

TITLE**SENSITIVITY OF EPICARDIAL ELECTRICAL MARKERS TO ACUTE ISCHEMIA
DETECTION****AUTHORS****Kedar Aras, PhD**

Bioengineering Department, Scientific Computing and Imaging Institute, CVRTI,
University of Utah, Salt Lake City, UT, USA

Brett Burton, BS

Bioengineering Department, Scientific Computing and Imaging Institute, CVRTI,
University of Utah, Salt Lake City, UT, USA

Darrell Swenson, PhD

Bioengineering Department, Scientific Computing and Imaging Institute, University of
Utah, Salt Lake City, UT, USA

Rob MacLeod, PhD

Bioengineering Department, Scientific Computing and Imaging Institute, CVRTI,
University of Utah, Salt Lake City, UT, USA

CORRESPONDING AUTHOR ADDRESS**Kedar Aras**

Scientific Computing and Imaging Institute, University of Utah
Warnock Engineering Building
72 South Central Campus Drive, Room 3705
Salt Lake City, UT 84112
Phone: 269 - 519 - 3818
Fax: 801 - 585 - 6513
Email: kedar.aras@gmail.com

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ABSTRACT (153 words)

Introduction: We hypothesize that electrocardiographic measurements from the intramyocardial space contain more sensitive markers of ischemia than those detectable on the epicardium. The goal of this study was to evaluate different electrical markers for their potential to detect the earliest phases of acute myocardial ischemia.

Methods: We conducted acute ischemia studies in open chest animal, by creating finely controlled demand or supply ischemic episodes and recording intramyocardial and epicardial potentials.

Results: Under the conditions of mild perfusion deficit, acute ischemia induced changes in the T wave that were larger and could be detected earlier on the epicardial surface than ST-segment changes.

Conclusions: Our findings indicate that in the setting of very acute ischemia, epicardial T waves have higher sensitivity to mild degrees of acute ischemia than epicardial ST potentials. These results suggest that changes in the T wave shape may augment shifts in ST segments to improve ECG based localization of ischemia.

INTRODUCTION (507 words)

Despite a century of research and practice, the clinical accuracy of the electrocardiogram (ECG) to detect and localize myocardial ischemia remains less than satisfactory¹. Myocardial ischemia occurs when the heart does not receive adequate oxygen-rich blood to keep up with its metabolic requirements and severe ischemia can lead to myocardial infarction and life threatening arrhythmias. Early and accurate detection is an essential component of managing this condition. Ischemia is known to be a dynamic condition that reflects changing imbalance between blood supply and metabolic demand so that it is natural that examination under physical stress conditions or exercise testing (ET) is in widespread clinical use. However, ET is characterized by poor sensitivity (68%) and specificity (77%)², limiting its diagnostic usefulness.

The most common clinical ECG marker for myocardial ischemia detection is the ST segment, that portion of the ECG time signal that lies between the QRS and the T wave. The ST segment represents approximately the period when the ventricles are depolarized i.e. the ventricular action potentials are all in the plateau phase and in a healthy heart have approximately the same transmembrane potential. As a result, this phase is approximately isoelectric in a normal ECG. Changes in the ST segment arise in response to spatial heterogeneity of plateau potential and can occur within 15-30 seconds after the onset of ischemia³ and hence are considered one of the earliest markers of the condition.

The mechanism for ST segment potential shifting above (ST elevation) or below (ST depression) the baseline during myocardial ischemia is the flow of what are known as

“injury currents”. These currents are the result of voltage gradients between normal and ischemic regions that occur because of reduced amplitude and duration of ischemia action potentials. Changes in the action potentials can affect not only the ST segments but also the morphology of other electrical features of the ECG including the QRS complex^{4,15} and the T wave^{5,15}.

ECG leads that show ST elevation are spatially linked to the region of ischemia and thus provide a means of localizing transmural ischemia from the body surface. However, the ability of ST depression to locate ischemia is considered much less specific^{6,15}. ST depression is seen in patients with acute occlusion of the left circumflex artery (LCx) in leads V2-V3 and is an effect of ischemia in the free (postero) lateral wall. Moreover, patients with demand ischemia during exercise testing (ET) paradoxically show maximum ST depression in lead V5. Acute ischemia studies with animal models have shown that even on the cardiac surface (epicardium), ST segment changes have poor sensitivity⁷. Thus the ST segment, by itself, is not a reliable index of ischemia.

Our goal in this study was to evaluate whether electrical markers other than the ST segment changes are visible during acute ischemia and thus could improve diagnosis and localization. To this end, we conducted a series of acute ischemia studies on animal model to measure epicardial surface and three-dimensional, transmural potential distributions while varying both local coronary supply and global metabolic demand.

METHODS (969 words)**Experimental Preparation**

The goal of these experiments was to evaluate ischemia-induced changes in epicardial electrical markers during the acute phase of short episodes of ischemia created by reduced coronary flow or increased heart rate. To this end, we performed experiments on 10 open chest, intact swines using multipolar intramural needle electrodes and epicardial surface electrodes, following the approval of the Institutional Animal Care and Use Committee at University of Utah and conforming to the Guide for the Care and Use of Laboratory Animals (NIH Pub. No 85-23, Revised 1996).

An open chest preparation following mid-sternal thorocotomy allowed direct access to the heart for recording epicardial and transmural electrical potentials. The animal was anesthetized by bolus injection of isoflurane gas (1-3% inhalant to effect), followed by maintenance doses administered as needed. After the thorocotomy, the heart was suspended in a pericardial cradle. A suitable left anterior descending (LAD) segment was then dissected and freed from the underlying tissue. The coronary flow was regulated using a hydraulic occluder (Access Technologies Inc) placed around the dissected segment of the left anterior descending artery. Calibration of the fluid volume injected enabled us to perform graded, reproducible reductions in coronary perfusion. The study protocol was designed to simulate two forms of acute ischemia: a) Demand ischemia, as would arise, for example, during a stress test with pacing as a surrogate for exercise and b) Supply ischemia, through episodes of reduced coronary perfusion to simulate spasm or other transient reduction in coronary artery flow. To create demand

ischemia, we progressively elevated metabolic demand (by reducing pacing interval stepwise in 30-50 ms increments) under stable (often below normal) perfusion conditions. Supply ischemia was induced by keeping the pacing rate constant (but often elevated) and decreasing the perfusion in steps of 25% of normal.

Figure 1 contains a schematic of the animal preparation. The experiment setup including the cartoon of the hydraulic occluder, 247 epicardial electrode sock and 25 plunge needles is shown in Panel A of the figure. An example study protocol (supply ischemia) can be seen in Panel B. Sample epicardial and intramural electrograms recorded during the experiments are shown in Panel C. Panel D shows epicardial electrical markers extracted for analysis. The threshold for localized ST40% potential elevation is calculated as shown in Panel E.

Experimental Protocols and Data Acquisition

Each resulting ischemic episode was 8-10 minutes in duration depending on the protocol, the intrinsic values of the animal, and the maximum heart rates tolerated. Each experiment consisted of 4-6 such episodes and the recovery period (at intrinsic heart rates and perfusion) between episodes was approximately 25-30 minutes. Electrical recordings were taken for 3 seconds every 15 seconds during the ischemic episode as well as during the recovery period.

Epicardial potentials were recorded from the surfaces of both ventricles using a 247 electrode flexible sock array⁸. In addition, 25 flexible fiberglass needles⁹, each carrying

10 electrodes along its length spaced at approximately 1.5 mm, were inserted into the left ventricle (LV) in and around the region presumably perfused by the occluded LAD, taking care to avoid injuring the epicardial arteries. The spacing between needles within the epicardial region they covered did not exceed 1 cm. Localized ST segment elevations in the needle electrograms were considered indications of nearby ischemia and served as the gold standard for the presence and location of ischemic regions. The potentials from sock and needle electrodes were recorded using a custom acquisition system¹⁰.

At the end of the experiment, the locations of preselected sock electrodes and all the plunge needles on the cardiac surface were digitally recorded using a Microscribe 3D digitizer (Microscribe Inc, Oella, Maryland). Interactive visualization of the resulting spatio-temporal maps of cardiac potentials was by means of SCIRun (<http://www.sci.utah.edu/software/scirun.html>)

Post Experiment Imaging and Signal Processing

Following each experiment, the anatomical MRI scans of the excised heart were segmented to identify the atria and ventricles using the Seg3D program (<http://www.sci.utah.edu/software/seg3d.html>) and the segmentations became the basis of a volumetric tetrahedral mesh created using BioMesh3D (<http://www.sci.utah.edu/software/biomesh3d.html>). The digitized sock and needle electrodes were then registered to this mesh geometry and visualized in SCIRun.

The global root mean squared (RMS) signal computed from the electrograms at all the sock and needle electrode were used to identify the J point and T peak time instants. The value of potentials at 40% of the ST segment between the J point and the peak of the T wave (ST40%) provided the metric for local ischemia. The peak amplitude of the T wave also served as a T-wave marker. Other markers evaluated in this study included the peak to peak amplitude of the QRS complex, and the R-wave and S-wave amplitudes.

A key step in the signal processing was determining the regions of the heart that showed electrical indications of ischemia. For this, we computed potential differences between ST-segment potentials (ST40%) recording during each ischemic episode relative to immediately pre-ischemia controls. We defined a threshold for ischemic ST elevations in the resulting difference maps as two standard deviations from control values.

True positive (TP) was defined as the number of sock electrodes that correctly detected the underlying intramural ST potentials above a threshold. False negative (FN) was defined as number of sock electrodes that identified the underlying intramural ST potentials above the threshold as normal. True negative (TN) was defined as the number of sock electrodes that correctly identified intramural ST potentials below the threshold. False positive (FP) was defined as the number of sock electrodes that identified the underlying intramural ST potentials below the threshold as ischemic.

From these values we computed sensitivity as $(TP/(TP+FN))$ and specificity as $(TN/(TN+FP))$ of the epicardial electrical markers.

RESULTS (679 words)

For this study, we conducted 10 experiments in which there were 44 episodes of supply (22) and demand ischemia (22). All animals participated in the study and we rejected data from 6 episodes because of animal preparation degradation during the course of the experiment resulting in ischemia persisting at control conditions. We show here representative data from only the supply ischemia experiments, depicting the spatial and temporal progression of epicardial ST and T wave changes during acute ischemia.

Figure 2 highlights data from one of the swine ischemia studies designed to induce graded decrease in LAD perfusion at a maintained heart rate of 172 BPM (supply ischemia). The figure includes electrograms recorded from one plunge needle and the overlying epicardial sock electrode with the locations of the plunge needle and the sock electrode shown in Panel A. Panel B shows the study protocol while Panel C shows examples of epicardial and intramural electrograms recorded at control and during acute ischemia episode at the designated stages of perfusion deficit. At 75% perfusion (A), changes in the intramural electrograms included elevated and upright T waves and to a smaller extent changes in the QRS and ST segment. On the epicardial surface, there were only corresponding change in the T-wave, which became elevated and upright. At 50% reduction (B), there were additional, progressive changes in all markers from the intramural electrograms while on the epicardial surface, the electrogram

displayed only slightly elevated ST segments in addition to the progressively elevated T wave. At 25% perfusion (C), the epicardial electrode displayed elevated R wave, ST segment, and T wave, matching transmural ischemic conditions represented by the underlying plunge needle electrograms but delayed in their time of onset. Thus, the first changes seen anywhere on the epicardium were in the T waves, subsequently followed, under conditions of increased ischemic load, by corresponding ST segment and R wave changes. This progression in the appearance of changes in electrograms were not dependent on time but rather on the extent of ischemia induced by progressive reduction in coronary perfusion levels.

Figure 3 highlights data from the same swine study and includes spatio-temporal progression for epicardial and intramural electrograms. The locations of the sock and the plunge needle electrodes as well as the study protocol are seen in Panel A. Panel B highlights the corresponding epicardial ST40% and T-wave potential difference maps at control and at different perfusion rates. The thresholds for the epicardial markers were 1.5 mV (ST40%) and 3 mV (T-wave), respectively, corresponding to two SD from baseline conditions. At 75% perfusion (A), there was diffused epicardial ST elevation over the anterior apical region, but sharp T wave elevation on the anterior apical and mid-regions. At 50% perfusion (B), there was marked increase in size of the elevated T wave regions on the epicardial surface. Moreover, the ST potential map displayed the first sharply elevated regions in the mid and apical region. At 25% perfusion (C), there was a progressive increase in the elevated T-wave regions and to a lesser extent in the ST elevated regions on the epicardial surface. Panel C highlights the corresponding

intramural ST40% and T-wave difference maps within the volume of the ventricle at the corresponding time points, from which it was possible to compute size of the intramural regions exceeding the respective thresholds. There is a strong spatial correlation seen between the T wave and ST potentials at the intramural level and also on the epicardial surface. Panel D displays the receiver operating characteristics (ROC) curves for the three most sensitive epicardial markers (ST40%, T-wave, R-wave) at 75% and 50% perfusion, relative to intramural ST elevations documented in Panel C. At 75% perfusion (mild acute ischemia) the epicardial T-wave marker consistently showed higher sensitivity at similar values of FPR, when compared to ST40% and R-wave epicardial markers. At 50% perfusion (moderate acute ischemia), the predictive value of epicardial T-wave and ST40% became comparable. Even so, the epicardial T-wave exhibited slightly higher sensitivity compared to ST40% at similar FPR values.

DISCUSSION (847 words)

The aim of this study was to evaluate the sensitivity and specificity of epicardial electrical markers of acute ischemia relative to markers derived from intramural electrograms. To that end, we conducted a series of acute ischemia *in situ* experiments on swines and profiled the resulting intramural and epicardial potentials. As seen in Figures 2 and 3, we demonstrated that early in development of acute ischemia, while the intramural electrograms was characterized by shortening of QRS potentials and elevation of T wave and ST potentials, the corresponding epicardial electrograms showed only changes in the T wave morphology. As the severity of acute ischemia increased, the epicardial electrograms eventually showed ST segment shifts and

changes in the QRS morphology. The key finding from this study is that the epicardial T wave is a more sensitive index of acute ischemia than epicardial ST-segment changes, especially in the early stages of acute ischemia development.

The findings of this study depend on the assumption that local shifts in extracellular ST-segment potentials can be detected with sufficient spatial resolution and that they reflect the underlying ischemia. While an indirect marker of what is fundamentally a perfusion deficit, intramural extracellular ST potentials have been shown to be sensitive marker for ischemia and correlate well with regional blood flow⁷. Moreover, the spatial resolution of our intramural recordings, which was 1.5 mm along the axial direction (the recording needle shaft) and approximately 10 mm along the longitudinal direction (between adjacent needles), has never been achieved in any previously reported study to our knowledge. The resulting identification of intramural ischemia is therefore precise enough for comparison with nearby epicardial potentials recorded from a high-resolution epicardial sock electrode.

While our results are suggestive of new metrics for evaluating acute ischemia, they are based on epicardial and not body-surface potentials. Poor sensitivity of standard ECG stems, at least in part, from the fact that the magnitude of body surface potentials varies inversely with the distance between the recording leads and the heart¹¹. Thus body surface electrodes, even those placed over the ischemic zone, would be expected to record lower ST deviation than cardiac surface electrodes placed near the ischemic area. The rationale of our approach is that while good performance of an epicardial

marker is no guarantee of similar results on the body surface, any useful body surface marker must perform at least as well on the epicardium. Moreover, an open chest preparation combined with intramural measurements, provides unparalleled documentation of the electrical consequences of ischemia and thus a robust ground truth for any more remote marker.

Within this framework, our results show that, even on the epicardial surface, the ST segment by itself has poor sensitivity during the early development of acute ischemia that does not extend to the epicardial wall, i.e., non-transmural acute ischemia. Several other groups have described limited sensitivity of epicardial ST segment to acute ischemia^{7,12}. For example, Smith et al¹². reported that epicardial ST elevation implied ischemic injury, however, lack of ST elevation did not exclude the possibility of ischemia being present. Our results are consistent with these reports and suggest that epicardial ST segment has high specificity but low sensitivity to acute ischemia especially under mild perfusion (75%) deficit conditions. These results also suggest that performance based on body surface ECGs will likely be even worse under these conditions.

Previously described, ischemia-induced changes in the T wave include the inverted T wave turning shallow, flat or upright¹³. These changes are attributed to shortening of the action potential duration in the ischemic cells, which reverses the direction of normal transmural potential gradients between the endocardium and the epicardium. Our results showed that the changes in epicardial T waves were highly sensitive to low levels of acute ischemia. Moreover, the epicardial T wave changes showed strong

spatial correlation to ischemia-induced changes in the intramural T wave and ST potentials. Miller et al.¹⁴ have suggested that during repolarization (T wave), the energy consuming process (Na⁺/K⁺ -ATPase) required to restore resting potential of the cell is likely to suffer from ischemia-induced hypoxia. As a result, this phase of the action potential might be expected to be more sensitive than others to the reduction in perfusion and energy substrate supply. Our results support these studies.

Of critical importance is the question of how these results might translate to the body surface, where ST-segment and T-wave changes certainly arise during ischemia but have yet to be linked precisely to the degree of intramural ischemia, as in this study. It should be noted that our studies were, by design, focused on the early development of ischemia as characterized by the degree of perfusion and on measurements performed during this very acute phase. This restriction may limit translation to the broad clinical setting, as patients with acute supply ischemia are not likely to have their ECG recorded during the first few minutes of the ischemia episode. However, during exercise testing or other acute ischemic events, e.g., during surgery, our findings are likely to be, once again, relevant.

CONCLUSIONS (125 words)

In summary, our results show that in the setting of very acute ischemia, epicardial T waves have higher sensitivity to mild degrees of acute ischemia than epicardial ST potentials. Epicardial QRS potentials show even less sensitivity to mild ischemia than the ST segments and thus are likely to have very limited ability to localize the spatial

extent or degree of myocardial ischemia. These results suggest the possibility of combining epicardial ST and T wave markers to provide a more reliable index of acute ischemia than either in isolation, a topic of ongoing research. These results have the largest potential clinical consequences in settings such as acute ischemic episodes, stress testing or in surgery, settings in which early and precise detection of ischemia is currently problematic.

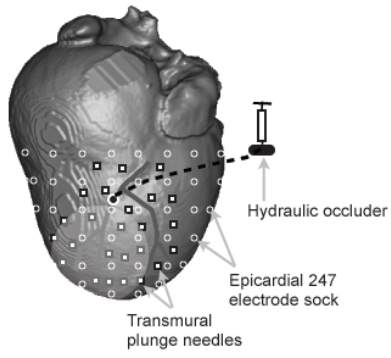
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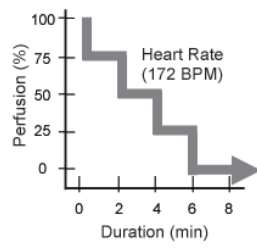
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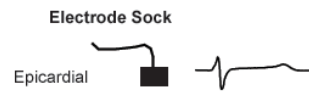
A) Experiment Setup



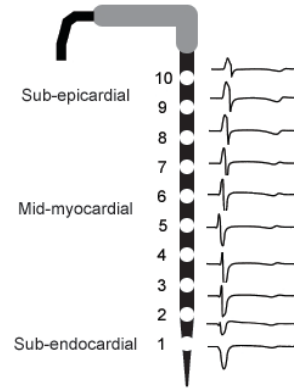
B) Study Protocol



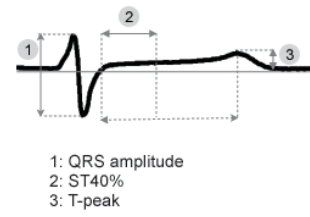
C) Electrode Recordings



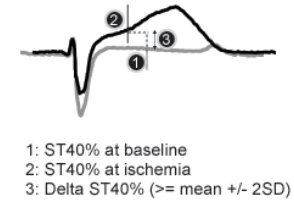
Plunge Needle



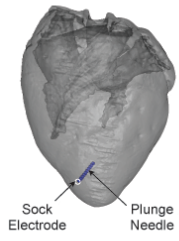
D) Epicardial Markers



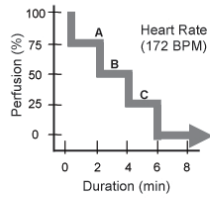
E) Acute Ischemia Threshold (Local ST Elevation)



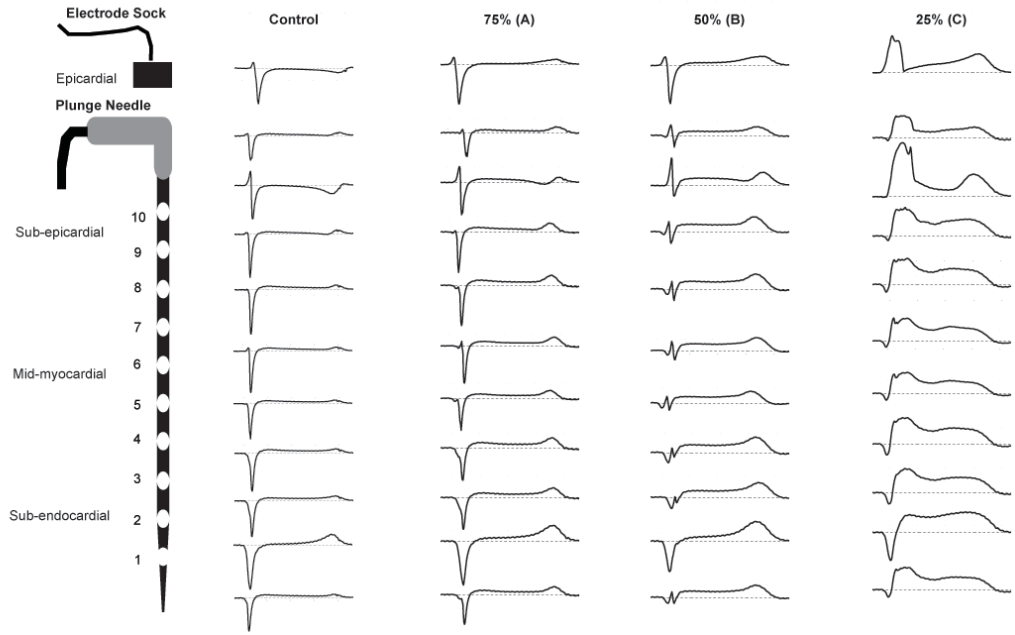
A) Electrode(s) Location



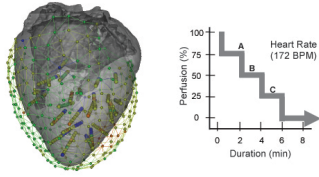
B) Study Protocol (Swine)



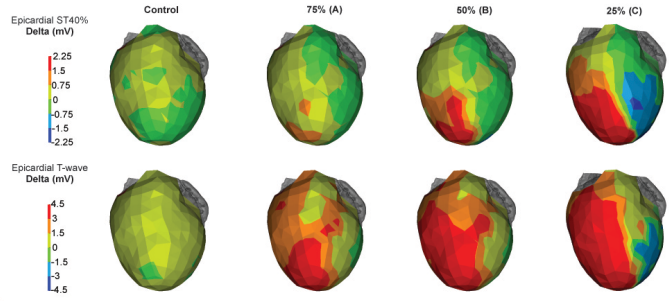
C) Sensitivity of Epicardial ST & T Markers during an Acute Ischemia Episode



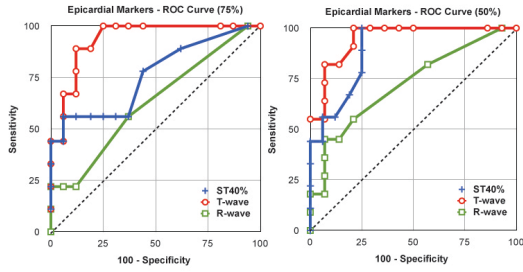
A) Electrode Locations & Study Protocol (Swine)



B) Spatio-Temporal Progression of Epicardial and Intramural ST & T Markers during an Acute Ischemia Episode



D) Epicardial Markers ROC Curves



Epicardial Marker	Area Under Curve (75%)
T-wave	9491
ST40%	7632
R-wave	6285

Epicardial Marker	Area Under Curve (50%)
T-wave	9590
ST40%	9067
R-wave	7327

C) Spatial Correlation of Intramural ST & T Markers during an Acute Ischemia Episode

