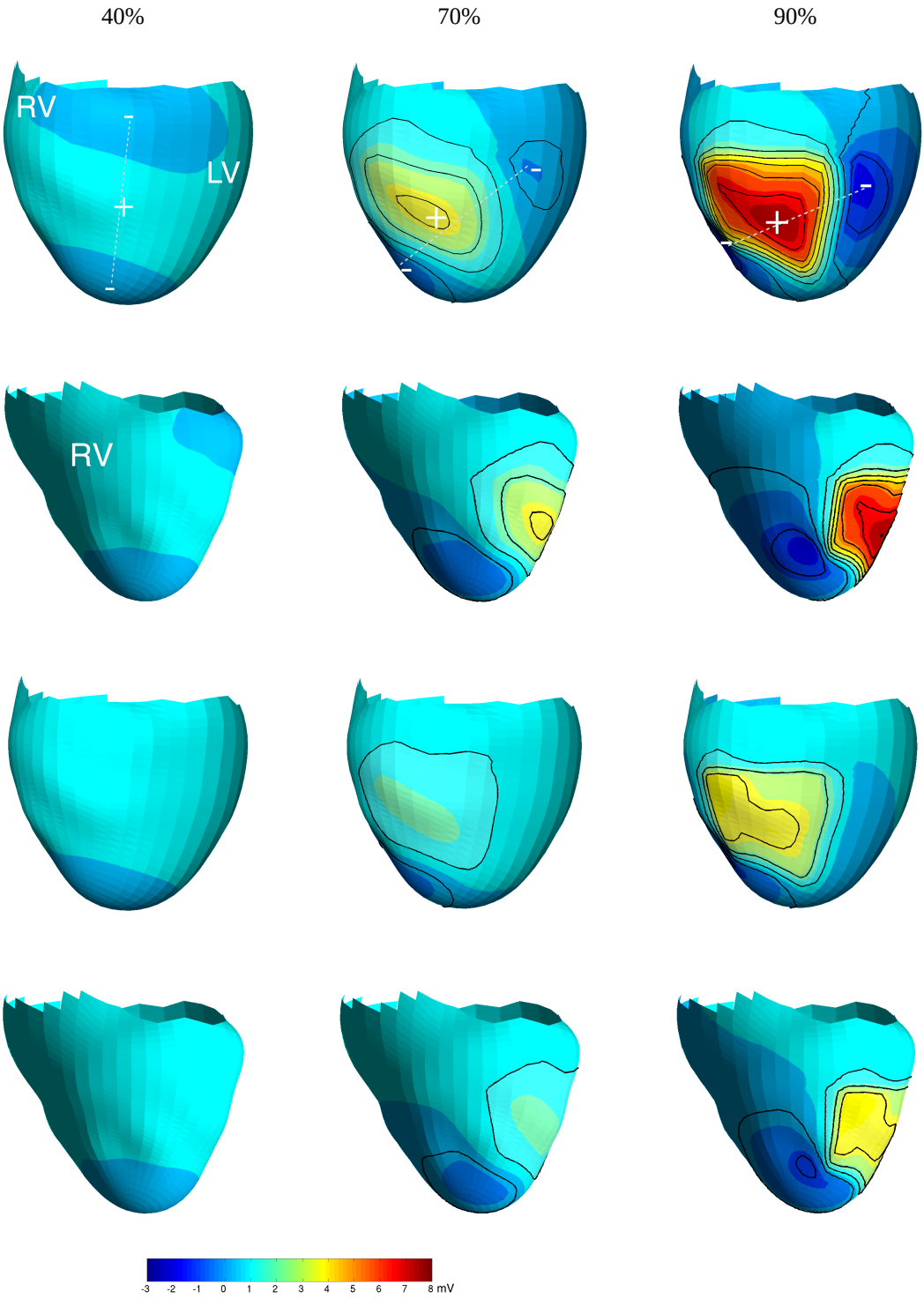

Fig. 2. Epicardial distributions resulting from various degrees of transmural ischemia. The percentage transmural ischemia is shown at the top of each figure. The top two rows and bottom two rows show simulation results of stage 2 and stage 3 ischemia, respectively. The first and third rows show anterior 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.

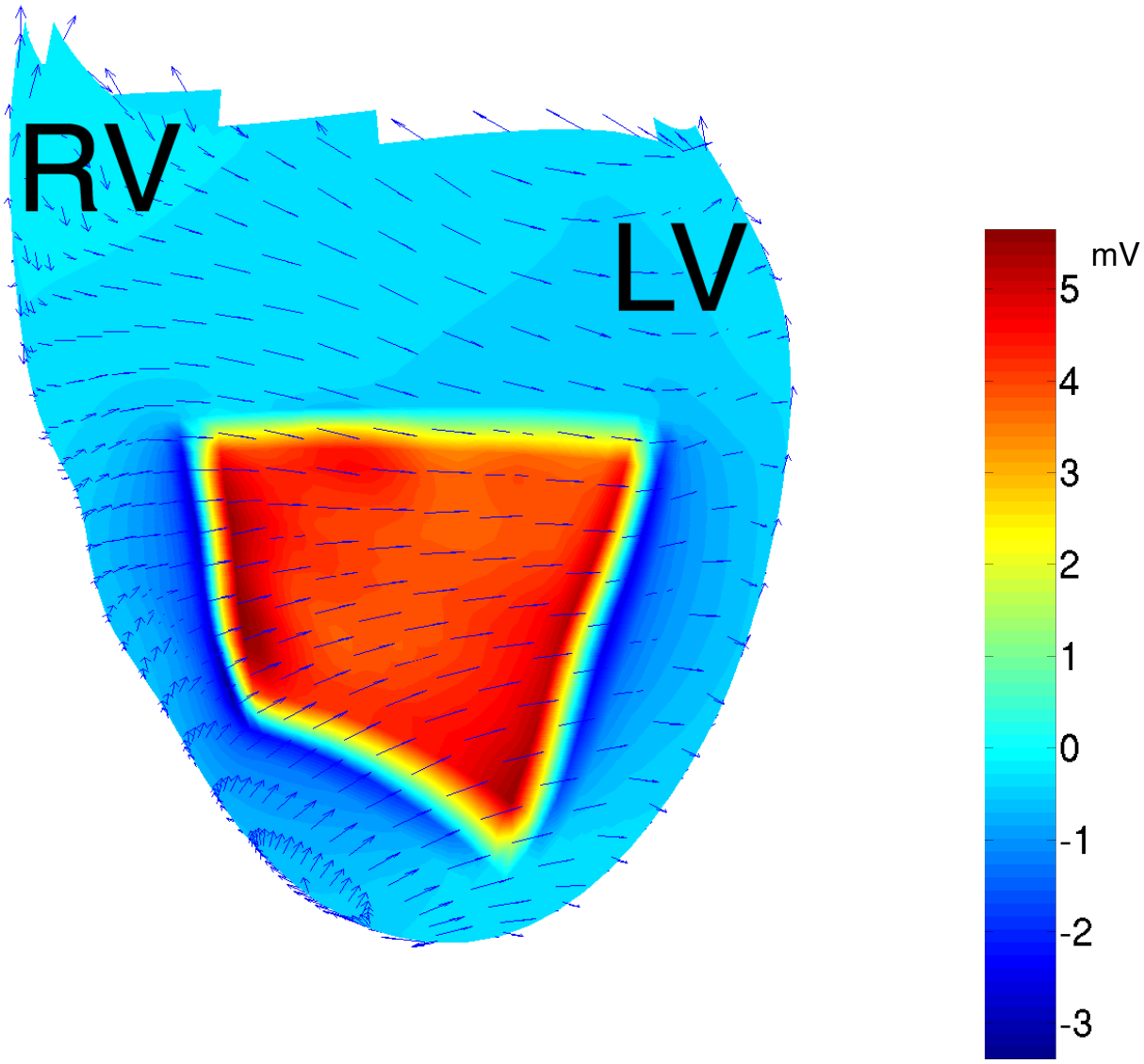

Fig. 3. Extracellular potential distribution on an internal heart layer, showing the effect of fiber orientation on the voltage drop across the ischemic boundary (indicated by the positive potential values).

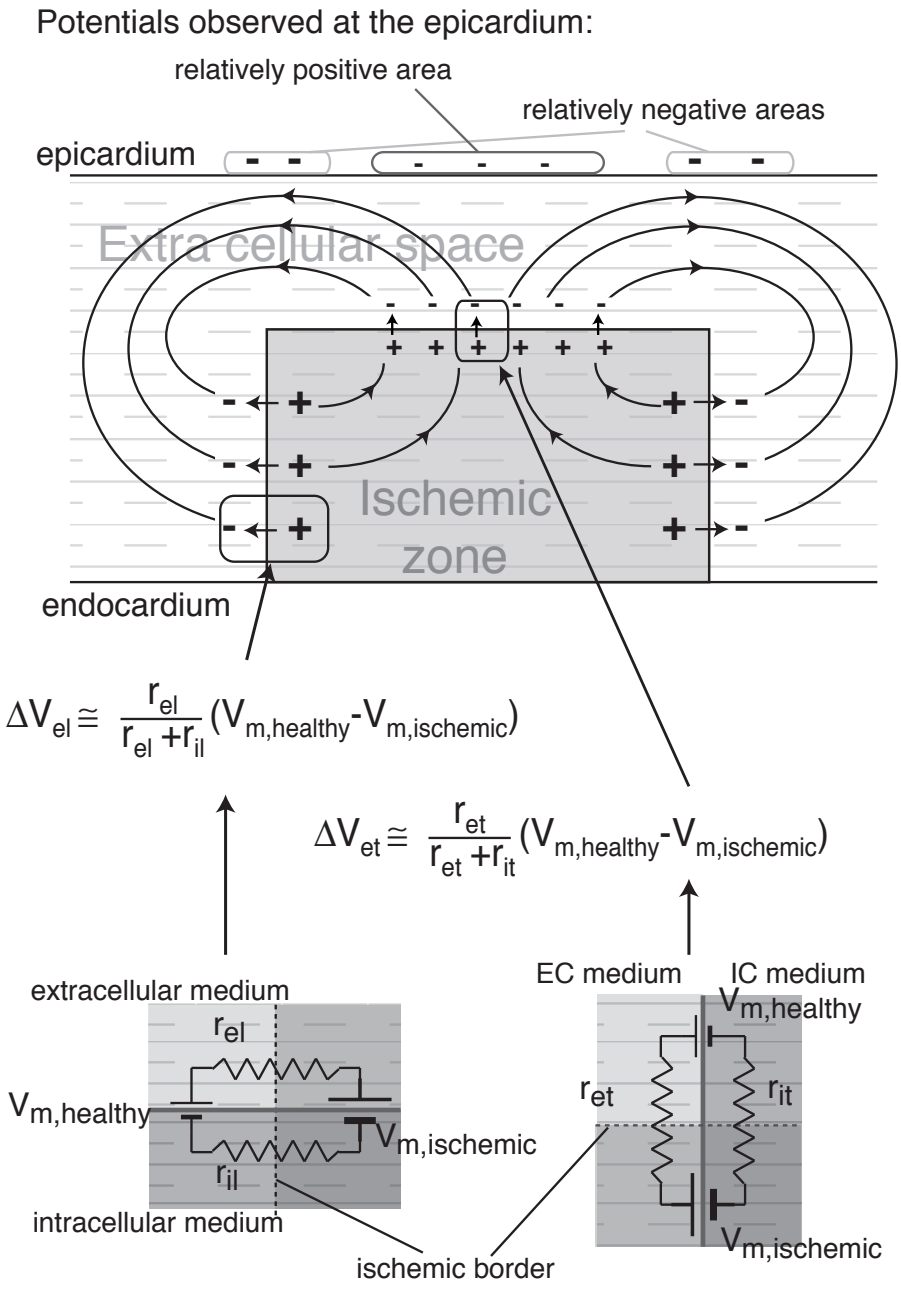

Fig. 4. Current flow and voltage drops in an ischemic heart. The voltage drop across the lateral ischemic boundary is greater than the voltage drop across the transmural boundary, as indicated by the size of the + and - symbols. Most current flows directly across the ischemic boundary, as indicated by 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 thence to the healthy tissue on the lateral boundary. The voltage drop ΔV_e is greater across the lateral than 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 ischemia boundary must flow and are oriented with respect to fiber orientation; at the lateral boundary, the resistors are parallel to the fiber direction and are thus displayed horizontally while 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 while 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.