

Quantifying the Spatiotemporal Influence of Acute Myocardial Ischemia on Volumetric Conduction Speeds

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Abstract

*Acute myocardial ischemia compromises the ordered electrical activation of the heart, however, because of sampling limitations, volumetric changes in activation have not been measured. We used a large-animal experimental model and high-resolution volumetric mapping to study the effects of ischemia on conduction speeds (CS) throughout the myocardium. We estimated CS and electrocardiographic changes (ST segments) and evaluated the spatial and temporal correlations between them across 11 controlled episodes. We found that ischemia induces significant conduction slowing, reducing the global median speed by 25 cm/s. Furthermore, there was a high **temporal correlation** between the development of ischemic severity and CS (corr. = 0.93) through each episode. The **spatial correlations** between ST-segment changes and CS slowing were more spatially complex than expected with substantial slowing at the periphery of the zones with ST-segment changes. This is the first study that has documented in an experimental model volumetric changes of CS during acute myocardial ischemia and explored the relationships between ischemia development in space and time. We showed that conduction speed changes are spatiotemporally correlated to ischemic severity and illustrated the biphasic response long proposed from cellular studies.*

1. Introduction

Myocardial ischemia occurs when coronary perfusion to the heart is inadequate. This perfusion shortfall initiates an electrochemical cascade known to influence the ST and repolarization phases of the ECG but it also has a marked effect on propagation (QRS).[1] These effects are thought to drive several time periods during acute myocardial ischemia that are arrhythmogenic, which can lead to sudden cardiac death (SCD).[2] These effects are highly dynamic

and spatially complex and they occur within the ventricular walls, making their experimental study especially challenging. Such studies require intramural sampling to measure volumetric conduction speed and study propagation during episodes of controlled ischemic stress.

Previous studies have shown the feasibility of volumetric measurements using intramural plunge needles to quantify the spatial extent and severity of ischemic stress based on electrocardiographic parameters, typically ST-segment shifts.[3, 4] CS changes in the presence of acute ischemia have also been documented during cellular studies [1] but not yet in the intact heart. These cellular studies also showed a biphasic response in excitability of the tissue early in the ischemic evolution, but the anticipated changes in CS also have not been replicated.

Conduction speed must be estimated from spatially distributed measurements and published studies have so far been limited to surface-based measurements.[5] We have created and validated a novel volumetric CS estimation technique based on intramural measurements and demonstrated its accuracy.[6] Applying this method to measurements made during our experiments was the logical next step in the study of arrhythmogenesis during acute ischemia.

This study examined the spatiotemporal relationship between the intramural development of ischemia as detected through ST-segment shifts and changes in conduction speed. We identified high temporal correlations between ischemic stress and CS slowing. Less anticipated were the complex spatial relationships we documented between CS slowing and around regions of ischemic stress.

2. Methods

Experimental Preparation: Signals were acquired from two *in situ* canine experiments as described previ-

ously. [3, 4] In brief, each experiment consisted of 5–6 episodes of controlled acute myocardial ischemia. Hearts were then removed and imaged using high-resolution MRI and geometric models were created that merged anatomy with electrode positions as described previously. [4, 7, 8]

Estimating Volumetric Conduction Velocity: To estimate volumetric conduction velocity, we (1) reconstructed the activation wavefront,[6] (2) calculated the element-wise gradient to approximate propagation direction, and (3) estimated conduction speed with an inverse-gradient technique.[9] All steps were based on activation times estimated from electrograms recorded with intramural plunge needle arrays. Higher resolution activation times were then reconstructed on the nodes of the geometric model of the heart using radial basis interpolation. The geometric model was then clipped by the outer bounds of the measurement electrodes and the blood pool, leaving only the region sampled by the intramural plunge needles, which we refer to as the ‘needle envelope’. We estimated the wavefront direction by calculating the direction of the gradient of activation times throughout the needle envelope. We estimated conduction velocity using an inverse-gradient technique, which inverts the activation gradient and takes its partial derivative on an element-wise basis.[6, 9] The result is a conduction velocity vector assigned to each element in the geometric model from which we computed CS.

Quantifying CS Changes During Ischemia: CS and ST40% distributions were calculated throughout the 11 ischemic episodes. For each episode, a continuous 3-second ‘run’ was captured every 15 seconds and a representative beat selected from each run, resulting in 25–35 beats per episode. The ST40% was defined as the potential value 40% between the end of the QRS and the peak of the T-wave.[3] Measured ST40% values were interpolated into the needle envelope using the same radial basis interpolation scheme described above. We compared the CS and ST40% values before the induction of ischemia with those at the peak of each ischemic episode. We evaluated the differences in the skewed distributions using a two-sample Kolmogorov-Smirnov test (KS-test) and the episodic changes were determined to be significant when the p-value was less than 0.05.

Temporal Examination of Conduction Changes: To determine the temporal relationship between CS slowing and ST40% development, we measured the temporal correlation of median ST40% and median CS values throughout the ischemic episodes. Medians were computed across all nodes and for each representative beat within an episode of ischemia to form a time series (*e.g.*, Figure 2B).

Spatial Examination of Conduction Changes: We performed a spatial analysis to determine if different levels of ischemic stress as quantified by ST40% values influence changes in CS. We analyzed the ST40% distribution at

the peak of each episode and found the regions within the needle envelope with ST40% values in the lowest and the highest quartiles. We then calculated the relative change of CS in each of the identified regions during peak ischemia. Statistically significant differences were determined using a Student t-test with $p < 0.05$. The Student t-test was used to detect whether the changes in the two-cohorts across the 11 episodes of ischemia were significant and the distribution of changes were normal.

3. Results

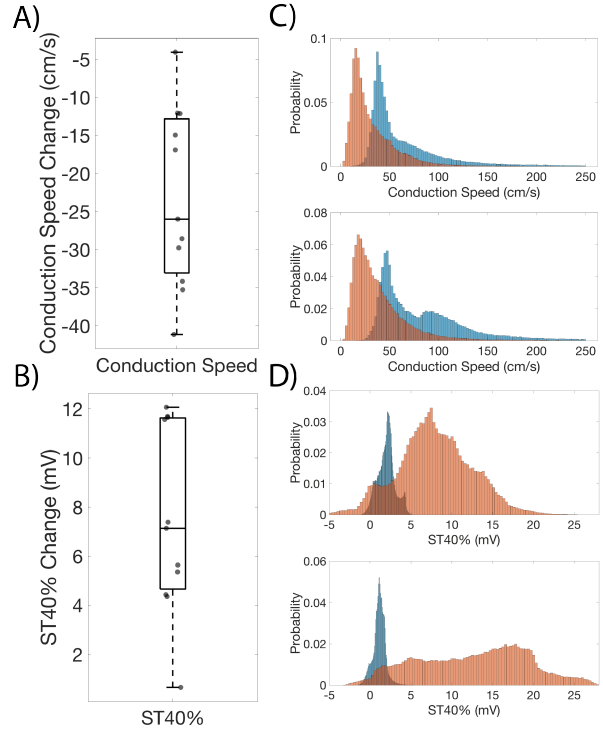


Figure 1. Changes in CS and ST40% distributions between peak and control periods of the ischemic episodes. **A)** The change in median CS across 11 episodes of ischemia. **B)** The change in median ST40% across 11 episodes of ischemia. **C)** Two sample CS distributions prior to the induction of ischemia (blue) and at the peak (orange) of the ischemic episodes. **D)** ST40% distributions for the same episodes as in Panel C.

Quantifying the Global Conduction Speed Changes: Figure 1A and Figure 1B show the median ST40% and CS changes between peak and control periods across the 11 episodes of ischemia. Figure 1C shows two sample distributions of CS at control (blue) and the peak of the ischemic episodes (orange). Similarly, Figure 1D shows the ST40% distributions for the same episodes. The median drop in CS was approximately 25 cm/s across the 11 episodes. Median ST40% changes were approximately 7 mV. The CS distributions at control and peak across the 11 episodes were each determined to be significantly different ($p < 0.05$).

Temporal Examination of Conduction Changes: Figure 2A shows the measured temporal correlation across the 11 episodes with a median correlation of 0.93. Figure 2B shows examples of temporal changes of the median CS and ST40% over three ischemic episodes from early, middle and late in a single experiment. These episodes were representative of a general trend: CS slowing typically lagged behind the elevation of ST40% early in the experiment, whereas in the later episodes, CS changes typically preceded ST40% changes. Another interesting result observed across both experiments was a biphasic response in CS (*e.g.*, Figure 2B) during episodes induced near the middle of the experiment.)

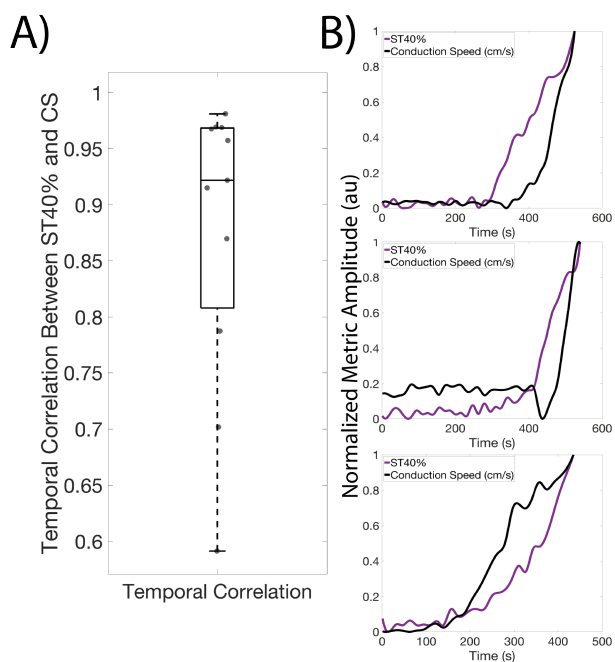


Figure 2. Temporal evolution of ST40% and CS during ischemia. **A)** The temporal correlation between the CS and ST40% across 11 episodes of ischemia. **B)** Three examples of the normalized values of CS and ST40% during the ischemic episode. Episodes from early (**Top**), middle (**Middle**) and near the end of the experiment (**Bottom**).

Spatial Examination of Conduction Changes: Figure 3 contain results from an analysis of spatial overlap between ST40% and CS. Panel A shows that significantly larger conduction slowing occurs only in the most severe ischemic tissue. Panel B shows the intramural needles (grey spheres) within the myocardium. Panel C shows the spatial distribution of the regions of extreme ST-elevation (blue) overlaying regions of extreme conduction slowing (red), showing a complex spatial relationship between the two volumes.

4. Discussion

This study has shown for the first time the utility of using volumetric estimations of CS to study propagation changes during acute myocardial ischemia. We were able to reconstruct the spread of activation with adequate resolution to compare the temporal and spatial correlations between CS slowing and ST40% elevation through 11 different episodes of controlled ischemia in 2 experiments using a canine model.

We found significant conduction slowing that occurred within a needle envelope from the putative perfusion zone during acute ischemic events. While our intramural measurements could only include part of the left ventricle, we continue to replicate previous studies and identify localized regions of ST-segment elevation that arise during acute ischemia and were able for the first time to examine them for propagation changes. We showed that the time course of conduction slowing was correlated with an increase in ST40%, which we associated with the severity of ischemia. A further notable temporal response was the paradoxical appearance of transient increases in CS early in an ischemia episode. During four of the ischemic episodes across both experiments, we observed such biphasic responses in CS. Qualitative examination suggests this early quickening happens in the less severe ischemic tissue, supporting observations made decades ago in cellular studies.[1]

A parallel comparison of the spatial progress of ST40% and CS was much more complex than the temporal correlation but also consistent enough to suggest systematic observations. For example, we observed the largest absolute changes in CS within the subendocardium, where the CS was fastest at control. Ischemia clearly has a widespread impact on CS but only at the extremes does it show correlation with changes in ST40%. Contrary to our expectations, regions of high ST40% elevation did not overlap consistently with CS slowing. Instead, regions of slowed CS were often at the edges of the zones with high levels of ischemia.

The combination of spatial heterogeneity of CS and its temporal progression lead naturally to speculations related to the arrhythmogenesis that previous studies have shown occurs in early ischemia. Of course, such speculation must also include information about repolarization, the parameters of which are also available from our studies. It is essential to show regions of functional unidirectional block that our ongoing studies will seek to identify.

Our preparation shares the limitation of all mapping studies in that spatial sampling and coverage are always a compromise between achievable electrode densities and maintaining a viable, living organ under physiological conditions. Our sampling is relatively dense in the radial direction (1.5–1.7 mm), which is ideal for studying endocardial

