Simulating the Impact of the Transmural Extent of Acute Ischemia on the Electrocardiogram

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Abstract

During acute cardiac ischemia, electrophysiological properties of the affected tissue are altered in the subendocardium firstly. If the occlusion worsens, the effects spread transmurally. Diagnosis of cardiac ischemia, which should be improved by computer simulations, is based on shifts of the ST segment. In this work, we simulated heterogeneous ischemic regions with varying transmural extent. The excitation propagation and ECGs were calculated for the different setups. We showed that ST segment polarity can be dependent on the transmural extent of the ischemic region. In case of subendocardial ischemia, short action potentials were initiated in the ischemic zone causing a slight transmural gradient of the transmembrane voltage. Therefore, the ST segment was depressed in leads near the ischemic region in the chosen case. During transmural ischemia, this gradient showed in the opposite direction from epicardium to endocardium leading to ST segment elevation.

1. Introduction

Acute cardiac ischemia, which often leads to lethal heart failure or severe ventricular arrhythmias, is characterized by a deficient blood supply of the heart muscle due to the occlusion of a coronary artery. Consequently, a shortage of nutrients and oxygen as well as an insufficient removal of metabolic waste products can be observed. Mainly three effects occur during the course of acute ischemia: hyperkalemia, acidosis and hypoxia. Due to these changes, some electrophysiological characteristics are modified: The resting transmembrane voltage increases, the action potential duration (APD) decreases, the refractory period is prolonged, the conduction velocity (CV) is reduced and the excitability is altered [1]. Furthermore, these effects appear in the subendocardium at first (*subendocardial ischemia*). This is due to the greater distance to the coronary arteries and the greater myocardial contraction, blood flow and metabolic activity there. If the occlusion of the artery worsens or continues for longer periods, ischemia and later on necrosis spread transmurally towards the subepicardium [2], which is called *transmural ischemia*.

In clinical practice, shifts of the ST segment of the electrocardiogram (ECG) are an important indicator of cardiac ischemia. They are caused by so-called injury currents flowing between ischemic and healthy tissue. The direction of the shift depends on the transmural extent of ischemia [3]. This can be explained by vectors caused by the injury currents. During subendocardial ischemia, this ST vector points away from the injury region leading to ST depression in leads close to the ischemic region, whereas it is directed towards the injury in case of epicardial ischemia causing ST elevation [4]. However, the exact mechanisms responsible for these shifts are still incompletely understood and the diagnosis based on ST segment elevation or depression is discussed extensively [4].

In this work, the impact of the transmural extent of ischemia on the ECG is investigated using computer simulations. The aim is to better understand the underlying effects and to improve the early diagnosis of ischemia.

2. Methods

The anatomical models of the ventricles and thorax used for the simulation of cardiac excitation propagation and for the calculation of body surface potential maps (BSPM) were derived from MR images of a healthy volunteer. The cardiac fiber orientation was modeled using a rule-based method as in [5].

The electrophysiology of ventricular endocardial, midmyocardial and epicardial cells was described based on the cardiac cell model developed by ten Tusscher et al. in 2006 [6]. Modifications of Weiss et al. [1] modeled the main effects of acute cardiac ischemia ten minutes after the occlusion of a coronary artery: hyperkalemia, acidosis and hypoxia. For this purpose, e.g. an ATP-sensitive potassium current was added. However, the formulation of the half-maximum inhibition constant K_m of this channel was adjusted, so that the current was inhibited at healthy ADP concentrations leading to $K_m = (-151.0919 + 75.5379 \cdot [ADP]_i^{0.256}) \cdot K_{m,factor}$. Furthermore, electrophysiological transmural and apico-basal heterogeneities were incorporated to allow a realistic excitation and repolarization

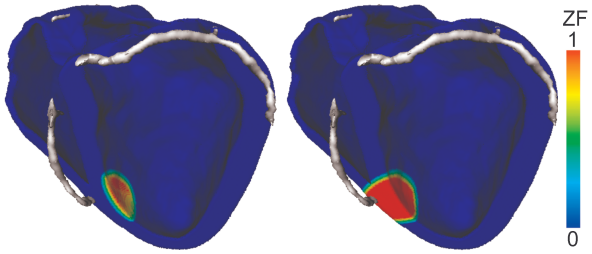

Figure 1. Schematic sections of the ventricles showing the main coronary arteries and the ischemic regions using the zone factor (ZF). Ischemic region with smallest (*left*) and biggest (*right*) radius in transmural direction.

pattern. As in [5], the ventricular wall was divided into 40% endocardial, 40% midmyocardial and 20% epicardial tissue. According to the original cell model of ten Tusscher et al., the conductivities g_{Ks}, g_{to} and the corresponding channel kinetics differed transmurally. Additionally, g_{Ks} was two times larger at the apex than at the base [5]. The ischemic effects were modeled heterogeneously as well. In addition to transmural variation of the effects, regional differences caused by the occlusion of a coronary artery were included. This was achieved by a so-called zone factor (ZF), which described healthy tissue ($\mathrm{ZF} = 0$), the central ischemic zone (CIZ, $\mathrm{ZF} = 1$) and the border zone (BZ) between them [1]. The ischemic regions were modeled as ellipsoids with their centers placed next to the endocardium (see also figure 1). In this work, an occlusion of the left anterior descending coronary artery was investigated. A short axis of the ellipsoids was varied in transmural direction. Thereby, 15 different setups with linearly increasing transmural extent were obtained. In figure 1, the setups with smallest (*Ischemia1*) and largest (*Ischemia15*) radius are shown, describing subendocardial and transmural ischemia. The width of the BZ was constant ($4\,\mathrm{mm}$) in all setups. Furthermore, the size of the endocardial surface of the ischemic region was also constant, so that the transmural extent and the total size of the ischemic region were the only differences between the setups. The size of the ischemic region was 1.36% of the left ventricle in case of subendocardial and 3.85% in case of transmural ischemia. In addition to that, a control case without effects of cardiac ischemia was simulated for better comparison of the results.

The parallel monodomain solver *acCELLerate* [7] was used for the simulation of electrical excitation propagation in consideration of an anisotropic conduction in cardiac muscle fibers. An endocardial stimulation profile mimicking the conduction system initiated ventricular activation [5]. The effects of ischemia were first initialized in a single-cell environment, until the requested ischemia stage (ten minutes after occlusion) was reached. Then, the transmembrane voltages of a single heart beat ($450\,\mathrm{ms}$) were simulated using the 3D ventricular model. These calculations took 8.5 hours on 16 cores (Apple Intel Xeon 5400, $2.8\,\mathrm{GHz}$). To obtain the corresponding BSPM and ECG, the forward problem of electrocardiography was solved using inhomogeneous and anisotropic tissue conductivities as described in [5]. Since small ischemic regions were modeled, only local changes were expected in the BSPMs. Due to this, the focus of ECG analysis was on the precordial (chest) leads.

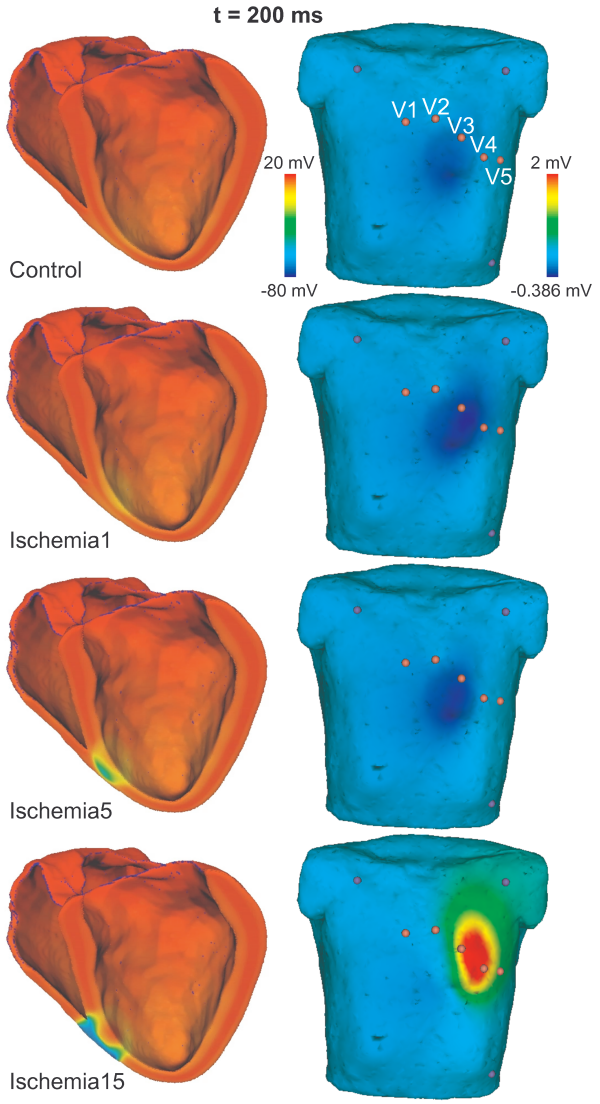

Figure 2. Transmembrane voltages in the ventricles (*left*) and corresponding BSPMs (*right*) of control case and different ischemia setups at $t = 200\,\mathrm{ms}$ after stimulation.

3. Results

In comparison to the control case, the cardiac excitation propagation was altered during acute ischemia. The most prominent changes, which were also visible in the ECG, could be observed during the ST segment. In the control case, a relatively homogeneous plateau phase of the ventricles could be seen after 200 ms. Consequently, there was almost no gradient of voltage in the completely activated ventricles. Thus, the potential became approximately zero on the body surface, which is illustrated in figure 2, *top*. There, the virtual ECG electrodes, which are the precordial leads V_1 to V_6 (V_6 on the back, not shown) and the Wilson central terminal as reference, are presented.

In case of apical septal subendocardial ischemia (setup *Ischemia1*), the electrical excitation entered the ischemic region, where shorter action potentials (APs) with lower amplitude were initiated. Therefore, the repolarization already started there after 200 ms, leading to a gradient of the transmembrane voltage from endocardium to epicardium. This caused a slight unipolar decrease of the body surface potential close to the ischemic region (see figure 2). In case of this occlusion site, leads V_3 and V_4 were most affected by the ischemic changes.

As the transmural extent of the ischemic region was increased and the BZ touched the epicardium (setup *Ischemia5*), the excitation also activated this region. However, the APs initiated in the epicardial BZ were shorter due to the heterogeneity of the ATP-sensitive potassium channel. Due to this, two opposite gradients of the transmembrane voltage, one from the ischemic to the healthy epicardium and the other from the ischemic epicardium towards the ischemic endocardium, existed. As a result, the potential on the body surface became nearly zero.

Further increase of the radius of the ellipsoidal ischemic region (setup *Ischemia15*) created completely transmural ischemia. In this case, the epicardial CIZ was not excited, which led to a gradient of the transmembrane voltage from epicardium towards endocardium. Consequently, an unipolar increase of the body surface potential next to the ischemic region can be seen in figure 2, *bottom*.

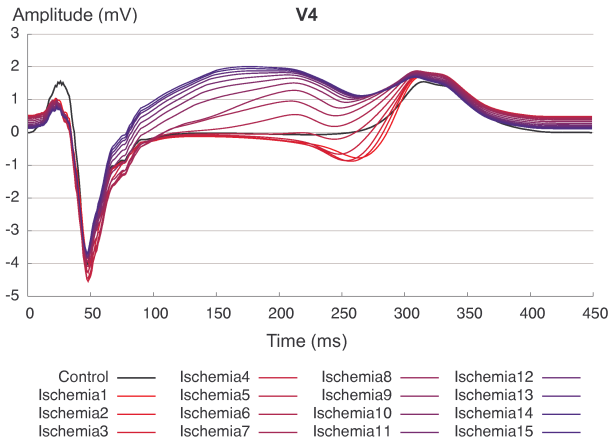

Figure 3. ECGs (precordial lead V_4) of control case and 15 setups with different transmural extent of ischemia.

The resulting ECGs of all ischemia setups and the control case are visualized in figure 3. The BSPMs illustrated in figure 2 indicate that the largest changes of the ST segment could be observed in lead V_4. Generally, the baseline of all ischemia setups was shifted towards positive values, whereas the ECG of the control case had a zero baseline. The Q peak was lower in case of ischemia. Furthermore, the R peak was more negative during subendocardial ischemia than in the control case. The ST segment showed a great variety of morphologies in lead V_4. Subendocardial ischemia led to slight ST depression, whereas transmural ischemia caused pronounced ST elevation. Between them, the ST segment of setup *Ischemia5* was approximately a zero baseline comparable to the control case. In addition, the T wave was broadened in case of ischemia.

4. Conclusions and discussion

Normally, the diagnosis of cardiac ischemia is based on the ECG, especially shifts of the ST segment [8]. In this work, we showed that during acute subendocardial ischemia ST depression can be observed in leads close to the ischemic region and ST elevation during transmural ischemia. For this purpose, the excitation propagation was simulated in a heterogeneous human ventricular model including anisotropic conduction and realistic description of ischemia effects. Based on Poisson's equation, the corresponding BSPMs were calculated.

Other groups, as e.g. Benson et al. [9] produced similar results. However, they simulated a strand of the ventricular wall and determined a pseudo-ECG. In [10], the propagation of action potentials was not simulated, since only the ST segment was regarded. The difference in transmembrane voltage between healthy and ischemic tissue at a certain time during the ST segment was used instead. However, some effects observed in the body surface ECGs during this work, as e.g. the reduced Q peak or the broadened T wave, could not be seen there.

The most prominent changes of the ECGs were visible in V_4, therefore, only this lead was shown. There, the Q peak was lower in case of ischemia, since the occlusion was located at the point of early activation of the ventricles in this example. The injury currents responsible for the ST segment shifts also caused the more negative R peak. Furthermore, the repolarization started earlier next to the ischemic region, which resulted in a broadened T wave.

In lead V_4, the baselines (TQ segments) of the ECGs of setup *Ischemia1* to *Ischemia15* were shifted towards pos-

itive values due to the increased resting voltage in the ischemic region. However, a comparison of the ST segment shifts with the control case would be closer to the clinical setting, if the baseline was also shifted to zero in case of ischemia. For this purpose, the ischemia related offset of the baseline in lead V_4 should be subtracted, which happens in clinical practice during baseline wander removal using high-pass filters. In this case, the ST segments of the ischemia setups would be more negative. As a consequence, a setup between *Ischemia6* and *Ischemia7* instead of *Ischemia5* would show a similar ST segment as the control case. However, the shift of the TQ segment gives further information about the occlusion site, since it can be observed only in leads close to the ischemic region. Due to this, the baseline was not corrected in case of ischemia.

The diagnosis and localization of acute cardiac ischemia can sometimes be very difficult. The example presented in this work showed that the detection of some non-transmural ischemia setups can be hard. For example, the ST segment shift was small or not visible, which would be even worse in real measurments with noise. In general, the diagnosis of acute ischemia using ECG measurements strongly depends on the occlusion site and the location of the electrodes. As proposed in [11], the electrode positions should therefore be optimized regarding this diagnostic task.

As already described in [8], ST depression does not necessarily have to be the reciprocal effect of ST elevation in leads whose positive pole is directed opposite to the lead registering ST depression. Our simulations also showed that subendocardial ischemia with injury currents in transmural direction causes negative ST segment shifts in leads close to the ischemic region as well.

However, the simulations of cardiac ischemia still can be improved. The morphology of the ischemic regions could be modeled more realistic using a diffusion model of the blood supply in the coronary arteries. Furthermore, other occlusion sites, different sizes of the ischemic region and relations between CIZ and BZ should be simulated for extended investigation of the effects of cardiac ischemia.

Acknowledgements

This work has been partially funded within the framework of the nationwide "Initiative for Excellence" from the Karlsruhe Institute of Technology (KIT).

References

[1] Weiss D, Ifland M, Sachse FB, Seemann G, Dössel O. Modeling of cardiac ischemia in human myocytes and tissue including spatiotemporal electrophysiological variations. Biomed Tech 2009;54:107–125.

[2] Colonna P, Cadeddu C, Montisci R, Chen L, Meloni L, Iliceto S. Transmural heterogeneity of myocardial contraction and ischemia. Diagnosis and clinical implications. Ital Heart J 2000;1:174–183.

[3] Li D, Li C, Yong A, Kilpatrick D. Source of electrocardiographic ST changes in subendocardial ischemia. Circ Res 1998;82:957–970.

[4] Hurst JW. Thoughts about the abnormalities in the electrocardiogram of patients with acute myocardial infarction with emphasis on a more accurate method of interpreting ST-segment displacement: part I. Clin Cardiol Aug 2007; 30:381–390.

[5] Keller DUJ, Weber FM, Seemann G, Dössel O. Ranking the influence of tissue conductivities on forward-calculated ECGs. IEEE Transactions on Biomedical Engineering 2010;57:1568–1576.

[6] ten Tusscher K, Panfilov A. Alternans and spiral breakup in a human ventricular tissue model. Am J Physiol Heart C 2006;291:H1088–100.

[7] www.ibt.kit.edu/accellerate.php. Cardiac Electrophysiology and Tension Development Software.

[8] Wagner G, Macfarlane P, Wellens H, Josephson M, Gorgels A, Mirvis D, Pahlm O, Surawicz B, Kligfield P, Childers R, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischemia/infarction: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009; 53:1003–1011.

[9] Benson A, Hodgson E, Bernus O, Holden A. Quantifying the Effects of Ischaemia on Electrophysiology and the ST Segment of the ECG in Human Virtual Ventricular Cells and Tissues. In Computers in Cardiology, 2008, volume 35. 2008; 705–708.

[10] Potse M, LeBlanc A, Cardinal R, Vinet A. ST elevation or depression in subendocardial ischemia? In Engineering in Medicine and Biology Society, 2006. EMBS '06. 28th Annual International Conference of the IEEE. 2006; 3899 –3902.

[11] Jiang Y, Qian C, Hanna R, Farina D, Dössel O. Optimization of the electrode positions of multichannel ECG for the reconstruction of ischemic areas by solving the inverse electrocardiographic problem. International Journal of Bioelectromagnetism 2009;11:27–37.

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