HHS Public Access

Author manuscript

J Electrocardiol. Author manuscript; available in PMC 2018 November 29.

Published in final edited form as:

J Electrocardiol. 2018 ; 51(6 Suppl): S116–S120. doi:10.1016/j.jelectrocard.2018.08.017.

Temporal Performance of Laplacian Eigenmaps and 3D Conduction Velocity in Detecting Ischemic Stress

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Abstract

Background: Myocardial ischemia has a complex and time-varying electrocardiographic signature that is used to diagnose and stratify severity. Despite the ubiquitous clinical use of the ECG to detect ischemia, the sensitivity and specificity of ECG based detection of myocardial ischemia are still inadequate.

Purpose: The purpose of this study was to compare, using animal models, the performance of several traditional ECG-based metrics for detecting acute ischemia against two novel metrics, the Laplacian Eigenmap (LE) parameters and a three-dimensional estimate of Conduction Velocity (CV).

Methods: LE is a machine learning technique that reduces the dimensions of simultaneously recorded time signals using a non-linear embedding followed by an singular value decomposition to represent each multichannel recording as a single trajectory on a manifold. Perturbations in the trajectories suggest the presence of myocardial ischemia. CV was computed using a tetrahedral mesh created from the electrode locations of transmural plunge needles. To validate the results, we used electrograms collected over 95 episodes of acutely induced myocardial ischemia in 15 canine and 2 porcine subjects. The LE and CV metrics were compared against traditional metrics derived from the ST segment, the T wave, the QRS of the same electrograms. The response time and robustness of each metric was quantified using parameters we defined as time to threshold (TTT) and contrast ratio (CR).

Results: The temporal performance of the metrics evaluated throughout the ischemic episodes showed a consistent relationship; the LE metrics changed earlier than those from the T wave, which were followed by those from the ST segment, and finally from the QRS.

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Declarations of Interest: none

The CV results showed median drops in conduction velocity throughout the perfusion bed of more than 23 % in canines and over 12% during half of the induced ischemia episodes in swine. The other half of the episodes in swine produced a 76% drop.

Conclusions: Our results suggest that the LE metric is more sensitive to acute ischemia than traditional single parameters used in previous studies, likely because it incorporates the entire QRST across multiple electrodes in a way that captures their most salient features in a low-dimensional space. The estimates of conduction velocity suggest substantial, in some cases dramatic slowing of the spread of activation, a finding that is not surprising but has not been documented in such three-dimensional detail before. The experiments and these new metrics provide a means to both explore details of the acute ischemic response not available from humans and suggest a path to translate this knowledge into improvements in clinical scoring of ischemia.

Introduction:

Myocardial ischemia has a complex and time-varying electrocardiographic signature that is used to diagnose the presence of life threatening ischemia and to stratify its severity [1]. This ischemic ECG signature is often based on shifts in the ST segment of the ECG, an otherwise isoelectric portion that deflects under ischemic stress [2]. Despite its ubiquity over many decades of daily use, ECG detection of myocardial ischemia still shows unsatisfying sensitivity and specificity, even under the controlled setting of a stress test [3]. The purpose of this study was to compare the temporal performance of several traditional metrics used to detect ischemia against two novel metrics: Laplacian Eigenmap (LE) parameters using machine learning and three-dimensional (3D) conduction velocity (CV). The traditional metrics compared in this study came from the repolarization phase of the ECG, two from the ST segment, ST40% and ST60 shifts; two from the T wave, Tpeak and the T-wave integral. ST40% is the potential value from each electrogram at a time 40% of the interval between the J point and the peak of the T wave. ST60 is the potential measured 60 ms after the J point. Finally, we used a single QRS-derived metric, the integral of the QRS. All of these metrics except 3D CV can be derived from ECGs and from cardiac electrograms captured anywhere in the heart; 3D CV requires intramyocardial electrograms measured simultaneously using transmural plunge needle electrodes.

We focused our studies on the progression of acute ischemia during a simulated stress test by following all the ischemic metrics derived from continuous electrogram recordings. A particular strength of our approach is the use of large animal models, which allowed tight control over many conditions in the experiment. The ischemic episodes used for this analysis were not separated based on ischemic subtype (i.e., supply versus demand) as our goal was to evaluate the ability of these metrics to separate normal from ischemic states, independent of origin. The results showed that the metrics responded in a consistent sequence: first to reflect ischemia were LE parameters followed by T-wave changes, ST- segment shifts, and finally QRS changes. We propose that the novel LE parameters performed best because they incorporate the ECG signal from all leads and entire beats and are able to extract the most salient features from them.

Methods:

Laplacian Eigenmaps

Laplacian Eigenmaps (LE) is a non-linear dimensionality reduction method that can be used to reduce the complexity of multiple, simultaneously recorded time signals into a trajectory on a manifold [4]. In our method, as described by Erem et al., each sample time point measured across the entire set of recording electrodes is represented by a single location on the trajectory [5]. The method consolidates information from multiple time signals, in this case electrograms from 247 electrodes spaced uniformly over the epicardial surface of both ventricles. The resulting manifold contains a single trajectory for each beat that includes information from all recorded signals. To obtain the trajectories, it is necessary to construct a matrix of inverse exponentials of pairwise Euclidean distances between all time points across all electrodes, and then to compute its singular value decomposition (SVD). The inverse exponentials are scaled to emphasize local relationships in the data, preserving some of the spatial context of the original signals, reflected in the shape of the computed trajectory. The SVD determines and ranks the significance of the coordinates of the manifold, from which the three largest usually capture enough information to represent key features of the original signals, but in a much-reduced space. The new coordinates define a space we refer to as the “LE space”, which is a manifold specific to the recorded signals.

In this study, each trajectory came from the entire QRST of all 247 measured epicardial electrograms captured continuously during repeated ischemic episodes in dogs and pigs. Each episode began with a control period followed by a ramp of progressively more ischemia stress, either by increasing the heart rate or reducing the coronary blood flow, followed by a return to control conditions. Beats during the initial control period, before any ischemic episodes were induced, were used to define the LE space for that episode. Once the LE space was identified, it was populated with subsequent beats over repeated episodes of induced ischemia. We defined the QRST to span the QRS onset to the end of the T wave determined manually from the root-mean-squared (RMS) curve from each beat. To compare beats from potentially different heart rates, we resampled each QRST to 1000 time points. An example trajectory corresponding to one control recording is shown in Figure 2A and the subsequently populated manifold for a single ischemic episode is shown in Figure 2B.

To detect ischemia, we then need to define a metric that captured the change in the trajectories within each manifold over the ischemic episode. We first computed the Euclidean distance in the LE space between each point on the healthy trajectory and its corresponding point on each subsequent trajectory for each beat. Those regions of the trajectory that responded most consistently to ischemia and with the greatest mean distance to the healthy trajectory were then further analyzed to find which of these points responded most quickly. We selected the distance between trajectories at this point as the LE parameter for that ischemia episode. As an example, the magnitude of displacement of the trajectories along the blue arrow in Figure 2C was used as the LE metric for this ischemic episode [6].

3D Conduction Velocity

To calculate conduction velocity in a volume of tissue, we extended the two-dimensional (2D) triangulation technique outlined in Cantwell et al. [7] to three dimensions and estimated the mean conduction velocity for each tetrahedral volume element in our mesh. Briefly, Cantwell describes several 2D approaches to determining conduction velocity with guidelines on minimum edge lengths and activation time differences at nodes. We extended this concept to 3D conduction velocity (CV) estimation over a region sampled by transmural plunge needles. The electrode locations formed the nodes of a tetrahedral mesh. We used interpolation to compute the CV magnitude and direction for every face of each tetrahedral element, using the edge lengths, differences in recorded activation times, and the angles that separate the edges. A resulting CV vector was summed across the four faces to produce a single representative vector for the entire tetrahedron. This algorithm assumes that excitation is a planar wave moving through each tetrahedral element with a constant local speed and direction. For this study, we computed a median value of CV across all the tetrahedra in the perfusions bed and defined it as our CV metric to detect ischemia. To identify ischemia, we used the difference in the CV metric values measured at rest and during each sampled beat during the ischemic episode.

Inducing Acute and Controlled Myocardial Ischemia

The signals for this study were cardiac electrograms measured from 17 *in situ* experiments (15 canine and 2 porcine) during which 95 episodes (85 canine and 10 porcine) of acute myocardial ischemiawere induced. The porcine episodes were included to show how CV may vary between the two species and their results were not Included in the temporal analysis. Experiments were performed under deep anesthesia using procedures approved by the Institutional Animal Care and Use Committee of the University of Utah and conformed to the Guide for the Care and Use of Laboratory Animals. Each ischemic episode lasted 5–8 minutes with a 30-minute rest between episodes to allow the tissue to return to baseline electrical recordings. The electrocardiographic response to ischemia was measured using 20–40 transmural plunge needles, each with 10 unipolar electrodes evenly distributed within the myocardial tissue, and a 247-electrode eplcardlal sock array that surrounded the ventricles of the heart [8] [9]. Anywhere from 3–8 interventions were performed per animal, using protocols designed to produce ischemia via a supply-demand mismatch in the tissue perfused by the left anterior descending (LAD) artery. Three-second recordings were taken every 15 seconds during the ischemic episodes and every 10 minutes during the rest periods. From each recorded time interval, a representative beat was selected for analysis, first using the PFEIFER framework to filter, baseline correct, and manually identify fiducial markers of each of the major features of each beat [10].

The role of the needle electrograms was to estimate the 3D conduction velocity in the LAD perfusion bed and to detect the timing and extent of local ischemia within the heart volume. Eplcardlal electrodes, by contrast, record remote superficial evidence of the underlying electrical activity in the heart and can, therefore, provide ambiguous information. In this regard, they resemble body surface ECGs, although body-surface potentials are even more attenuated and further blur the cardiac activity.

Analyzinq the Temporal Performance of the Metrics

To compare the temporal performance of each metric, we plotted their values from each representative beat during the induced ischemic episodes in the form of a time series we call a “run-metric plot”. Figure 2 shows how such a run-metric plot was generated and interpreted relative to a threshold determined for that metric and episode. The metrics chosen for this study were the QRS integral (QRSint) [11], shift of the ST segment at the ST40% [9] and ST60 [12] time points, the T-wave integral (Tint), and the peak value of the T wave (Tpeak) [9] along with the two novel metrics described previously, LE and CV.

We applied similar metrics to the electrograms from the needle electrodes to determine which episodes resulted in detectable ischemia, a ground truth for subsequent comparison of the metrics generated from epicardial potentials. For a positive detection, we required that the value of the metric exceed the value measured at control by two standard deviations for least 5 consecutive beats. The result was a set of 85 episodes in which ischemia was detected by at least one of the metrics applied to the needle electrograms. We then developed two confidence measures for the epicardial electrograms to capture the time to detection of ischemia and its robustness in that detection. The time to detection was quantified using the time to threshold (TTT), which measured the time at which a metric exceeded an automatically computed threshold determined using the TTT formula included in Figure 1. The robustness of a metric detection was captured by the contrast ratio (CR), which measured the ratio of the peak value achieved by the metric and its value at baseline. Because the goal of this study was to compare both the sensitivity and the temporal performance of the metrics, we included a separate analysis of those episodes (n=25) for which all metrics detected ischemia.

Results:

Temporal Performance of the Metrics

Table 1 provides statistical support for the trend in Figure 3 and shows the superior performance of the LE metric both in terms of overall sensitivity (45 of 85 ischemic episodes detected) and early detection (273 +/− 88 s) compared to all the other metrics. While the LE metric showed superior sensitivity, it was not the most robust metric; Tint and Tpeak showed slightly higher CR values than the LE metric and all three were at least marginally superior to the other metrics.

3D Conduction Velocity

3D CV served to capture the changes in the spread of activation that follow ischemia and the results in Figure 3 and both tables indicate clear the drops we observed in CV with ischemia. The CV metric responded at approximately the same time as the epicardial ST40% and Tint metrics (Table 1) with reductions that ranged from 14.7 to almost 70 cm/s depending on the animal and episode (Table 2). If we separated the 10 porcine episodes into two cohorts based on changes in CV, the first experienced a mild drop (10.8 cm/s) during ischemia while the second cohort showed a large drop (66.9 cm/s). These cohorts spanned both animals and the cohort that experienced large drops in CV (porcine cohort 2) typically occurred in the latter half of the experiment.

Discussion:

This study evaluated two novel metrics for detecting ischemic stress, LE and CV, and investigated their sensitivity and temporal performance against five traditional metrics. Understanding the temporal dynamics of the electrocardiographic signals during ischemic stress has the potential to both reveal mechanisms and inform clinicians of the underlying physiologic changes occurring during acute, transient ischemic episodes. Such episodes arise clinically during cardiac stress testing, surgical procedures, and in acutely ill, critical-care patients and are often poorly managed.

The LE metric consistently showed the largest and earliest change after onset of ischemia of all the metrics, which likely suggests that signs of ischemic effects exist within a very lower-order space that can be quantified with simple metrics based on deformations of the resulting manifolds. An additional advantage of this approach is that the LE approach maintains the spatial and temporal context of the input signals while representing them in a space that accentuates local relationships in the input dataset. This maintenance of the temporal information allows the changes seen in regions of the LE space to be related to specific intervals of the ECG. Within the LE manifold, we were able to identify intervals over which the deformations of the trajectories were largest and then define an LE metric that could follow and detect the ischemic episodes. The intervals most often selected by the LE metric were roughly 20% and 95% into the QRST, corresponding approximately to the ends of the QRS and the T wave, respectively. The superior performance of the LE parameters suggests a complementary role for this metric as a diagnostic tool in evaluating ischemic stress. With the graded stress protocol, we showed that the LE metric indicated ischemia on average 38 seconds earlier than the next best traditional metric, Tpeak, and 50 seconds earlier than the best ST-segment-derived metric. This superior temporal performance was also supported by the number of episodes each metric was able to detect from the epicardial surface; metrics with a faster response time tended to detect more of the induced episodes than those with slower response times.

The 3D CV results from our canine subjects confirmed those observed by others in 1D and 2D measurements [13] [14]. However, these are the first to our knowledge based on three-dimensional measurements. The results from the porcine study also showed clear reductions in CV values during ischemia, in some episodes quite dramatic reductions of up to 76% of control values. It is premature to speculate at this stage on the origins of these substantial differences in some episodes because of the small numbers of subjects. We routinely see variability in the progression of ischemia across episodes in the same animal that might lead to such fluctuations in overlap.

The main limitations of the study stem from the experimental challenges. First, the number of porcine experiments studied was limited so that extensive speculation about their responses is premature. The sampling of the needles in the perfusions bed was not uniform, with finer sampling along the shaft of the needle (1–2 mm) than in the space between the needles (1–3 cm). Furthermore, the CV measurement was limited to the intramyocardial extent of the 3D measurements, i.e., within the convex hull containing all the needle electrode sites

The analysis of the signals and their metrics underscored the observation that the electrocardiographic signature of ischemia is transient and spatiotemporally complex and hence challenging to capture and interpret in clinical settings. Only by characterizing these patterns in the controlled setting of animal experiments can we hope to infer the underlying level of ischemic stress present and generate useful and practical metrics. The differences in the temporal evolution of the metrics we tested, e.g., LE changes preceding T-wave changes, etc., suggest that novel metrics may exist that could improve the clinical performance of the ECG. Furthermore, the use of experiments allows us to capture and use run-metric curves to evaluate the temporal dynamics of several measures that cannot be reasonably measured in humans, especially the novel three-dimensional conduction within in the perfusion bed.

Acknowledgements:

Support for this research was provided in part by the NIH/NIGMS Center of Integrative Biomedical Computing (CIBC), P41 RR0112553 and the Nora Eccles Treadwell Foundation at the Cardiovascular Research and Training Institute (CVRTI) funded the experiment data collection. The authors would like to thank Brett Burton, Jess Tate, and Kedar Aras for their assistance in carrying out the experiments and data collection.

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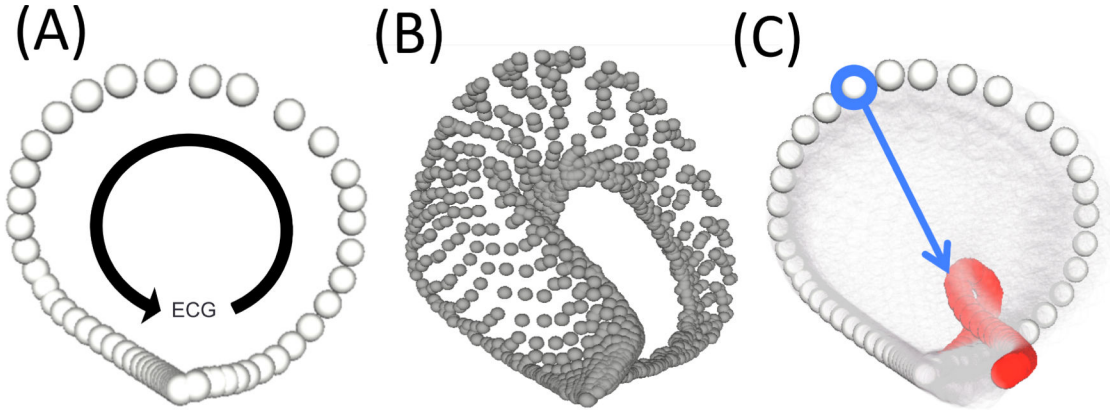

Figure 1 -

Laplacian Eigenmap manifolds. A) This manifold consists of a single trajectory corresponding to a representative beat extracted during the rest period, before the induction of ischemia. The progression of the ECG and its relation to the trajectory are shown by the black arrow. B) This manifold shows several runs mapped into the same manifold space. Each trajectory corresponds to a single run during the episode. C) This final manifold shows the trajectory of the run taken at rest (white) and the final run of the ischemic episode (red) with all other trajectories set to be transparent. The blue arrow corresponds to the point on the trajectory that shows the greatest sensitivity to the underlying ischemic stress.

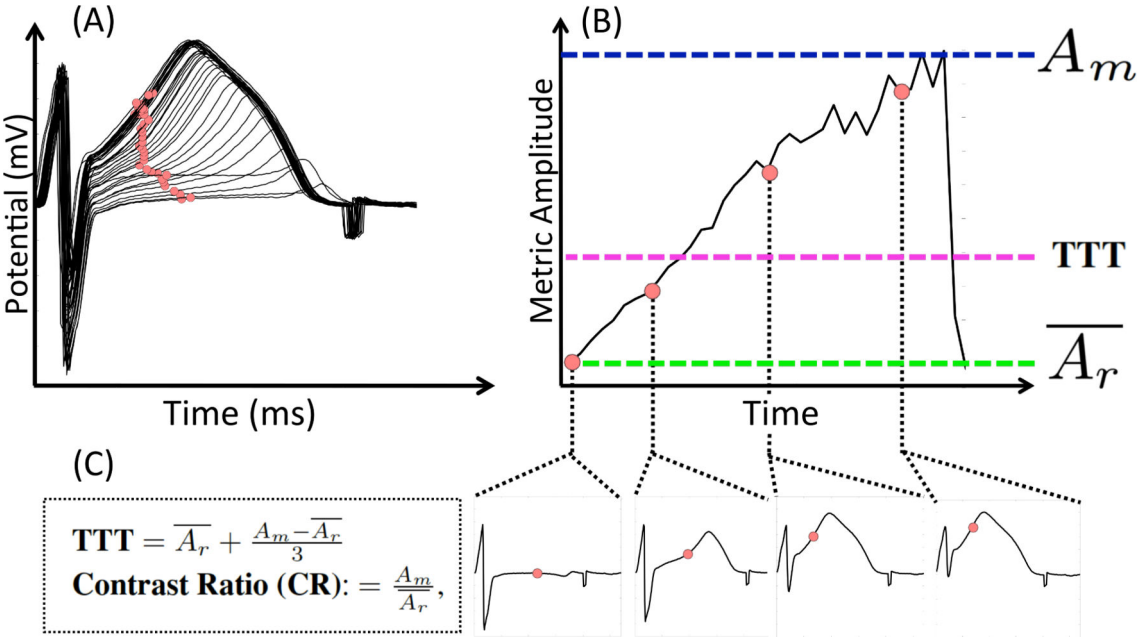

Figure 2 -

The generation of a run-metric plot for the ST40% metric over an episode of ischemia. A) An overlay of each representative beat recorded on a single electrode during an episode of ischemia. The red spheres show the ST40% time instants for every beat. B) A run-metric showing the potential values of the ST40% time instants over the course of the ischemic episode. Blue line: Max value achieved by that metric during the episode. Green line: Average value of the metric during the beats recorded before the ischemic episode. Magenta line: The amplitude of the predetermined threshold. C) The formulas used to calculate the predetermined threshold (TTT) and the contrast ratio calculation.

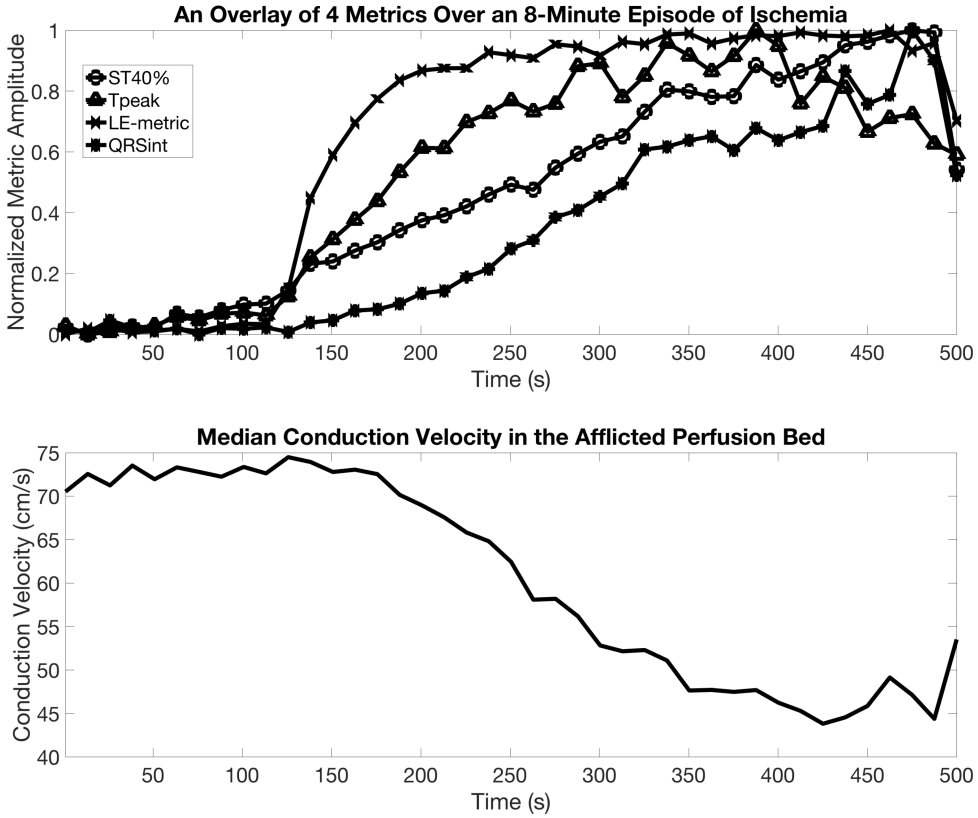

Figure 3 -

Time series showing the response of various metrics to a single 8-minute episode of ischemia. TOP: An overlay of the ST40%, Tpeak, LE-metric, and QRSint metrics. BOTTOM: The value of the 3D CV metric during the same episode of ischemia seen above.

Table 1 -

Temporal Performance of Various Metrics on the Epicardial Surface. The time to threshold (TTT) measures the response time of the metric and the contrast ratio measures the robustness of its response. Episodes detected quantifies the number of episodes of ischemia detected by the metric.

	Time to Threshold (TTT) [s]	Contrast Ratio (CR)	Episodes Detected
LE-Metric	273 +/−88	4.7 +/− 3.2	45/85
ST40%	323 +/−90	1.7 +/− 4.7	34/85
ST60	356 +/−90	2.2 +/− 5.2	34/85
Tpeak	311 +/−97	5.1 +/− 3.3	41/85
Tint	323 +/− 100	6.9 +/− 5.2	39/85
QRSint	379 +/− 55	1.9 +/− 2.1	26/85
CV	322 +/−82	4.5 +/− 6.9	n/a

Table 2 -

Conduction Velocity Across 95 episodes of Ischemia in canine and porcine experiments. This table shows the median 3D conduction velocity across episodes of ischemia. Clustering the 10 episodes from the porcine experiments by CV values (peak and change from control) showed two very divergent responses to ischemia.

	Control Recordings (cm/s)	Peak Episode Recordings (cm/s)	Difference (cm/s)
Canine (n=85)	61.1 ± 13.1	46.6 ± 11.9	14.7 ± 15.0
Porcine Cohort 1 (n=5)	87.1 ± 6.3	76.3 ± 7.0	10.8 ± 2.7
Porcine Cohort 2 (n=5)	87.7 ± 2.1	20.8 ± 3.8	66.9 ± 4.1