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Monitoring canine myocardial infarction formation and recovery via transthoracic cardiac strain imaging

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Abstract

Myocardial Elastography (ME) is an ultrasound-based strain imaging method. A survival canine model (n=11) was employed to investigate ME's ability to image myocardial infarction (MI) formation and recovery. Infarcts were generated by ligation of the left anterior descending coronary artery. Canines were survived and imaged for four days (n=7) or four weeks (n=4), allowing sufficient time for recovery via collateral perfusion. A radial strain-based metric, percentage of healthy myocardium by strain (PHM_e), was developed as a marker for healthy myocardial tissue. PHM_e was strongly linearly correlated with actual infarct size as determined by gross pathology ($R^2 = 0.80$). Mean PHM_e was reduced 1–3 days postinfarction ($p < 0.05$) at the papillary and apical short-axis levels; full recovery was achieved by day 28, with mean PHM_e returning to baseline levels. ME was capable of diagnosing individual myocardial segments as non-infarcted or infarcted with high sensitivity (82%), specificity (92%), and precision (85%) (ROC AUC = 0.90).

Keywords

strain imaging; acute myocardial infarction; animal model; transthoracic echocardiography

Introduction

Acute coronary syndrome (ACS) refers to acute myocardial ischemia and/or myocardial infarction (MI) that manifests due to an abrupt partial or total occlusion of coronary blood flow. ACS affects more than 780,000 Americans annually (Amsterdam et al. 2014; Ibanez et

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Disclosures

The authors have no relationships to disclose.

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al. 2018; O’Gara et al. 2013; Roffi et al. 2016) and must be treated early to be successfully managed (Fibrinolytic Therapy Trialists’ (FTT) Collaborative Group 1994).

MI is typically suspected in patients with severe chest pain and a history of coronary artery disease (CAD) (Amsterdam et al. 2014; Ibanez et al. 2018; O’Gara et al. 2013; Roffi et al. 2016). Unfortunately, the symptoms associated with MI are diverse and can be inconsistent among patients, leading to misdiagnosis or undertreatment (Brieger et al. 2004). Patients with suspected ACS are immediately monitored by ECG, as a hallmark of MI is ST-segment elevation (O’Gara et al. 2013; Roffi et al. 2016). However, ST-segment elevation can occur due to other conditions, and ACS frequently manifests absent ST-elevation (Roffi et al. 2016; Wang et al. 2003). Troponin remains a reliable biomarker for MI, but may require several hours to process, and may not be sufficient to confirm MI even in conjunction with an abnormal ECG (Amsterdam et al. 2014; Ibanez et al. 2018; O’Gara et al. 2013; Roffi et al. 2016). Consequently, emergency coronary angiography is the preferred diagnostic approach due to its high negative predictive value (Amsterdam et al. 2014; Ibanez et al. 2018; Keeley et al. 2003; O’Gara et al. 2013; Roffi et al. 2016). However, angiography may not be available at all medical care providers, and necessitates radiation exposure.

Primary percutaneous coronary intervention (PCI) is frequently the preferred treatment in patients with confirmed MI (Amsterdam et al. 2014; Ibanez et al. 2018; O’Gara et al. 2013; Roffi et al. 2016). This treatment must be applied urgently in order for the reperfusion to be successful. Patients may need to be transferred from a non-PCI-capable hospital to a PCI center, delaying treatment (Dauerman et al. 2015). Thus, timely diagnosis and treatment of ACS and MI is complicated by inconsistent and atypical symptom patterns; diagnostic approaches that are insufficiently specific, too slow, or invasive; and long transfer times between non-PCI-capable hospitals and PCI centers. A rapid method of diagnosing MI accurately would improve patient outcomes by decreasing the delay between first medical contact and primary PCI.

Strain and strain rate imaging with ultrasound has been proposed as a quick and non-invasive means of diagnosing MI (Collier et al. 2017; Hoit 2011). A few minutes following the onset of MI, the acutely ischemic myocardium gradually loses its ability to actively contract, and therefore can no longer generate sufficient contractile force (Holmes et al. 2005). Infarcted tissues thus exhibit reduced strain and strain rate compared to healthy myocardium. The relationship between strain and infarction has been extensively studied in large animal models via sonomicrometry (Gallagher et al. 1980; Gallagher et al. 1984; Gallagher et al. 1985; Roan et al. 1981; Savage et al. 1981). Noninvasive approaches to assessing strain began with strain rate imaging using Doppler ultrasound to characterize MI (Edvardsen et al. 2002; Jamal et al. 2001; Urheim et al. 2000; Zhang et al. 2005). However, as strain rate is typically estimated in 1D, the inherent angle dependence of this approach may lead to inaccurate estimates or increased variability between measurements (Castro et al. 2000; D’hooze 2000). Strain imaging with speckle tracking allows for 2D estimation of displacement and strain, mitigating angle dependence (Amundsen et al. 2006). Speckle tracking for MI characterization of infarct size or mass has been validated in patients (Delgado et al. 2008; Eek et al. 2010; Gjesdal et al. 2007; Gjesdal et al. 2009; Grenne et al. 2010). These studies focused on estimating global longitudinal strain (GLS), which is

obtained from the long-axis echocardiographic view. GLS is generally the preferred strain estimation approach: ultrasound imaging has superior resolution in the axial direction, and there is a greater area of myocardial tissue available in the long-axis compared to the short-axis view. Furthermore, GLS is comprised of several mean strain values taken over the entirety of the myocardial wall, which allows for increased robustness in the measurement (Collier et al. 2017). The cost of a global strain metric is reduced diagnostic resolution; it lacks the sufficient precision to localize an infarct to a specific myocardial segment. Regional deformation measurements (i.e. estimates of strain in individual myocardial segments) measured by speckle tracking currently suffer from poor reproducibility, intervendor strain estimation variability, and a lack of reference values; consequently, the American Society of Echocardiography and the European Association of Cardiovascular Imaging have recommended against its use in the clinic in their latest guidelines (Collier et al. 2017; Lang et al. 2015).

Myocardial Elastography (ME) is a transthoracic ultrasound-based strain imaging technique. Although ME does not explicitly measure elastic properties of the myocardium, the strain imaging technique is based on the signal processing approach detailed in the first publication defining elastography (Ophir et al. 1991). Previous applications have included ablation monitoring in canines and humans (Bunting et al. 2018; Grondin et al. 2015), tracking the progression of acute ischemia in an open-chest canine model (Lee et al. 2011), and imaging suspected coronary artery disease (CAD) patients (Grondin et al. 2017). ME has also been used to image MI in a murine model (Luo et al. 2007). Speckle tracking, which is the typical method currently employed in clinical scanners, estimates axial and lateral displacements by using a 2D kernel on Bmode images (Amundsen et al. 2006). In contrast, ME uses 1D cross-correlation of radiofrequency (RF) data in a 2D search to estimate displacements (Lee et al. 2007). By leveraging both envelope and phase information, RF-based displacement estimation has been shown to yield strains with lower variability and increased resolution compared to speckle tracking (Ma and Varghese 2013).

A canine model was employed to demonstrate the ability of ME to monitor MI. Canine cardiac physiology differs from the human one in that the former will recover from acute ischemia solely by coronary collateral perfusion, and it has been shown that canine myocardial infarcts produced via surgical ligation of a coronary artery gradually recover over several weeks (Hearse 2000; Jugdutt and Amy 1986; Levy et al. 1961; Maxwell et al. 1987; Schaper et al. 1967). Thus, the canine model allows ME to be evaluated during infarct formation and recovery. Imaging during recovery can inform whether ME will be a useful tool to monitor reperfusion therapy in MI patients.

We developed a metric based on the observed systolic radial strain to identify infarcted myocardium, *percentage of healthy myocardium by strain*, or PHM_e . Infarctions were generated in canines ($n = 11$) via ligation of the left anterior descending (LAD) coronary artery. One group of canines ($n = 7$) were survived for four days, while a second group ($n = 4$) were survived for four weeks. True infarct size was determined by gross pathology and triphenyltetrazolium chloride (TTC) staining. The diagnostic capabilities of ME and PHM_e were investigated with a receiver operating characteristic (ROC) curve and precision-recall curve (PRC).

The objectives of this paper are to 1) determine how well PHM_e correlates with actual infarct size, 2) investigate feasibility of ME as a method to track infarct formation and recovery, and 3) test whether ME can localize infarct to specific myocardial segments. We find that ME is an accurate means of diagnosing MI, and is a potentially useful addition to the clinic as a method to rapidly identify and localize infarcts and monitor recovery.

Materials and Methods

Experimental protocol

The study protocol was in compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and conducted with approval by the Institutional Animal Care and Use Committee (IACUC) at Columbia University. Infarcts were induced in 11 Class A mongrel canines acquired from Marshall BioResources (24 ± 2.4 kg, 100% male). Transthoracic baseline ultrasound images in the parasternal short axis view were acquired prior to the ligation procedure. With the canine under anesthesia, a lateral thoracotomy was performed to expose the myocardium. The proximal left anterior descending (LAD) coronary artery (at the first diagonal) was dissected free and ligated (Harris 1950). The ligation location was chosen to create an infarct in the anterior, antero-septal and antero-lateral segments at papillary and apical short axis levels. Perfusion at the mitral/basal short-axis level was unaffected. Following the surgery, the canines were provided postoperative care (antiarrhythmic drugs, antibiotics, and pain management). Randomization was not employed in this study as all animals received LAD ligation, and consequently, the investigators were not blinded. Given the extensive literature detailing the relationship between strain and infarct via sonomicrometry in large animal models (Gallagher et al. 1980; Gallagher et al. 1984; Gallagher et al. 1985; Roan et al. 1981; Savage et al. 1981), sham ligation procedures were not implemented in this study.

The subjects were split into two groups, defined by the duration of the survival period. By design, seven ($n=7$) canines were survived for three or four days after ligation surgery (*short-term canines*). Four ($n=4$) canines had a survival period of 28 days (*long-term canines*). The imaging schedule is summarized in Fig. 1. Separating the animals into two groups is necessary for gross pathology validation of ME during infarct formation and recovery stages: by day 28 the infarct size was substantially reduced due to the canine's collateral perfusion (Jugdutt and Amy 1986). All canines were imaged on days 1 through 4. The long-term group was additionally scanned on days 7, 14, 21, and 28. All imaging for this study was performed closed-chest. Prior to sacrifice, the canine was placed under anesthesia, and a lateral thoracotomy was performed to expose the myocardium for a separate electrophysiology study. The myocardium was then excised, sliced into transverse sections 0.5 cm thick. Sections were submerged in 1% tetrazolium chloride (TTC) and placed in an incubator at 37° for 40 minutes, flipping the sample at 20 minutes. TTC stains infarcted regions of the myocardium white. Photos of the stained samples were taken with a DSLR camera (Nikon EOS Rebel T3i, Tokyo, Japan).

Myocardial Elastography Imaging

All images were acquired transthoracically with the canine in the right lateral recumbency, and the transducer placed on the underside of the animal (Thomas et al. 1993). Note that because the imaging configuration differs between canines and humans, the orientation of the myocardial segments will not be identical. Parasternal short-axis images at the mitral, papillary, and apical levels were acquired on each scanning day. An ATL P4–2 phased array probe (20-mm 64-element aperture, 2.5 MHz, 0.32 mm pitch) was used with a research ultrasound system (Verasonics Vantage, Redmond, WA, USA). A compounding sequence employing 15 transmits, 60° angular aperture, 15° tilt, 300 Hz frame rate, and 14 mm depth was implemented (Sayseng et al. 2018). Two seconds of RF and ECG data were recorded to ensure at least one systolic event was captured.

Displacement and strain estimation were performed as previously described (Sayseng et al. 2018). Briefly, RF data was beamformed using delay-and-sum. Displacements were estimated from the beamformed RF signals using 1D normalized cross-correlation in a 2D search (4.6 mm axial window, 10% overlap) (Lee et al. 2007). Subsample displacement estimation was achieved with cosine interpolation (Lee et al. 2007). Lateral displacement estimation accuracy was increased by implementing a 10:1 linear interpolation between adjacent RF lines and employing three iterations of a previously described recorrelation method (Konofagou and Ophir 1998; Lee et al. 2007). Displacements were accumulated relative to the initial position of each pixel in the end-diastolic frame, i.e. the first frame of systole. Lagrangian strain was derived by applying a least-squares strain estimator (3.8 mm by 4.0°) on the axial and lateral cumulative displacements (Kallel and Ophir 1997). Radial cumulative strains were estimated from the 2D strain tensor and smoothed with a median filter (5.8 mm by 6°) (Fig. 2a). Epicardial and endocardial borders of the end-diastolic frame were manually segmented (excluding papillary muscles and valves); only strains within the mask were used for analysis. Infarcted areas were identified in the strain images by setting a strain threshold, ϵ_{thresh} ; strain values less than ϵ_{thresh} were labeled infarcted (Fig. 2b). Images acquired at the mitral and papillary short-axis level were divided into six myocardial segments using the standardized segmentation model of the American Heart Association; images at the apical level were divided into four segments (Cerqueira et al. 2002).

Image analysis and statistics

TTC stains infarcted tissue pale pink or white (Fig. 2c). Infarcted areas of the myocardium were identified from the gross pathology images using MATLAB 2016a (Natick, MA, USA). The epicardial and endocardial border of the tissue sample was segmented manually, excluding the papillary muscles and valves (Fig. 2d). A second region-of-interest (ROI) encompassing the infarcted area was manually drawn. Pixels within this ROI that were <70% of the maximum brightness were labeled as infarcted, thus generating a mask that more exactly conforms to the infarct borders compared to an exclusively manual segmentation approach (Fig. 2d). Gross pathology images were divided into six and four myocardial segments at the papillary and apical levels, respectively. The proportion of healthy tissue in relation to infarcted tissue was quantitatively defined using the *percentage of healthy myocardium in gross pathology*, or PHM_{pg} :

$$PHM_{pg}(\%) = \frac{A_{healthy}}{A_{total}} = \frac{A_{total} - A_{infarct}}{A_{total}} \quad (1)$$

where A_{total} is the area or number of pixels within the epicardial and endocardial borders, $A_{infarct}$ is the number of pixels identified as infarct within the epicardial and endocardial borders, and $A_{healthy}$ is the number of pixels labeled as healthy within the epicardial and endocardial borders. PHM_{pg} is inversely correlated with infarct size: high levels of PHM_{pg} indicates a small infarct, while low levels of PHM_{pg} indicates a large infarct. A PHM_{pg} of 100% indicates the tissue sample is free of infarct.

To compare ME radial strain images against gross pathology, the *percentage of healthy myocardium by strain*, or PHM_e , was implemented:

$$PHM_e(\%) = \frac{\sum_{i=1}^n \begin{cases} 1 & \varepsilon(i) \geq \varepsilon_{thresh} \\ 0 & \varepsilon(i) < \varepsilon_{thresh} \end{cases}}{n}, \quad (2)$$

where ε is an n -element array of strain values within a mask, and ε_{thresh} is the strain threshold. That is, PHM_e is the sum of all ME strain pixels within the masked region of interest that were labeled as healthy, divided by the total number of pixels within the masked region of interest. As with PHM_{pg} , PHM_e is inversely correlated with infarct size.

The gross pathology myocardium slice to be compared to a given strain image was chosen based on anatomical landmarks present in the Bmode. For example, the same papillary muscles visible in the infero-septal, inferior, and infero-lateral segments in the Bmode shown in Fig. 2b are the same ones observed in the tissue sample in Fig. 2d.

The linear regression between PHM_e observed on the animals' terminal day versus PHM_{pg} was calculated. The PHM_e was evaluated at range of thresholds, $\varepsilon_{thresh} = [-5\%, 40\%]$ (Fig. 3). The highest coefficient of determination (R^2) was achieved using $PHM_e(\varepsilon_{thresh} = 8.0\%)$, wherein $R^2 = 0.80$. In comparison, the coefficient of determination between radial strain and PHM_{pg} was lower, $R^2 = 0.63$.

The mean PHM_e ($\overline{PHM_e}$) and standard deviation across all animals (both short and long-term canines) was plotted through time at each short-axis level. The 95% bootstrap confidence interval was additionally plotted as an error band. The Tukey multiple comparison test was used to determine if there were statistical differences in $\overline{PHM_e}$ between different scanning days. Estimated $\overline{PHM_e}$ differences between scanning days and the associated confidence interval and p-values are summarized in Table A.1. To corroborate the $\overline{PHM_e}$ results, the PHM_{gp} ($\overline{PHM_{gp}}$) mean, standard deviation, and upper/lower bounds was calculated on days 4 and 28, the two sacrifice time points.

The diagnostic resolution of ME was investigated. Strain and gross pathology images were analyzed ($n=10$ animals), with each slice divided into six or four myocardial segments using the standards recommended by the American Heart Association (Cerqueira et al. 2002). Only segments from the papillary and apical levels were used in this analysis. Each

myocardial segment in the tissue sample images were labeled either healthy or infarcted; infarcted segments were defined as those where 80% of pixels within the segment were identified as healthy (i.e. >20% of pixels were labeled infarcted). For the strain image analysis, the discrimination threshold at which a myocardial segment was labeled healthy/infarcted was varied through the range 0–100%. For example, a discrimination threshold of 60% would indicate that myocardial segments where 60% of pixels were classified as healthy would be classified as infarcted segments; conversely, if >60% of pixels in a given myocardial segment area was labeled as healthy, that segment would be classified as healthy. The ME diagnosis of each myocardial segment was validated against the ground truth of gross pathology (n = 100 segments). A true positive (*TP*) was achieved if ME correctly diagnosed a myocardial segment as infarcted, while a false positive (*FP*) was declared if ME diagnosed a healthy segment as infarcted. A true negative (*TN*) was declared when ME correctly diagnosed a segment as healthy, while a false negative (*FN*) was an infarcted segment incorrectly diagnosed as healthy. *Sensitivity* (or *recall*, or true positive rate, *TPR*) measures the proportion of positives that were accurately identified as such:

$$sensitivity = \frac{TP}{TP + FN} \cdot \quad (3)$$

Specificity measures the proportion of negatives that were accurately identified as such:

$$specificity = \frac{TN}{TN + FP} \cdot \quad (4)$$

The receiver operating characteristic (ROC) curve was generated to demonstrate the diagnostic ability of ME-derived PHM_e. The ROC curve plots the true positive rate (TPR) against the false positive rate (FPR, equivalent to 1 – specificity). The performance of a classifier described by a ROC can be summarized by calculating the Area Under the Curve (AUC). The AUC is a scalar that can range from 0 to 1, where values closer to 1 indicate a better discriminator.

The diagnostic ability of ME was also evaluated with a precision-recall curve (PRC) for a range of discrimination thresholds, 0–100%. Precision measures the classifiers ability to predict positives; it is the ratio of true positives and the sum of true positives and false positives:

$$precision = \frac{TP}{TP + FP} \cdot \quad (5)$$

Recall is equivalent to sensitivity and TPR. By plotting precision against recall, the PR curve demonstrates the tradeoff between the former and the latter as a function of the chosen discrimination threshold. In the same way that AUC functions as a summary statistic for ROC curve, the PRC can be summarized by the average precision metric:

$$\text{average precision} = \sum_n (R_n - R_{n-1}) P_n, \quad (6)$$

where R_n and P_n are the precision and recall at the n^{th} threshold. Average precision ranges from 0 to 1, where values closer to 1 indicate a better discriminator.

Based on correlation with gross pathology, $\epsilon_{\text{thresh}} = 8\%$ was determined to be the optimal threshold. Given the variability inherent in setting a static threshold, the range within which ϵ_{thresh} can be yield acceptable results was investigated. ϵ_{thresh} was varied between -10% and 30% to measure its corresponding effect on diagnostic resolution, as measured by AUC and average precision. For clarification, note that ϵ_{thresh} is varied in two separate experiments: 1) to determine the effect on correlation with gross pathology, and 2) to determine the effect on diagnostic resolution.

Exceptions and study exclusions

Short-term animals ($n = 7$) were typically imaged for three days post-infarct (i.e. sacrifice on day 4). One short-term animal was instead sacrificed two days post-infarct (day 3).

The terminal day 4 images acquired for one short-term animal were discarded due to an aberrant reaction to anesthesia during imaging. The strains and gross pathology of this canine were excluded from the linear regression calculation between PHM_e and PHM_{gp} , and from the ROC and PRC calculations.

Results

The PHM_e observed on the animals' terminal scanning day was strongly linearly correlated with the PHM_{gp} observed in the tissue samples ($R^2 = 0.80$), as summarized in Fig. 4. The equation of the linear regression was as follows:

$$\text{PHM}_{gp}(\%) = 0.95 * \text{PHM}_e(\epsilon_{\text{thresh}} = 0.08) + 26. \quad (7)$$

The 95% confidence bounds for the slope coefficient and intercept were $0.77-1.1$ and $13\%-38\%$, respectively. The mitral level had the smallest range in percentage of healthy myocardium, $\text{PHM}_e = [65\%, 88\%]$ and $\text{PHM}_{gp} = [90\%, 100\%]$. The PHM_e and PHM_{gp} at the mitral level was consistently high for both short and long-term canines ($>65\%$ and $>90\%$ respectively). This is consistent with the ligation location being at the proximal LAD at the first diagonal, as perfusion at the basal level should be unaffected. At the papillary level, $\text{PHM}_e = [36\%, 92\%]$ and $\text{PHM}_{gp} = [62\%, 100\%]$ were found. The apical level had the widest range of values, $\text{PHM}_e = [17\%, 92\%]$ and $\text{PHM}_{gp} = [45\%, 100\%]$. This is consistent with the canine's anatomy. The LAD perfuses a larger area of the myocardium at the apical level compared to the papillary level. Consequently, the infarct size should be larger (and PHM_e and PHM_{gp} lower) in the former compared to the latter.

Radial and thresholded strains were estimated throughout the survival period. The strain and thresholded strain at the mitral, papillary, and apical short-axis levels as observed through time in one long-term animal is summarized in Fig. 5 and Fig. 6. At the mitral level, strain

and thresholded strain reflected healthy myocardium from baseline to day 28. In contrast, the infarct is present in the anterior segment at the papillary level and in all the segments at the apical level at day 1. The infarct manifests as regions of near-zero magnitude in the strain (Fig. 5), and as contiguous areas of blue in the thresholded strain (Fig. 6). At the papillary level, this anterior infarct reduces in size until baseline mechanical function returns on day 4. Mechanical behavior at the apical level does not return to normal until day 7; this is as expected, since a larger proportion of the myocardium at the apical level is perfused by the LAD compared to the mitral or papillary levels.

ME's ability to track infarct formation and recovery was evaluated in Fig. 7 by plotting the mean $\overline{PHM_e}$ and standard deviation across animals from baseline (day 0) through the end of the longterm survival period (day 28). As predicted, at the mitral level there was no statistical difference in the $\overline{PHM_e}$ on different scanning days. At baseline and on day 28, $\overline{PHM_e}$ was $78 \pm 1.9\%$ and $78 \pm 3.9\%$, respectively, at the mitral level. At the papillary level, $\overline{PHM_e}$ at baseline was $82 \pm 5.4\%$, dropped significantly post-ligation on day 1 ($\overline{PHM_e} = 53 \pm 3.5\%$), and slowly recovered back to normal mechanical functioning on day 28 ($\overline{PHM_e} = 80 \pm 4.1\%$). Statistically significant differences in papillary $\overline{PHM_e}$ were found between baseline and day 1 ($p < 0.001$), day 2 ($p < 0.05$), and day 3 ($p < 0.01$). At the apical level, $\overline{PHM_e}$ was $76 \pm 4.6\%$ during baseline, dropped heavily on day 1 ($\overline{PHM_e} = 39 \pm 2.7\%$), and returned to baseline $\overline{PHM_e}$ by day 28 ($74 \pm 5.9\%$). Statistically significant differences in apical $\overline{PHM_e}$ were found between baseline and day 1 ($p < 0.001$), day 2 ($p < 0.01$), and day 3 ($p < 0.01$).

The $\overline{PHM_e}$ trends were corroborated by the observed mean $\overline{PHM_{pg}}$ during the pathology time points at day 4 and day 28. At the mitral level, $\overline{PHM_{gp}}$ on day 4 and day 28 were $98\% \pm 4.0$ (min = 90%, max = 100%), and $100\% \pm 0\%$, respectively. At the papillary level, $\overline{PHM_{gp}}$ on days 4 and 28 were $79\% \pm 13\%$ (min = 62%, max = 99%), and $97\% \pm 4.7\%$ (min = 90%, max = 100%), respectively. Finally, $\overline{PHM_{gp}}$ at the apical level on day 4 and day 28 was $61\% \pm 23\%$ (min = 39%, max = 100%), and $92\% \pm 8.5\%$ (min = 82%, max = 100%). At day 4, $\overline{PHM_{gp}}$ reflects the trends shown by $\overline{PHM_e}$, wherein the infarct is present at the apical and papillary levels (with larger infarct area at the apical) and minimally present or non-existent at the mitral level. At day 28, $\overline{PHM_{gp}}$ is high in all three short axis levels ($>92\%$), in agreement with $\overline{PHM_e}$, indicative of the myocardium recovered from infarct.

The diagnostic capability of ME to classify myocardial segments as healthy or infarcted is summarized in the ROC curve and PRC in Fig. 8. As summarized by the ROC curve (Fig. 8a), ME demonstrated high sensitivity and specificity throughout the range of discrimination thresholds investigated. AUC and average precision were found to be 0.90 and 0.80, respectively. Weighing sensitivity and specificity to be of equal importance, the best performance was achieved when setting the discrimination threshold to 48% (i.e. ME classified a myocardial segment as infarcted if 48% of pixels within that segment were reported as healthy according to the $\overline{PHM_e}$ ($e_{\text{thresh}} = 8\%$)). At a 48% discrimination

threshold, sensitivity and specificity was 82% and 92%. ME also demonstrated high levels of precision across the range of discrimination thresholds threshold, summarized in the PRC (Fig. 8b). Weighting recall (or sensitivity) and precision to be of equal importance, the best performance was also achieved when setting the discrimination threshold to 48%, where precision was found to be 85%.

Diagnostic resolution as a function of ϵ_{thresh} is summarized in Fig. 9. Based on the summary statistics AUC and average precision, diagnostic resolution is robust against moderate changes in the strain threshold. Within the range $\epsilon_{\text{thresh}} = [0\%, 20\%]$, the minimum AUC and average precision is 0.84 and 0.76, respectively.

Discussion

The objective of this paper was threefold: 1) validate that PHM_e is a reliable marker for infarcted myocardial tissue, 2) determine to what extent that ME can track infarct formation and recovery, and 3) illustrate ME's diagnostic resolution in localizing infarct to specific myocardial segments. A canine model was employed, dividing the animals into two groups defined by the length of the survival period (4 days versus 4 weeks). The strain-derived metric PHM_e was highly correlated ($R^2 = 0.80$) to actual infarct size based on the TTC-stained gross pathology samples. Consistent with the ligation location, there was a statistically significant drop in PHM_e on days 1–3 at the papillary and apex levels, while PHM_e was unaffected at the mitral level. Finally, ME was capable of diagnosing individual segments as healthy or infarcted at a high level of sensitivity and specificity (AUC = 0.90, average precision = 0.80). At a 48% discrimination threshold, sensitivity, specificity, and precision was determined to be 82%, 92%, and 85%, respectively.

The equation of the fitted linear curve in Fig. 4 is defined in Eq 7. The curve was calculated to have a slope coefficient of 0.95 and an intercept of 26%. That is, PHM_e underestimates the proportion of healthy myocardium, and overestimates infarct size, relative to PHM_{gp} . This underestimation may be due to the mechanics of the infarcted myocardium, which is non-contractile and may behave as a passive material. In a phenomenon known as *tethering*, the active contraction of healthy myocardium immediately surrounding the infarct zone is mechanically limited (Holmes et al. 2005). Consequently, the area of zero or low-magnitude strain is larger than the area of infarcted tissue, which leads to underestimation of the percentage of healthy myocardium and an intercept with positive directionality (Eq 6). Nonetheless, the value of the slope coefficient indicates that PHM_e is clearly sensitive to variations in infarct size as defined by PHM_{gp} in this study, and is a useful marker for myocardial infarction.

ME was capable of distinguishing differences in infarct size at each short axis level during formation and recovery (Table A.1). The ligation location was selected such that perfusion would be obstructed downstream at the papillary and apical levels, without affecting it at the mitral level. This is reflected when plotting PHM_e against PHM_{gp} in Fig. 4. As summarized in the results section and in Fig. 4, the mitral level has the smallest range of PHM_e and PHM_{gp} values, followed by the papillary and apical levels. With respect to the $\overline{\text{PHM}_e}$ time series, the largest drop in $\overline{\text{PHM}_e}$ between baseline and day 1 was at the apical level (Fig. 7c,

37% drop), followed by the papillary level (Fig. 7b, 28% drop); there was no statistically significant decrease in $\overline{PHM}_e$ at the mitral level (Fig. 7a). This trend is consistent with the literature, which reports that infarct in the canine model achieves its ultimate size in 24 hours (Miura et al. 1987). These results indicate that ME may provide an important tool to estimate the location of the occlusion within a given coronary artery, allowing for better informed treatment plans.

While the images in Fig. 5–6 and the time series data shown in Fig. 7 indicate that ME was capable of detecting infarct recovery on day 4 and beyond, the study remains a feasibility one. Therefore, non-significant $\overline{PHM}_e$ differences between imaging time-points could either be attributed to equivalent systolic strain or low sample size. If the confidence interval of the $\overline{PHM}_e$ difference is acceptably narrow, then it may be concluded that the strain measured is practically equivalent. The confidence intervals of the $\overline{PHM}_e$ difference between baseline and scanning days beyond day 4 indicate a larger sample size is needed to confirm these promising initial findings that will be performed in future studies (Table A.1). However, within the framework of an initial feasibility study, these results remain promising. The evolution of $\overline{PHM}_e$ throughout the survival period is corroborated by the literature. The canine was a common model for infarct studies in the 1970s and 1980s, with several groups reporting canine recovery from coronary artery ligation via collateral perfusion (Hearse 2000; Jugdutt and Amy 1986; Levy et al. 1961; Maxwell et al. 1987; Miura et al. 1987; Schaper et al. 1967). Furthermore, the $\overline{PHM}_e$ is in close agreement with the ground truth, $\overline{PHM}_{gp}$, as derived from the gross pathology on day 4 and day 28, as reported in the Results.

The performance of ME in classifying myocardial segments as either healthy or infarcted was investigated with ROC and PR curve. A myocardial segment was labeled as infarcted if $\overline{PHM}_{gp}$ 80% within that segment. Based on analysis of the ROC and PRC, and assuming sensitivity and specificity are of equal priority, the best discrimination threshold was found to be $\overline{PHM}_e(e_{\text{thresh}} = 8\%) = 48\%$. Applying this value to the linear regression model described in Eq 6, the equivalent $\overline{PHM}_{gp}$ is 72% (95% CI = [50% 91%]), which is reasonably close to the discrimination threshold set for the ground truth gross pathology slices ($\overline{PHM}_{gp} = 80\%$).

Although the experimental conditions are different, it is worthwhile to gauge ME's diagnostic resolution based on this preliminary study compared to previously published assessments on MI diagnosis via ECG and troponin. With a sensitivity and specificity of 82% and 92%, ME compares very well to the ECG, particularly in sensitivity. In a large systematic review of diagnostic technologies for MI, out-of-hospital ECG was found to have a sensitivity and specificity of 68% and 97%, respectively, while continuous/serial ECG had a sensitivity and specificity of 39% and 88%, respectively (Lau et al. 2001). ME also performed well (ME AUC = 0.90) compared to the standard troponin assay two hours after administration (AUC = 0.71), and close to the diagnostic performance of newer high-sensitive cardiac troponin assays (AUC, 0.91–0.94) (Reichlin et al. 2009). It is worthwhile to reiterate that unlike troponin assays, the results found in this study suggest that ME may be able to localize infarct to specific myocardial segments, in addition to providing a general diagnosis of MI.

In choosing the best discrimination threshold below which to classify a myocardial segment as infarcted, sensitivity and specificity was weighed to have equivalence importance. Depending on the application, accurate identification of the positive (i.e. infarcted) class may be of higher priority. Clinically, it is reasonable that identification of all infarct cases would be of higher priority than avoiding false positives. Increasing the discrimination threshold from 48% would effectively increase the sensitivity of ME at the cost of specificity.

Both the ROC and PRC curves are presented in this paper. The ROC is the most popular method of performance evaluation in the life sciences (Saito and Rehmsmeier 2015). However, careful interpretation is essential when there is class imbalance in the data, as the ROC is insensitive to class distribution (Fawcett 2004; Saito and Rehmsmeier 2015). For data where the ratio of negative to positive instances is great, the ROC may present an overly optimistic depiction of a classifier's performance: a high AUC may be reflective of a high rate of true negatives, obscuring a low rate of true positives (Fawcett 2004; Saito and Rehmsmeier 2015). The PRC, in contrast, replaces FPR with precision, which is the fraction of true positives among all positive predictions. The PRC is thus more sensitive to class imbalance, and should be the preferred performance evaluation when correct identification of the positive class is prioritized. Since the data set analyzed in this paper was imbalanced (33% of the myocardial segments analyzed were positive for infarction), and correct identification of positive (infarcted) myocardial segments is emphasized, the PRC is a more appropriate performance evaluator than the ROC. Nonetheless, the ROC is presented because it remains the most common performance evaluator, and is the evaluator of choice in the studies evaluating MI diagnosis techniques that were cited here (Eek et al. 2010; Gjesdal et al. 2007; Grenne et al. 2010; Reichlin et al. 2009; Zhang et al. 2005).

The ROC and PRC analyses presented here are intended to measure the optimal diagnostic resolution achieved by ME in this study. Given that these analyses were conducted retrospectively (i.e., setting the discrimination threshold based on the available data), the precision, sensitivity, and specificity reported herein are upper bound values. Ultimately, for this method to be implemented clinically, the method will need to be optimized in large patient studies, with diagnostic resolution being tested on clinical cases that were not used to tune the discrimination threshold. In other words, the technique must be evaluated on validation or holdout samples with the discrimination threshold and other hyperparameters already set prior to the analysis.

This study employed a canine model to investigate ME's ability to image MI. Instead of using global strain metrics, ME was capable of accurate measurement of regional deformation and strain, allowing for diagnosis of individual myocardial segments as infarcted or healthy. Although previous referenced studies using strain or strain rate imaging to identify MI patients did not have the same level of diagnostic resolution, they were performed in patients in the clinic (Delgado et al. 2008; Edvardsen et al. 2002; Eek et al. 2010; Gjesdal et al. 2009; Gjesdal et al. 2009; Grenne et al. 2010; Zhang et al. 2005). While ME for MI diagnosis needs to be validated in a patient model, a previous study using ME to diagnose 66 patients with suspected CAD demonstrated that ME was capable of localizing ischemia to a specific perfusion territory (Grondin et al. 2017).

A significant difference in the cardiac physiology of canines versus humans is that the former is capable of reperfusion solely through increased collateral perfusion following MI. The potential of ME to track MI recovery following reperfusion therapy was investigated by employing short and long-term survival periods, allowing the animal's coronary perfusion sufficient time to recover the infarcted myocardium. In humans, reperfusion is achieved by reopening the occluded coronary artery, typically via PCI. While this study imaged gradual reperfusion of MI, future work will need to demonstrate that acute reperfusion (i.e. PCI intervention) can be imaged accurately as well. Furthermore, due to differences in animal anatomy, the rate of recovery from MI varied between subjects. Based on the gross pathology results, it was expected that infarct should still be present on day 4, the terminal day for the short-term canines. The difference in recovery rate between animals may have led to weaker differences between baseline and day 4 in the $\overline{PHM}_e$ time series analysis.

The threshold ϵ_{thresh} chosen to calculate $\overline{PHM}_e$ was based on canine infarct gross pathology. Given that gross pathology was held here as the gold standard, $\epsilon_{\text{thresh}} = 8\%$ yielded the best possible performance. However, as shown in Fig. 9, moderate variations in ϵ_{thresh} also provided reliable assessment with ME. Compared to $\epsilon_{\text{thresh}} = 8\%$, setting ϵ_{thresh} to any value between 0% and 20% reduces, at most, AUC and average precision by 0.06 and 0.04. Translating this technique for application in patients, the optimal ϵ_{thresh} would have to be adjusted. A future study would use a sufficiently large sample of ME acquisitions from human patients to recalculate an appropriate ϵ_{thresh} , and determine the threshold setting that provides the most diagnostic sensitivity and specificity for infarct diagnosis.

ME images were validated by examining the excised, sliced, and TTC-stained myocardium. The inherent assumption is that the ultrasound view and the excised myocardium slice used as the ground truth were in the same plane. Since both ultrasound imaging and gross pathology are 2D representations of 3-D anatomy and physiology, it is likely that ME images and myocardium slices were not perfectly coregistered.

The masks within which strain and $\overline{PHM}_e$ are calculated were manually delineated. This manual segmentation may constitute as a source of variability.

The purpose of this study was to determine the feasibility of using ME to image infarct. Strains were compared against gross pathology. Future work would include a comparison against other diagnostic techniques, including three-lead ECG interpretation and Bmode-based strain imaging. In addition to evaluating radial global and regional strain, a comprehensive comparison against speckle tracking would include ME measurements of circumferential and longitudinal strain. RF cross-correlation has previously been shown to accurately estimate strain rate (D'hooge et al. 2002) and global and regional circumferential (Lee et al. 2008) and longitudinal strains (Konofagou and Provost 2012).

Conclusion

Myocardial Elastography was shown to be a promising tool for MI diagnosis. The radial strain-derived marker $\overline{PHM}_e$ was highly correlated with actual infarct size ($R^2 = 0.80$). Infarct formation was tracked, with significantly ($p < 0.05$) lower $\overline{PHM}_e$ on days 1–3 at the

papillary and apical levels. Recovery was likewise monitored, with $\overline{PHM_e}$ returning to baseline levels by day 28 at the mitral, papillary, and apical levels; future work involving a larger sample size is necessary to confirm these initial findings. Achieving a ROC AUC of 0.90 and average precision of 0.80, ME was found to reliably distinguish between healthy and infarcted myocardial segments with high sensitivity (82%), specificity (92%), and precision (85%). Future work will investigate the clinical translation of these findings.

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Appendix

Deriving the 95% confidence interval is helpful in determining whether the non-significance between the $\overline{PHM_e}$ on different scanning days during infarct recovery is due to practically equivalent strain or the result of an underpowered comparison due to small sample size. Table A.1 lists the mean $\overline{PHM_e}$ difference (μ) between each possible combination of survival days (t_1 , t_2), the 95% confidence interval lower (CI_{low}) and upper (CI_{up}) bounds, and p-value (p). Values were derived based on a Tukey multiple comparison test, as described in the Methods.

Table A.1.

$\overline{PHM_e}(\epsilon_{\text{thresh}}=8\%)$ difference between survival days

Survival Days		Mitral				Papillary				Apex			
t_1	t_2	CI_{low}	μ	CI_{up}	p	CI_{low}	μ	CI_{up}	p	CI_{low}	μ	CI_{up}	p
0	1	-6.2	4.6	16	0.90	13	28	43	0.00	14	37	59	0.00
0	2	-0.98	9.6	20	0.10	2.4	17	31	0.01	7.9	30	52	0.00
0	3	-2.1	8.8	20	0.21	5.7	20	35	0.00	7.7	30	53	0.00
0	4	-7.1	6.3	20	0.84	-6	12	30	0.45	-7.8	20	48	0.34
0	7	-7.1	7.4	22	0.77	-6.6	13	33	0.45	-19	11	41	0.95
0	14	-16	0.49	17	1.00	-19	0.87	21	1.00	-18	12	43	0.92
0	21	-13	1.2	16	1.00	-20	-0.83	19	1.00	-22	8.4	39	0.99
0	28	-15	-0.13	14	1.00	-18	1.7	21	1.00	-29	1.6	32	1.00
1	2	-5.9	5	16	0.86	-26	-11	3.6	0.29	-29	-6.7	16	0.99
1	3	-7	4.2	15	0.95	-23	-7.5	7.6	0.80	-30	-6.4	17	0.99
1	4	-12	1.7	15	1.00	-34	-16	2.7	0.15	-45	-17	12	0.63
1	7	-12	2.8	18	1.00	-35	-15	5.1	0.31	-56	-26	5.2	0.18
1	14	-21	-4.1	12	1.00	-47	-27	-7.1	0.00	-55	-24	6.2	0.22
1	21	-18	-3.4	11	1.00	-49	-29	-8.8	0.00	-59	-28	2.3	0.09

Survival Days		Mitral				Papillary				Apex			
t ₁	t ₂	CI _{low}	μ	CI _{up}	p	CI _{low}	μ	CI _{up}	p	CI _{low}	μ	CI _{up}	p
1	28	-19	-4.8	10	0.98	-46	-26	-6.3	0.00	-66	-35	-4.4	0.01
2	3	-12	-0.85	10	1.00	-11	3.6	18	1.00	-22	0.32	23	1.00
2	4	-17	-3.3	10	1.00	-23	-4.7	13	1.00	-38	-9.9	18	0.96
2	7	-17	-2.2	12	1.00	-23	-3.7	16	1.00	-49	-19	11	0.54
2	14	-25	-9.1	7.1	0.67	-36	-16	3.7	0.20	-48	-18	12	0.62
2	21	-23	-8.4	6.1	0.64	-37	-18	2	0.11	-52	-22	8.6	0.35
2	28	-24	-9.8	4.8	0.44	-35	-15	4.6	0.26	-59	-28	1.9	0.08
3	4	-16	-2.4	11	1.00	-27	-8.3	10	0.87	-39	-10	18	0.96
3	7	-16	-1.3	13	1.00	-27	-7.3	13	0.96	-50	-19	12	0.54
3	14	-25	-8.3	8.1	0.78	-39	-20	0.37	0.06	-49	-18	13	0.61
3	21	-22	-7.6	7.2	0.77	-41	-21	-1.3	0.03	-53	-22	8.7	0.35
3	28	-24	-8.9	5.8	0.58	-39	-19	1.2	0.08	-59	-29	1.9	0.08
4	7	-16	1.1	18	1.00	-22	0.98	24	1.00	-44	-8.9	26	1.00
4	14	-24	-5.8	12	0.98	-34	-11	11	0.80	-43	-7.9	27	1.00
4	21	-22	-5.1	12	0.99	-36	-13	9.6	0.65	-47	-12	23	0.97
4	28	-23	-6.5	10	0.94	-33	-10	12	0.86	-53	-18	16	0.73
7	14	-26	-7	12	0.96	-36	-12	12	0.77	-36	1.1	38	1.00
7	21	-24	-6.2	11	0.97	-38	-14	9.9	0.62	-39	-2.8	34	1.00
7	28	-25	-7.6	10	0.90	-35	-11	12	0.83	-46	-9.6	27	0.99
14	21	-18	0.74	20	1.00	-26	-1.7	22	1.00	-41	-3.9	33	1.00
14	28	-20	-0.62	18	1.00	-23	0.83	25	1.00	-47	-11	26	0.99
21	28	-19	-1.4	16	1.00	-21	2.5	26	1.00	-43	-6.7	30	1.00

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Figure 1.
Timeline of imaging schedule for both *short-time* and *long-term* canines.

Figure 2.

Image processing methodology of strain and gross pathology. Systolic cumulative radial strain (ϵ) was calculated from transthoracic echocardiographic images of infarcted canines (a). Strain images were thresholded (here, $\epsilon_{\text{thresh}} = 8\%$) in order to calculate PHM_ϵ (Eq 2), a marker for healthy myocardial tissue (b). Strain images were validated against slices of the excised myocardium stained with TTC, which marks infarcted tissue white (c). Endocardial and epicardial borders were manually segmented (cyan borders), and the infarcted regions were masked using a combination of manual and automatic methods (black borders) (d). Strain, thresholded strain, and gross pathology images at the papillary and apical levels were divided into myocardial segments based on the standardized segmentation model recommended by the American Heart Association (b, d).

Figure 3.

The linear regression between PHM_{gp} (Eq 1) versus median radial strain (ϵ) or $\text{PHM}_{\epsilon}(\epsilon_{\text{thresh}} = [5,40])$ (Eq 2) observed on each animal's terminal scanning day was calculated. The coefficient of determination (R^2) of the regression was plotted against the range of ϵ_{thresh} values investigated. The highest coefficient was achieved at $\epsilon_{\text{thresh}} = 8\%$ ($R^2 = 0.80$). The coefficient between PHM_{gp} and median radial strain, denoted by the horizontal dashed red line, was comparatively low ($R^2 = 0.63$).

Figure 4.

PHM_{gp} plotted against the $PHM_{\epsilon}(\epsilon_{\text{thresh}} = 8\%)$ observed on each animal's terminal scanning day. Strain and gross pathology images were acquired on all three short-axis levels: mitral, papillary, and apical. The scatter plot was fitted with a linear curve (in purple, Eq 3) with its corresponding 95% confidence interval.

Figure 5.

Radial strain images acquired from a long-term (28-day survival) animal at each short-axis level. Infarct, manifesting as regions of near-zero magnitude strain, was found in the anterior segment of the papillary level on days 1–3, and throughout all the segments of the apical level on days 1–4. Consistent with the ligation location, the strain at the mitral level indicates this region was free of infarct throughout the survival period.

Figure 6.

Thresholded ($\epsilon_{\text{thresh}} = 8\%$) strain images based on the radial strain acquisitions from Fig. 5. Infarct, manifesting as contiguous blue regions, was found in the anterior segment of the papillary level on days 1–3, and throughout all the segments of the apical level on days 1–4. Consistent with the ligation location, the strain at the mitral level indicates this region was free of infarct throughout the survival period.

Figure 7.

Mean $\overline{PHM}_e(\epsilon_{\text{thresh}} = 8\%)$ ($\overline{PHM}_e$) across all canines from baseline to 28 days post-ligation at all three short-axis levels. Statistically significant differences in $\overline{PHM}_e$ between baseline and days 1–3 were found at the papillary and apical levels (Tukey multiple comparison, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Consistent with the ligation location, no statistically significant difference in $\overline{PHM}_e$ between scanning days was found at the mitral level.

Figure 8.

Receiver operating characteristic (ROC) curve (a) and precision-recall curve (PRC) (b) describing ME's diagnostic resolution in classifying individual myocardial segments at healthy or infarcted ($n = 100$). The ME classifier is represented by the solid blue curve, while a random classifier is represented by the dotted red line. The discriminator threshold (percentage of $\text{PHM}_e(e_{\text{thresh}} = 8\%)$ under which a myocardial segment would be labeled infarcted) was evaluated within a range of 0–100%. Weighing sensitivity and specificity to be of equal importance, the ROC indicates that the best discriminator threshold was 48% (sensitivity = 82%, specificity = 92%). Similarly, weighing precision and recall to be of equal importance, the PRC indicates that the best discriminator threshold was 48% (precision = 85%, recall = 82%).

Figure 9.

Diagnostic resolution summary statistics AUC (a) and average precision (b) as a function of ϵ_{thresh} . The optimal ϵ_{thresh} based on correlation with gross pathology (Fig. 3) is denoted by the dotted red line at 8%. Diagnostic resolution is robust against moderate variations in ϵ_{thresh} .