Novel Biomarker for Evaluating Ischemic Stress Using an Electrogram Derived Phase Space

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Abstract

The underlying pathophysiology of ischemia is poorly understood, resulting in unreliable clinical diagnosis of this disease. This limited knowledge of underlying mechanisms suggested a data driven approach, which seeks to identify patterns in the ECG data that can be linked statistically to underlying behavior and conditions of ischemic tissue. Previous studies have suggested that an approach known as Laplacian eigenmaps (LE) can identify trajectories, or manifolds, that are sensitive to different spatiotemporal consequences of ischemic stress, and thus serve as potential clinically relevant biomarkers.

We applied the LE approach to measured transmural potentials in several canine preparations, recorded during control and ischemic conditions, and discovered regions on an approximated QRS-derived manifold that were sensitive to ischemia. By identifying a vector pointing to ischemia-associated changes to the manifold and measuring the shift in trajectories along that vector during ischemia, which we denote as Mshift, it was possible to also pull that vector back into signal space and determine which electrodes were responsible for driving the observed changes in the manifold. We refer to the signal space change as the manifold differential (Mdiff). Both the Mdiff and Mshift metrics show a similar degree of sensitivity to ischemic changes as standard metrics applied during the ST segment in detecting ischemic regions. The new metrics also were able to distinguish between sub-types of ischemia. Thus our results indicate that it may be possible to use the Mshift and Mdiff metrics along with ST derived metrics to determine whether tissue within the myocardium is ischemic or not.

1. Introduction

The motivation for this research is the persistently poor performance of ECG based methods of diagnosing acute ischemia in the settings of both stress testing and the emergency department [1]. Diagnosis based on ECG has both a long history and a compelling rationale; ischemia generates changes in electrical behavior that should be visible in the ECG. However, identification of robust markers of ischemia remains challenging despite its long history. Here, we explore a recently reported novel approach to identification of electrogram based biomarkers of ischemia based on using all available information (all leads over the entire QRST) non-linearly projected onto a lower dimensional space from which differentiating features can be more easily extracted.

Ischemia, defined here as occurring when the blood flow to the heart is not sufficient to meet the demands of the tissue, is the physiological basis for ischemic heart disease (IHD), the leading cause of death in the world [2]. Ischemic tissues produce abnormal electrical signals that alter the recorded signal of the clinical electrocardiogram (ECG). Unfortunately, ambiguities based on the broad range of pathophysiologies seen in IHD and the nonunique nature of many of these abnormal features make IHD difficult to accurately diagnose. The ECGs that are captured in both the clinical and experimental settings suffer from high-dimensional perturbations that may or may not be the result of ischemia along with what are known as "injury currents" that arise between healthy and ischemic regions in the heart. Clinically, myocardial ischemia is identified by deviations from the expected isoelectric (zero) value of the ST segment in the ECG that exceed a predefined threshold measured at some standard time point between the end of the QRS and the peak of the T wave [3]. Ischemia alters the spread of excitation through the heart, suggesting that there should also be changes in the QRS complex [4]. We hypothesize that there are sensitive and robust biomarkers that occur within the QRS and that can be used to identify ischemic regions.

The approach we employ comes from a class of methods that reduce the dimensionality of data and identify meaningful patterns to uncover useful markers of underlying changes. The rationale for applying such an approach to identifying ischemia is that our experiments have indi-

cated that the electrical response to ischemia, as measured by a large number of electrodes in and on the myocardium, can be characterized as a set of dynamic perturbations induced in the tissue. We seek a lower-dimensional nonlinear manifold that can be extracted from this high dimensional data, since these changes are induced by a well-defined perturbation that should affect many local signals in a causally-linked fashion. This lower-dimensional space may emphasize the changes caused by the affected tissue which can than be mapped back into signal space to identify which electrodes in the high dimensional space contributed to the changes observed in the manifold space. The goal of this approach is to identify and localize the spatial and temporal features that identify the regions experiencing ischemia. As a test of this sensitivity, we also attempt to differentiate between two subtypes of ischemia, supply ischemia and demand ischemia.

2. Methods

We employed an approach known as "Laplacian eigenmaps" [5] (LE) as a manifold learning algorithm to investigate how cardiac signals, specifically the during QRS complex, are influenced by ischemic stress. We based our approach heavily on previous studies by Erem *et al.* [6] but extended the scope of the analysis to include electrograms acquired within the wall of the left and right ventricles during both supply and demand ischemia, and to study a much larger set of experiments and data. Briefly, 4 to 6 episodes of one sub-type of ischemia was induced in open-chest canine preparations, while recording potentials using 25 to 40 transmural needles. Each needle has 10 electrodes along its length and were placed with the intent of sampling the region in which we expected ischemia to be induced by repetitive occlusion of a coronary artery. (More experimental details are given below.) Shifts in the LE space from healthy to ischemic manifolds were calculated to determine which regions of the manifold, and thus which spatiotemporal segments of the QRS, were most sensitive to ischemia; this trajectory shift in manifold space is referred to here as the Mshift. The Mshift vector most sensitive to ischemia-associated changes was used to create a metric, the manifold differential (Mdiff), in signal space, on an electrode by electrode basis; the Mdiff was then used to determine the spatial distribution of ischemia over time.

2.1. Laplacian Eigenmaps

LE is a dimensionality reduction method that is capable of reducing many simultaneously recorded time signals into a trajectory on a manifold of lower dimensionality. In our method, each sample time point measured across the entire set of electrodes corresponds to a single point on the manifold. Figure 1A shows a typical trajectory formed using the QRS measured from the entire lead set. These trajectories were obtained by computing a matrix of inverse exponentials of pairwise Euclidean distances between all input points, and then truncating its singular value decomposition (SVD). The rapid decay of the inverse exponential with increasing distance emphasizes the importance of local relationships in the data. The SVD ranks and determines the significance of the new coordinates. We defined three relevant coordinates to be the second through the fourth columns of the right singular vector matrix. The first column is ignored because it is constant.

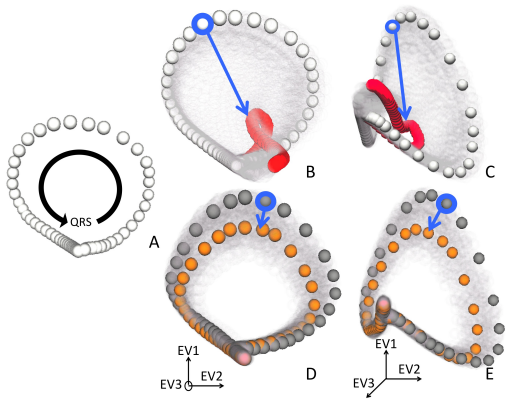

Figure 1. Manifolds created during induced episodes of supply (Red trajectory in B&C) and demand ischemia (Orange trajectory in D&E).Views of the manifold from the top in B and D and a rotated view in C and E, as shown by axes at the bottom. The blue arrows illustrate the associated Mshift vectors. **A:** Top view of a manifold showing how the time sequence of the QRS corresponds to the trajectory of the manifold. **B:** Top view of manifold created during supply ischemia. **C:** Rotated view of the same manifold. **D:** Top view of manifold created during demand ischemia. **E:** isometric view of the same manifold.

The manifold coordinates were learned using a series of control beats before the onset of ischemia. Once the coordinate space was identified we applied the same mapping to subsequent beats over repeated episodes of induced ischemia. A vector was constructed from each point on a trajectory from a beat before ischemia was induced and compared to its corresponding time point on a trajectory taken from a beat near the end of the ischemic episode. The most sensitive vector was determined by taking the time point that showed the largest magnitude shift along the defined vector. An example of the manifolds produced during supply and demand ischemia can be seen in Fig.1. The blue arrow shows the vector determined to be the most sensitive to ischemia in each of the sub-types of ischemia.

We next apply a method described in Erem *et al* [6] by which the inverse of the differential of the LE mapping

is used to map vectors in LE coordinates back to vectors in the data space. We refer to this data space vector as the manifold differential (Mdiff). In our experiments, we study whether the Mdiff can be thresholded to produce useful spatial representations of the ischemic regions within the myocardium.

2.2. Experimental Methods

In order to explore the electrophysiological consequences of acute myocardial ischemia we applied the LE algorithm to 20 *in situ* (open chest) canine experiments carried out in 2013 in which the left anterior descending artery was occluded and the perfusion bed was electrically monitored with the transmural plunge needles described earlier. The data from these experiments were used to examine the dynamic consequences of the development and spread of ischemia in response to ischemic stress of varying degrees. Two forms of ischemic stress were induced and analyzed, supply or perfusion based ischemia and demand or heart rate based ischemia.

Supply ischemia was induced by keeping the heart rate constant at 171 beats per minute (bpm) and reducing the level of perfusion in increments of 25%, starting at 100% every two minutes resulting in an 8 minute ischemic episode ending at 0% perfusion. Demand ischemia was induced by keeping perfusion constant at a level of 25% of normal and decreasing the pacing interval every 30 seconds from 400 ms to 290 ms in increments of 10 ms, once the minimal pacing interval was reached it was then held constant to produce an episode 8 minutes long. These interventions were repeated 4 to 6 times with 30 minute rest periods between each episode.

Data used in this study came from two experiments in which only one ischemic sub-type was induced. The results reported below are for a single experiment in which 5 episodes of supply ischemia was induced while the demand manifold was created from a second experiment with 5 induced episodes of demand ischemia. It should be noted that the rest of the experiments seem to show similar results, however, these results are not presented in this study.

3. Results

As described, we analyzed the ability of the Mshift and Mdiff metrics to reliably and consistently identify ischemic episodes and regions, and compared results to the standard ST segment shift. Specifically we used the current standard for identifying ischemic regions on an electrode by electrode basis, the ST40 metric [3] defined as the potential measured 40% of the way between the end of the QRS and the peak of the T wave. To evaluate the comparative reliability of the LE metrics and ST40, a signal to noise ratio (SNR) calculation was performed, dividing the mean amplitude of each metric during the final 200 seconds of the given ischemic episode by the mean amplitude during the first 100 seconds. In addition, we thresholded the ST40 and Mdiff metrics on the transmural plunge needles to determine and compare the volume of ischemic tissue identified by each metric. The threshold determined for the supply based experiment was determined manually by choosing a value corresponding to 50% of the peak amplitude for each signal.

3.1. Manifold Shift (Mshift)

The morphologies of the trajectories after several episodes of ischemia was highly dependent on the sub-type of ischemia that was induced. Supply based ischemia produced a large magnitude Mshift as well as a large change to the overall shape of the trajectory. Demand based ischemia produced a more subtle change to the manifold trajectory with a smaller change in waveform shape and a smaller magnitude Mshift. Typical changes are illustrated in Figure 1 above, with the red trajectory representing the manifold of a single beat at the end of five episodes of supply ischemia and the orange trajectory representing the manifold of a single beat after five demand episodes of ischemia in two separate animals. During supply ischemia the Mshift became increasing large at the latter phases of the QRS whereas the demand manifold was essentially unchanged during the initial and final phases of the QRS and only deviated during the middle of the QRS complex.

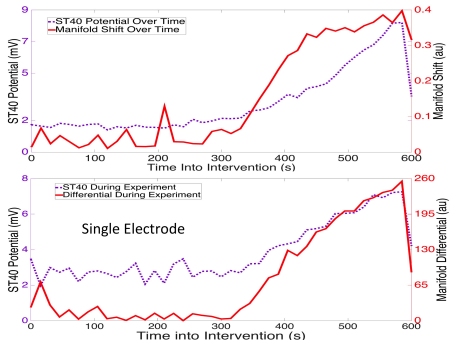

Figure 2. LE derived metrics versus ST40 during a single episode of supply ischemia. **Top:** The mean ST40 metric on all electrodes versus Mshift. **Bottom:** The ST40 metric measured on a single electrode versus Mdiff on the same electrode. [Purple = ST40; Red = Mshift(top), Mdiff(bottom)]

The plot showing the Mshift compared to the ST40 metric can be seen in Figure 2. The figure shows results from successive heartbeats during a prolonged ischemic intervention as described above. During this episode the Mshift was judged to be more sensitive than the ST40 metric as it resulted in a higher SNR, 10.6 versus 3.3.

3.2. Manifold Differential (Mdiff)

Plotting the ST40 and the Mdiff of a single electrode over an episode of ischemia in Fig. 2 illustrates typical behavior, that while they both reach their maximal value at the same time point the SNR of Mdiff is larger than that of the ST40 metric, here 7.3 versus 2.2 respectively.

Comparing the spatial distribution of the ischemic regions detected using the ST40 and Mdiff metrics shows a large degree of similarity (Fig. 3) with a DICE coefficient of 0.75.

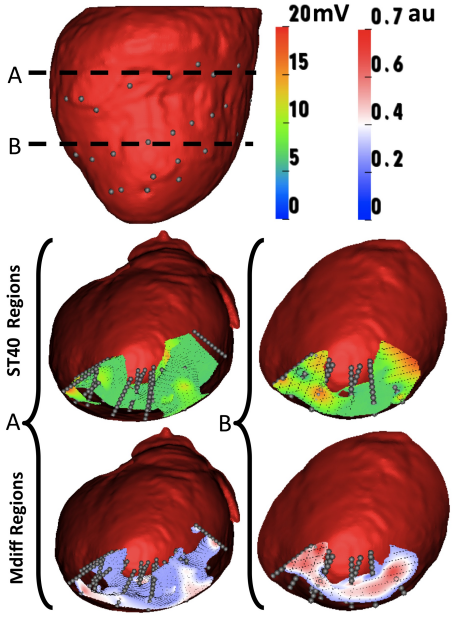

Figure 3. The spatial distribution created by thresholding both the ST40 and Mdiff metrics. Two cross sections are shown at positions A & B in the top image. The cross sections below are looking inferiorly from the base of the heart. [Colorbars at top right show ST40 values in mV in left bar and Mdiff, in arbitrary units, in the right bar.]

4. Discussion

As initially reported in Erem *et al.* [6], we found observable changes in the QRS in the analyzed data that were indicative of ischemia-induced changes to the underlying electrophysiology of the myocardium. The sensitivity of the Mdiff to the presence of ischemic tissue within the transmural wall was generally comparable to that of the ST40 metric and could potentially serve as a useful tool for detecting ischemic volumes within the myocardium. The Mshift, used here to determine the Mdiff, may also help to discriminate between subtypes of ischemia directly in the LE space. This difference can be difficult to discern in signal space.

During the initial episodes of ischemia the ST40 metric typically reaches a maximal value earlier than the Mdiff metric during the first episode or two of induced ischemia, suggesting ST40 is initially more sensitive. However, during the latter episodes the Mdiff metric responded to the ischemia earlier than the ST40 metric. This shift in sensitivity may be the result of impending irreversible tissue death or myocardial stunning that has a lasting effect on propagation through the tissue but does not produce the injury currents responsible for ST segment changes. The influence of ischemia on propagation could also explain why isolated ischemic regions detected by the ST40 metric as illustrated in Fig. 3 are connected to larger ischemic regions by the Mdiff metric, as the region has a more macroscopic influence on propagation than simply localized injury current. While the changes in signal space that are actually driving these changes are difficult to discern directly from observation of the recorded data, in part due to the large number of channels and thus sheer data volume and complexity, our results indicate that with the LE analysis we were able to identify that the QRS is indeed sensitive to acute episodes of myocardial ischemia and can also be used to differentiate between sub-types of ischemia as well.

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