

The Role of Reduced Left Ventricular, Systolic Blood Volumes in ST Segment Potentials Overlying Diseased Tissue of the Ischemic Heart

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Abstract

Myocardial ischemia is the response of the heart to reduced coronary blood flow, leading to changes in ST segment potentials. ST segment depression is regarded as an indicator of nontransmural myocardial ischemia; however, not all nontransmural ischemia results in ST depression. This apparent discrepancy may be the result of many complex factors in cardiac response mechanisms to reduced blood flow. As a result, sophisticated computer models have emerged that have provided key insights into this complex phenomenon and the circumstances surrounding ST depression. Though these models have been able to produce ST depressions, many have neglected the effect of intracavitary blood volume, associated with different phases of the cardiac cycle. To explore the influence of the cardiac blood volume variability on epicardial potentials during nontransmural ischemia, we incorporated a thin, subendocardial ischemic zone geometry into an anatomically realistic, image-based ventricular model, and generated a finite element, static bidomain solution to determine the resulting epicardial surface potentials. It was first determined that, under baseline conditions (i.e., expanded left ventricular volumes corresponding to diastole), a predictable ST depression developed over the ischemic region. Left ventricular volume was then incrementally reduced, while maintaining the size and general shape of the ischemic region, in order to reflect the systolic phase of the cardiac cycle. As blood volume geometries decreased, epicardial ST depression overlying the ischemic region first increased in surface area as blood volume was reduced and before dramatically reducing near 30% blood volume reduction - accentuating the role and importance of blood volume variation in computational models of ischemia.

1. Introduction

Myocardial ischemia is the response of the heart to inadequate coronary blood flow. The lack of blood to a region of cardiac tissue leads to physiological changes that

are reflected in local and far field electrical signals. Within seconds of ischemia onset cellular ATP is reduced leading to a net efflux of intracellular potassium, and subsequently causing a slight depolarization in resting membrane potential with respect to healthy tissue [1]. The rise in resting potential also decreases the conductance of key sodium channels involved in cellular activation resulting in an overall reduction in action potential amplitude and upstroke [2]. The net result of these physiological changes is the deviation (e.g., elevation or depression) of the ST segment in ECG and electrogram recordings.

It is generally accepted that nontransmural ischemia leads to ST segment depressions in regions overlying the ischemic zone [3,4]. Additionally, recent simulation studies have suggested that ST segment depression, resulting from nontransmural ischemia, is not solely the result of transmural extent, but also requires changes in intracellular or extracellular anisotropy ratios as well as the presence of large, thin, subendocardial ischemic regions [5,6]. These simulations, however, were performed on models with static cardiac geometries in which the mechanical function of the heart was not considered among the many variable inputs. In this work, we expand these studies to include the effect that geometric reductions in blood pool geometry have on ST potentials under ischemic conditions. We hypothesize that reduced ventricular blood geometries, representative of the end systolic phase of the cardiac cycle, will reduce or effectively eliminate the presence of ST segment depressions in epicardial leads overlying the ischemic zone.

2. Methods

To test our hypothesis, we generated computer models that consisted of cardiac geometry; fiber structure; blood pool and ischemic zone geometry; and associated conductivity parameters. Simulations were performed using baseline (fully expanded) and reduced left ventricular (LV) blood pool geometries in which LV volumes were incrementally reduced to mimic systolic contraction that originates during the ST segment. ST segment depressions on

Table 1. Anisotropic conductivity ratios

Conductivity	Healthy Tissue	Ischemic Ratio
σ_{il}	1	1/10
σ_{it}	1/20	1/1000
σ_{el}	1	1/2
σ_{et}	1/3	1/4
σ_b	3	3

the epicardial surface and injury current flow within the tissues were analyzed to determine overall effect of the ventricular blood volume on ischemic ST potentials.

2.1. Computational Model

Image-based reconstructions of cardiac geometries were extracted from experimental canine models of ischemia with atrial geometry removed. Ischemic zone geometries were modeled as large cylindrical regions that extended along, and conformed to, the endocardial wall. An ischemic zone thickness of 20% transmural extent was calculated for all LV geometries so as to reflect, as closely as possible, the movement of the ischemic region, in conjunction with LV motion, within the cardiac tissue (Figure 1 top).

In addition to cardiac geometry, fiber direction fields were acquired from diffusion tensor imaging (DTI) and used to assign normalized anisotropic conductivity tensors consistent with those used in previous studies [7] (see Table 1). Intracellular and extracellular conductivity values were assigned to each element of the cardiac geometry as representative parameters of the bidomain passive current flow equation [7]

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

where $\bar{\sigma}_i$ and $\bar{\sigma}_e$ represent the intracellular and extracellular conductivity tensors, respectively, V_e represents extracellular potentials, and V_m signifies the transmembrane potential difference between healthy and ischemic tissue.

2.2. Modeling Ischemia

A transmembrane potential difference of 35 mV was assigned within the ischemic region to represent the weakened activity of the cardiac tissue during the ST segment. A transition region (border zone) from the diseased to healthy tissue was also applied [8].

Conductivity ratios, corresponding to longitudinal and transverse conduction pathways, were assigned and normalized with respect to the intracellular, longitudinal conductivity value $\bar{\sigma}_{il}$ within both intracellular ($\bar{\sigma}_i$) and extracellular ($\bar{\sigma}_e$) domains as defined in Table 1. Blood was treated as an isotropic extracellular volume conductor.

2.3. LV Blood Pool Modeling

During a normal cardiac cycle, ventricular contraction initiates during the plateau phase of the cardiac action potential, corresponding to the ST segment of ECG recordings. The subsequent reduction of LV blood volume during systole reduces the overall LV capacity to approximately 30% of its initial, fully expanded, diastolic volume [9].

To replicate LV volume reduction, we incrementally reduced our original blood volume from 100% to 30% of its initial baseline value. With reduced blood volumes defined, cardiac tissues were remeshed to conform with newly defined LV boundaries. Though the cardiac muscle undergoes a complex mechanical shift during the cardiac cycle, for this study we considered only the reduction of blood volume (Figure 1).

Final cardiac geometries and fiber directions, obtained by experimental DTI scans, were morphed to fit each new blood volume geometry by isolating a subset of closest node pairs (*i.e.*, correspondence points) between the baseline heart and the reconstructed, reduced LV geometry. A thin plate spline algorithm was applied to morph the original baseline mesh into the reduced LV space. Fiber vectors were mapped and normalized from the baseline heart to the morphed geometry by way of linear interpolation. In this way, endocardial and epicardial fibers were forced to maintain their pre-morphed direction while intramural distributions and directions followed the same rotational patterns, albeit through a thicker LV wall, as the original DTI recordings (not shown).

2.4. Data Analysis

A trademark of subendocardial ischemia is the presence of ST depressions overlying the ischemic zone (Figure 1 bottom) [7]. We used a connected component algorithm to isolate overlying ST depressions from which we extracted the surface area of the depressed region. We determined the percentage of the overlying depressed region with respect to the uncapped epicardial surface (Figure 2).

Additionally, intracardiac injury currents were generated by computing the gradient of the simulated extracellular potentials. Apart from qualitative visualization of injury currents within the tissue, injury current fields within the blood were analyzed to assess the alignment of current flow to the longitudinal axis of the LV blood volume by using a dot product map to identify all potential gradient vectors within a 90% range of the overall LV direction.

3. Results

Figure 1 illustrates the ischemic zone and blood volume changes (top) representative of ventricular contraction under ischemic conditions. Large, thin zones led to in-

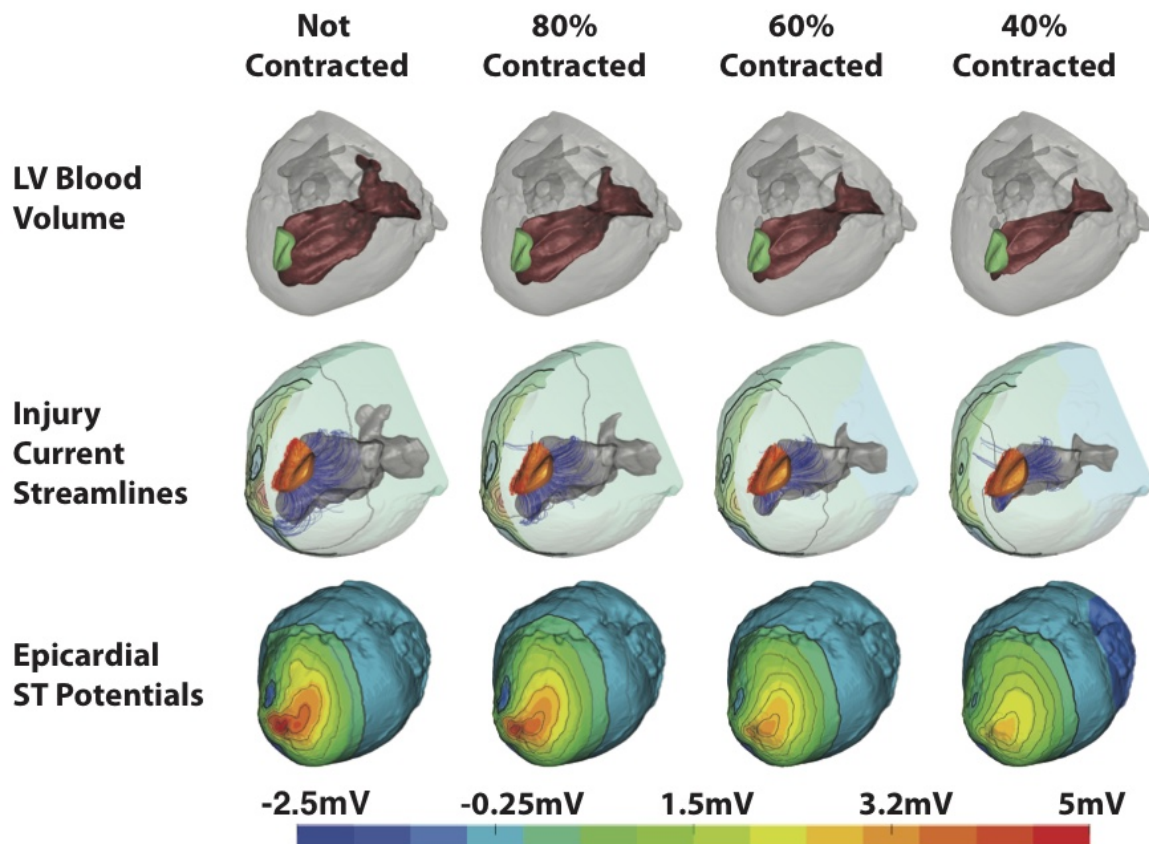


Figure 1. Effect of Blood Volume Reduction on Epicardial and Intracardiac Potentials. To simulate the effect of cardiac cycle on epicardial ST potentials, blood volumes were incrementally reduces (top row) from baseline (*i.e.*, image based) blood volume levels to 40%. ST depressions over the ischemic region (middle row) disappeared after blood volume was reduced to 40%. The thick isocontours represent the 0 potential line on the epicardium. Streamlines within the tissue also show the propensity of intracavitary currents to diminish and flow along the length of the blood pool. Isocontours of the transmural cardiac potentials (bottom) illustrate the effective ST depression within the wall of the heart. As blood volume is reduced, the proximity of negative potential distributions to the epicardium is diminished.

jury currents within the volume (middle) [6] that resulted in overlying, epicardial ST segment potential depressions (bottom). Baseline LV blood volumes result in a region of depressed epicardial potentials overlying the ischemic zone, which initially grew as blood volume was reduced before shrinking rapidly—starting at 70% LV volume (Figure 2 line).

Additionally, the flow of injury currents within the tissue and blood volume geometries was altered as LV volumes were reduced. With an expanded LV volume, injury currents followed a relatively isotropic conduction pathway. Small blood volumes (Figure 1 middle) produced injury currents that flowed preferentially along the longitudinal LV axis. A dot product map revealed that, under relaxed ventricular conditions, approximately 30% of injury currents within the blood pool were oriented along the LV longitudinal axis (Figure 2 bar), which initially diminished

as blood volume decreased. At an LV volume of 70% the preferential current flow, orientated along the LV axis, became more pronounced.

4. Discussion

Traditionally, regions of ST segment depression overlying an ischemic zone have been attributed to current flow between healthy and ischemic tissues during both the TQ and ST segments of the ECG [3, 10]. Elevations or depressions that occur during the plateau phase of the cardiac action potential are considered "true" ST deviations. Adaptations to classic ECG theory regarding ischemia detection have also considered anisotropic fiber structure, altered conductivity ratios, and various ischemic zone geometries as key components in the formation of ST depressions [6, 7]. In this work we have attempted to address and

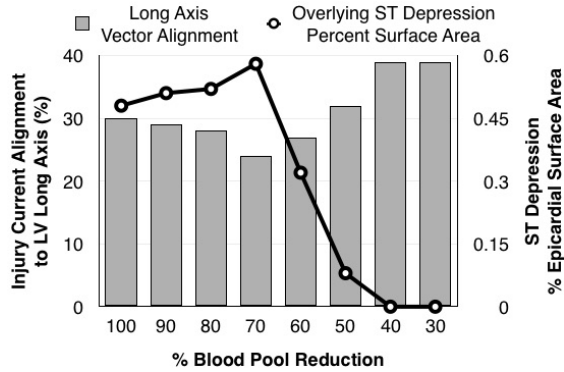


Figure 2. Injury current direction (bar) aligns more prominently with the left ventricular longitudinal axis as blood volume decreases, while overlying surface potential depressions (line) diminish and effectively disappear as blood volume is reduced.

analyze another contributing factor to ST depression as it relates to "true" ST deviation—cardiac blood volume.

When considering ST depression, we must also consider the state of the heart during the ST segment. The contraction of the heart is thought to begin during the ST segment. This contraction continues after the heart has completely depolarized, reaching peak contraction during the T wave—all while LV volume is decreasing.

We observed that as LV volume reduced, the initial area of ST elevation on the epicardium increased, peaking at 70% LV volume, which likely corresponds to the middle of the ST segment. After 70%, the overlying epicardial ST depression diminished until being effectively absent between 30 - 40% LV volume. This may be due to the directional flow of injury currents within the tissue as well as in the blood (Figure 2). Because blood conductivity is larger than that of the surrounding tissue, injury currents that arise as a result of transmembrane potential differences between healthy and diseased tissues are augmented within the blood volume due to the Brody Effect [11]. This leads to injury current loops that flow through the blood and return to the ischemic border through the cardiac tissue [5]. As blood volume decreases past 70% LV volume, so too does the influence of the Brody Effect on epicardial potentials, leading to slightly more directed injury current flow within the blood that parallels the long axis of the LV volume and causes the strength of injury currents reaching the epicardial surface to diminish. This, in turn, leads to diminished regions of epicardial ST depression.

5. Limitations

In this study, we were able to show that reduced ventricular blood volumes resulted in diminished ST segment depressions and alterations in injury current flow pat-

terns; however, we did not consider all physiological occurrences, such as torsion, conductivity differences, basal-apical shortening with the associated wall thickening.

Acknowledgements

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References

- [1] Carmeliet E. Cardiac ionic currents and acute ischemia: from channels to arrhythmias. *Physiological Reviews* July 1999;79(3):917–1017.
- [2] Shaw R, Rudy Y. Electrophysiologic effects of acute myocardial ischemia. a mechanistic investigation of action potential conduction and conduction failure. *Circ Res* January 1997;80(1):124–38.
- [3] Fozzard H, DasGupta D. ST-Segment potentials and mapping: Theory and experiments. *Circulation* 1976;54:533–537.
- [4] Holland RP, Brooks H. TQ-ST segment mapping: critical review and analysis of current concepts. *The American Journal of Cardiology* 1977;40(1):110–129.
- [5] Hopenfeld B, Stinstra J, MacLeod R. The effect of conductivity on ST segment epicardial potentials arising from subendocardial ischemia. *Ann Biomed Eng* 2005; 33(6):751–763.
- [6] Potse M, Coronel R, Falcao S, LeBlanc A, Vinet A. The effect of lesion size and tissue remodeling on ST deviation in partial-thickness ischemia. *Heart Rhythm* 2007;4(2):200–6.
- [7] Hopenfeld B, Stinstra J, MacLeod R. Mechanism for ST depression associated with contiguous subendocardial ischemia. *J Cardiovasc Electrophysiol* 2004;15(10):1200–1206.
- [8] Swenson D, Stinstra J, Burton B, Aras K, Healy L, MacLeod R. Evaluating the effects of border zone approximations with subject specific ischemia models. In Doessel O, Schlegel WC (eds.), *World Congress on Med. Phys. and Biomed. Eng.*, volume 25/IV. Heidelberg: Springer, 2009; 1680–1683.
- [9] White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circ* 1987;76(1):44–51.
- [10] Samson W, Scher A. Mechanism of ST-segment alteration during acute myocardial injury. *Circ Res* 1960;8:780–787.
- [11] Brody DA. A theoretical analysis of intracavitary blood mass influence on the heart-lead relationship. *Circulation Research* 1956;.

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