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# ST elevation or depression in subendocardial ischemia?

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***Abstract*— ST-segment depression in epicardial electrograms can be a "reciprocal" effect of remote myocardial ischemia (MI), and can also be due to local partial-thickness or "subendocardial" MI. Experimental studies have shown either ST elevation or depression in leads overlying a subendocardial ischemic region. Those reporting elevation have shown depression over the lateral borders of the ischemia. Simulation studies with anisotropic models have explained the ST-elevation results. Presently, while experimentalists may have difficulty understanding the ST elevation, most model studies fail to explain ST depression in overlying leads during partial-thickness ischemia. We have simulated partial-thickness ischemia in a 3-dimensional model of the human heart. Our results show that the conductivity of the intracavitary blood, geometry of the ischemic region, and bidomain anisotropy ratios can all have a decisive influence on the sign of the ST deviation. We hypothesize that ST depression in leads overlying an ischemic zone is due to subendocardial ischemia in tissue where a redistribution of gap junctions has taken place.**

## I. Introduction

Ischemia leads to a higher resting membrane potential of cardiac myocytes, and subsequently to a lower plateau potential [1]. In extracellular electrograms, this leads to a depression of the TQ segment and an elevation of the ST segment, respectively (Fig. 1). In electrograms measured with AC-coupled amplifiers, only the difference between ST-segment and TQ-segment potential can be observed. In this paper, we will use the term "ST deviation" for this difference.

Transmural ischemia causes ST elevation in epicardial leads overlying the ischemic area and "reciprocal" depression over its lateral borders. For ST depression in overlying leads, partial-thickness ischemia is a necessary condition [2]. In epicardial leads, ST depression has been observed when subendocardial ischemia or injury was produced in the in-situ dog heart [2], [3]. These studies suggested that the ST depression area on the epicardium coincided with the ST elevation area on the endocardium. However, other studies have shown that the deepest ST depression is located over a lateral border of the ischemia [4], [5]. Moreover, this negative zone does not change position during a transition from partial-thickness to full-thickness ischemia [5], suggesting that it is of the same "reciprocal" nature. The disparity of the results obtained in different studies suggests that partial-thickness ischemia is not a sufficient condition for ST depression in overlying leads.

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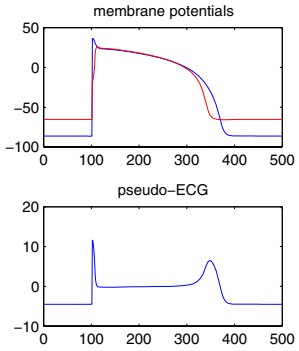


Fig. 1. Top panel: normal (blue) and ischemic (red) action potentials, the latter due to increased extracellular potassium concentration. Bottom panel: pseudo-ECG recorded over a one-dimensional preparation containing one half normal and one half ischemic cells. TQ-segment depression can be observed, which would appear as ST-segment elevation in an AC-coupled ECG. In addition, an increase in T-wave amplitude can be seen. For this example, all cells were stimulated simultaneously, so that there are no effects of propagation in this pseudo-ECG.

Recent computer simulations of subendocardial ischemia have predicted ST elevation in epicardial leads overlying a partial-thickness ischemia [6], [7]. Depression of the ST segment was found laterally, as in the more recent experimental studies [4], [5]. Anisotropy and conductivity values are critically important to obtain correct results [8], [6], [9]. Consequently, the above studies were based on realistic tissue conductivities for healthy myocardium. However, in a heart that has already undergone ischemia and reperfusion, or in a hypertrophic heart, the intracellular conductivity may be abnormal due to a redistribution of gap junctions [10], [11]. If ischemia (re)occurs in such a heart, the modified conductivity will affect the ST deviation. In this study we investigate the possibility that conductivity changes account for ST depression in epicardial leads overlying a subendocardial ischemic area. We investigated also the effect of size and transmural extent of the ischemic region, as well as the influence of intracavitary blood. Our results show that a very large but nontransmural ischemia may also cause ST depression in overlying leads. However, such a geometry is unlikely. Therefore we propose that ST deviation in epicardial leads overlying a subendocardial ischemic zone may be caused by gap junctional remodeling that results from a previous ischemia and reperfusion, or from tissue hypertrophy.

## II. Methods

Extracellular potentials throughout the heart were simulated using a bidomain model of the human heart that was described previously [12], [13]. Simulation was limited to

TABLE I

ASSUMED NORMAL BIDOMAIN CONDUCTIVITY VALUES IN MS/CM.

| | transverse | longitudinal | ratio |
|---|---|---|---|
| intracellular | $\sigma_{\mathrm{iT}} = 0.3$ | $\sigma_{\mathrm{iL}} = 3.0$ | 10 |
| extracellular | $\sigma_{\mathrm{eT}} = 1.2$ | $\sigma_{\mathrm{eL}} = 3.0$ | 2.5 |
| blood | isotropic $\sigma_{\mathrm{e}} = 6.0$ | | |
| connective tissue | isotropic $\sigma_{\mathrm{e}} = 2.0$ | | |

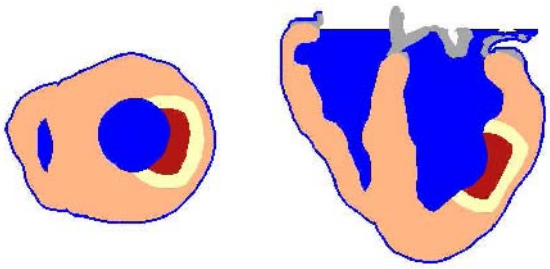

Fig. 2. Transverse and longitudinal sections of the model anatomy, with ischemic area (red) and border zone (yellow) in the LV lateral wall. Blue indicates blood (in the cavities and in a thin layer on the epicardium); gray indicates connective tissue. The zero reference for the extracellular potential was taken in the vicinity of the aortic root.

the ventricles. For this study, the heart was discretized in 3 dimensions at 0.25-mm resolution. Extracellular potentials were computed at 22 million nodes connected with an anisotropic bidomain tissue model incorporating an endocardial to epicardial rotation in fiber direction. Since we were only interested in the amount of ST deviation, we did not use the model's capability to simulate propagating action potentials. As is commonly done for the study of ST deviation [6], [7], we assumed that during the ST segment the difference in membrane potential between ischemic and normal tissue was $-30\,\mathrm{mV}$ with respect to the difference during the TQ segment [4], [8]. The model was then used to compute the corresponding extracellular potential offsets. Results are reported in terms of difference in extracellular potential between TQ and ST segment that would result from this hypothetical ischemia. Normal conductivity values were taken from a review paper by Roth [14]. An overview of these values is given in Tab. I.

A subendocardial ischemic area was created in the lateral wall of the left ventricle. This area was surrounded by a border zone which had the same tissue conductivities as the ischemic zone, and the same membrane potential as the healthy tissue. The anatomy of the model is illustrated in figure 2.

## III. RESULTS

Figure 3 shows simulated extracellular potentials in a section of the heart, for an ischemic region with a radius $r = 10\,\mathrm{mm}$ and a transmural extent of 50 %. In the supposedly normal case with anisotropic intracellular domain, the lower membrane potential in the ischemic area causes current to flow mainly in the direction of the fibers. This creates two current sinks in the extracellular domain adjacent to the

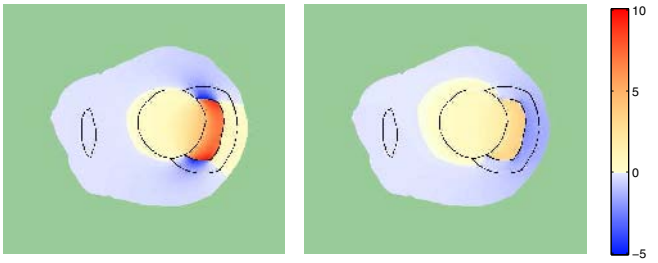


Fig. 3. ST deviations in the extracellular domain, shown in a transverse section of the heart. Potential differences are shown as pseudocolors, the scale is in mV. Left panel: normal anisotropy ratio 10 for the intracellular domain. Right panel: isotropic intracellular domain. In the normal anisotropic case, ST elevation is measured on the epicardium. In the isotropic case, ST depression is obtained. Due to the Brody effect, the epicardium is more negative than the endocardium adjacent to the ischemia.

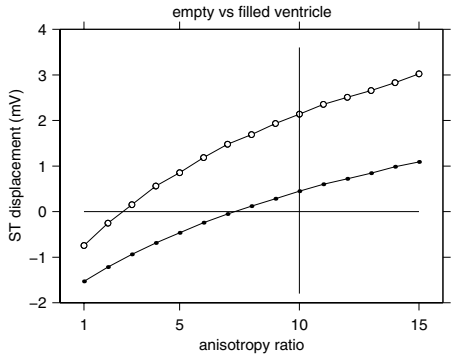


Fig. 4. ST deviation as a function of intracellular anisotropy ratio. Filled circles represent results obtained with blood-filled cavities, open circles empty cavities. In the blood-filled heart, transition from ST elevation to ST depression occurs when the anisotropy ratio drops below 7. Simulations in an empty heart would predict a much larger range of anisotropy ratios where ST elevation occurs. The vertical line marks the assumed normal anisotropy ratio of 10.

ischemic area, and a positive area on the epicardial side, as explained previously by Hopenfeld et al. [6].

In contrast, in a fully isotropic intracellular domain, current flows equally in all directions leading to a current sink area in the extracellular domain surrounding the ischemic area. The epicardium overlying the ischemia now obtains a negative potential at the measuring site. This effect is enhanced by the intracavitary blood (the Brody effect).

In order to implement gap junctional remodeling with the bidomain model we varied the anisotropy ratio of the intracellular domain stepwise around its normal value of 10 [14]. This was done by modifying $\sigma_{\mathrm{iL}}$, while $\sigma_{\mathrm{iT}}$ was fixed at 0.3 mS/cm. Results of this analysis are shown in Fig. 4. The ST elevation is seen to reduce gradually with a reduction in anisotropy ratio, and to change into depression when this ratio is below 7. The analysis of intracellular anisotropy ratio was repeated without intracavitary blood. The results are shown with open circles in Fig. 4. In this case, the ST elevations were much larger and reversal occurred only at an anisotropy ratio of 2.5.

The effects of ischemic area and extent in a heart with normal anisotropy are illustrated in Fig. 5. Each row illustrates the effect of the endocardial extent of the ischemic area

for a constant transmural extent. A small central maximum is found on the epicardium overlying the smallest ischemic region. Larger areas lead to near-zero potentials over the ischemic zone. Increased transmural extent leads to slightly elevated potentials. Minima are found over the lateral borders in all cases. A minimum overlying the ischemic zone only occurs for the largest ischemic region ($r = 37.5\,\mathrm{mm}$) and only for up to $70\,\%$ transmural extent.

## IV. Discussion

Simulation of an isolated heart, without torso coupling, is useful to explain findings in Langendorff-perfused hearts and in-vivo hearts suspended in a pericardial cradle. In the former, intracavitary blood is usually absent, while in the latter the heart is functioning normally. While Langendorff setups are also used to study ischemia [15], the experimental studies reviewed here used in-vivo hearts [2], [3], [4], [5], i.e. with intracavitary blood. The model study by Hopenfeld et al. used an isolated heart without intracavitary blood [6], while MacLachlan et al. used a blood-filled heart embedded in a human torso [7]. We have shown that intracavitary blood has an important influence that should be taken into account when an in-situ heart is simulated. It is to be expected that the conductivity of the torso has an equally important influence, which has to be accounted for when an experiment is simulated that involves endocardial or epicardial electrodes in a closed-chest situation [7].

Our results show that mild ST depression on the epicardium overlying the ischemic zone can occur if the ischemic area is large enough. Small subendocardial ischemia results in ST elevation. Potential minima are always found over the borders of the ischema. If the area is large enough, however, another local minimum appears over the center of the ischemic area.

Although a large ischemic area may explain ST depression, the size that is necessary is unrealistically large. A local minimum can also occur, and be of larger amplitude, if the intracellular anisotropy ratio is reduced below 7 (in the blood-filled heart). A possible mechanism for a reduction of intracellular anisotropy is the redistribution of gap junctions that is thought to occur after ischemia and reperfusion, as well as in hypertrophied myocardium [10]. Gap junctions are formed by connexins. In the human ventricle, Connexin 43 (Cx43) is the most important of these. Ischemia reduces expression of connexins. Reperfusion makes them reappear, but with a different distribution [10], [11]. It is not known if the reappearing connexins are bound to the cell membrane and if they are part of functional gap junctions. If they are, transverse intracellular conductivity could be closer to longitudinal conductivity than it is in healthy tissue. According to our simulation results, this modification in tissue conductivity would be an important determinant of ST depression in a subsequent partial-thickness ischemia (Fig. 4).

Like previous authors [16], [6], [5], we found that accurate knowledge of the anisotropic bidomain conductivity values is necessary to understand ST deviation. Unfortunately, the conductivity values are not accurately known [14]. For a complete understanding of ST deviation, better estimates of these values are sorely needed [5]. Measuring anisotropic intracellular and extracellular conductivity in tissue is difficult, and has so far only been possible in papillary muscles. Conductivity changes in ischemia have been measured, but anisotropy was not reported [17]. As long as the conductivity values are uncertain, mathematical models can only predict the effect of changes in parameters. Sign and magnitude of ST deviation cannot be predicted with certainty.

Despite the uncertainty about the conductivity values, it may be concluded from simulation studies such as ours and MacLachlan's [7] that epicardial ST deviations resulting from subendocardial ischemia in blood-filled ventricles are in the range of $\pm 2\,\mathrm{mV}$. Larger amplitudes, such as reported by Li et al. [4], would suggest that the transmural extent of the region with abnormal membrane potentials is near $100\,\%$.

In our simulations we have ignored the gradient of membrane potential in the ischemic border zone [18]. This may have affected epicardial potential values.

Our results cannot be easily extrapolated to the surface ECG. Inhomogeneities in the thoracic conductivities, such as the lungs, the major arteries and veins, and the skeletal muscle layer, have an important influence on the ECG leads [19]. Offset in Wilson's central terminal may influence the appearance of ST deviation patterns, notably in case of posterior ischemic regions. An anisotropic model of the heart coupled to an inhomogeneous torso model is required to predict ST-segment changes in the ECG correctly [7].

## V. Acknowledgment

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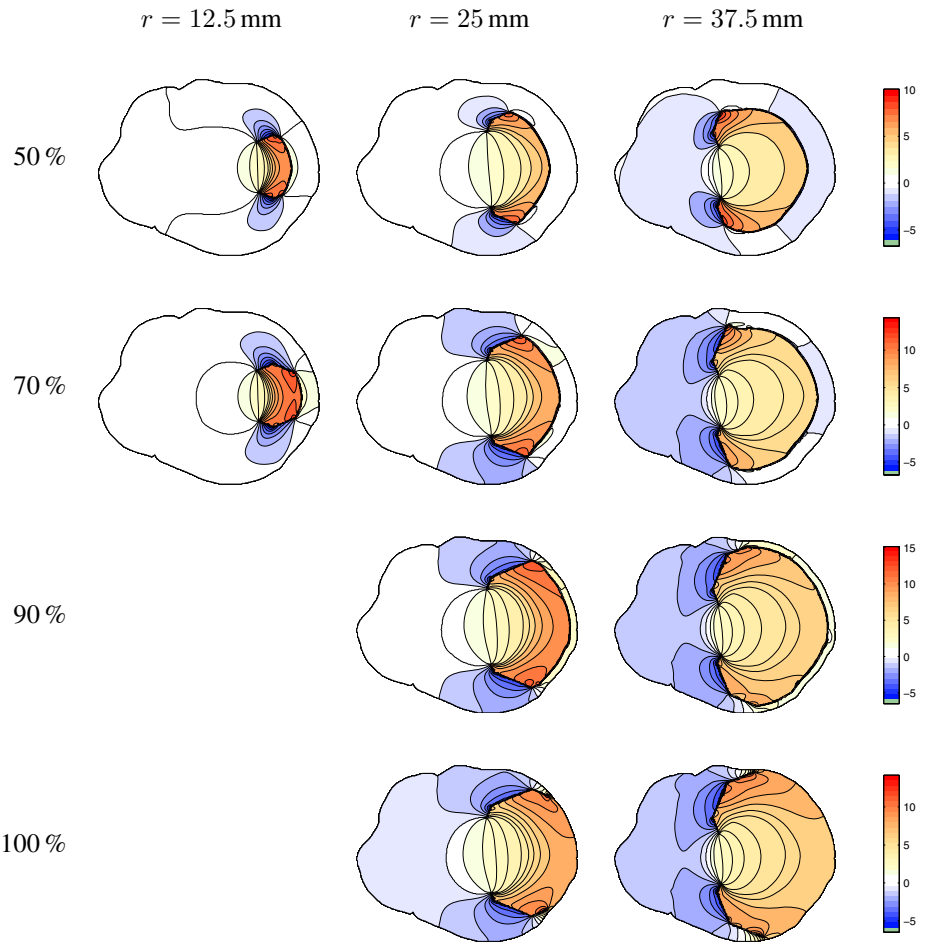


Fig. 5. Extracellular potentials in a transmural slice of the heart, resulting from 10 different ischemic regions. Potentials are shown with colors and isopotential lines at 1-mV interval. From left to right, the radius of the ischemia varies from 12.5 to 37.5 mm. From top to bottom, transmural extent increases from 50 to 100 %. Normal anisotropy is assumed. Due to the orientation of fibers parallel to the surfaces, large potentials are confined to the interior layers of the heart. A small central maximum is found on the epicardium overlying the smallest ischemic region. Minima are found over the lateral borders in all cases. A third minimum occurs over the center of the largest ischemic region. The region with $r = 12.5\,\mathrm{mm}$ and 50 % transmural extent corresponds approximately with the region shown in Fig. 3.


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