A New Method for Cardiac Computed Tomography Regional Function Assessment: Stretch Quantifier for Endocardial Engraved Zones (SQUEEZ)

Pourmorteza et al: SQUEEZ: CT Regional Cardiac Function

1Amir Pourmorteza MSc, 2Karl H. Schuleri MD, 1Daniel A. Herzka PhD,
1,2Albert C. Lardo PhD, FAHA, FACC, and 1Elliot R. McVeigh PhD

1Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD, USA
2Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine Baltimore, MD, USA

Correspondence to
Elliot McVeigh
720 Rutland Avenue, Suite 720 Ross Building,
21205, Baltimore, MD
Tel: 410-955-3132
Fax: 410-502-9814
Email: emcveigh@jhu.edu

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Abstract

**Background**—Quantitative assessment of regional myocardial function has important diagnostic implications in cardiac disease. Recent advances in computed tomography (CT) imaging technology allow fine anatomical structures such as endocardial trabeculae to be resolved and potentially used as fiducial markers for tracking local wall deformations. We developed a method to detect and track such features on the endocardium to extract a measure that reflects local myocardial contraction.

**Methods and Results**—First-pass CT images and contrast enhanced CMR images were acquired for a total of 11 infarcted (n=8) and healthy (n=3) pigs. We tracked the left ventricle wall motion by segmenting the blood from myocardium and calculating trajectories of the endocardial features seen on the “blood-cast”. The relative motions of these surface features were used to represent the local contraction of the endocardial surface with a metric we termed “stretch quantifier of endocardial engraved zones” (SQUEEZ). The average SQUEEZ value and the rate of change in SQUEEZ were calculated for both infarcted and healthy myocardial regions. SQUEEZ showed significant difference between infarct and remote regions (p<0.0001). No significant difference was observed between normal myocardium (non-infarcted hearts) and remote regions (p=0.8).

**Conclusions**—We present a new quantitative method for measuring regional cardiac function from high resolution volumetric CT images which can be acquired during angiography and myocardial perfusion scans. Quantified measures of regional cardiac mechanics in normal and abnormally contracting regions in infarcted hearts were shown to correspond well with non-infarcted and infarcted regions as detected by delayed enhanced CMR images.

**Key Words:** myocardial contraction, computed tomography, regional function, wide range detector, volumetric cardiac imaging
Coronary angiography is currently the most prevalent use of cardiac computed tomography (CT). In this paper, we aim to assess systolic regional cardiac function from high resolution volumetric cardiac CT acquisitions, which can be acquired in conjunction with routine CT angiography. Assessment of regional myocardial function has value in the diagnosis and monitoring of myocardial ischemia and myocardial dyssynchrony\(^1,2\). Most mechanical analysis in the clinical setting is based on echo methods derived from two-dimensional motion data. Not all tomographic imaging modalities are capable of producing data with adequate temporal and spatial resolution for detailed regional function assessment. One difficulty with quantitative tomographic methods to estimate myocardial function is inability to obtain adequate landmarks in the heart due to poor spatial resolution.

Cardiac magnetic resonance (CMR) tissue tagging – currently considered the reference method – has been validated and is accurate, but it is slow, has poor resolution in the slice selection direction, requires extended breath-holding, and its image analysis is time consuming because of the manual segmentation required to detect the myocardial borders. In addition, CMR imaging is still considered a contraindication in the rapidly growing population of patients with implanted pacemakers or implantable cardioverter defibrillators (ICD).

Recent dramatic advances in cardiac CT imaging techniques allow for volumetric functional imaging of the entire heart with a few gantry rotation\(^3-9\). The high temporal resolution acquisitions of the entire cardiac volume with wide range detector CT allows a contrast bolus to be imaged over a short window in the heart cycle with very high spatial resolution, making visible fine anatomical structures such as trabeculae on the endocardial surface. We took advantage of the resolution now available with wide-range detector CT to develop a method to detect and track the fine curvature-based geometric features on the endocardial surface, which
are used to extract a metric that reflects the cardiac muscle contraction. It has been previously shown that differential geometry features of the myocardial surfaces can be used to estimate the motion field from 3D anatomical images\textsuperscript{10-12}; however, the low spatial resolution of the images has been a limitation. Here we evaluate the feasibility of tracking the LV wall motion and assessing local cardiac function in high resolution first-pass volumetric cardiac CT images using a fast non-rigid surface registration algorithm that matches geometric features of the surface over time.

**Methods**

**Animal model.** All animal studies were approved by the Johns Hopkins University Institutional Animal Care and Use Committee and comply with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication no. 80-23, revised 1985). Pigs with chronic myocardial infarctions (MI) were created as previously described\textsuperscript{13}. Briefly, MI was induced by engaging the left anterior descending coronary artery (LAD) with an 8-F hockey stick catheter under fluoroscopic guidance. Then, a 0.014-inch angioplasty guide wire was inserted into the LAD and a 2.5 × 12-mm Maverick balloon (Boston Scientific, Natick, Massachusetts) was inflated to 4 atm just distal to the second diagonal branch of the LAD. After 120 min, occlusion of the vessel was terminated by deflating the balloon, and restoration of flow in the LAD was confirmed by angiography. CT and MRI studies were performed approximately 130 to 180 days after MI induction. A total of 11 infarcted (7 chronic and one acute) and healthy (n=3) animals were studied.
**CT Imaging**

Each animal was scanned, with electrocardiographic monitoring, using a 0.5-mm × 320-detector scanner (Aquilion ONE, Toshiba Medical Systems Corporation, Otawara, Japan). Animals received intravenous metoprolol (2 to 5 mg) and/or amiodarone (50 to 150 mg) to achieve a heart rate < 100 beats/min. After scout acquisition a 50-60 ml bolus of iodixanol (Visipaque, 320 mg iodine/ml, Amersham Health, Amersham, United Kingdom) was injected intravenously and a first-pass cardiac perfusion scan for the entire cardiac cycle was performed. During CT acquisition, respiration was suspended and imaging was performed using a retrospectively gated CT protocol with the following parameters: gantry rotation time 350 ms, temporal resolution of up to 58 ms using multisegment reconstruction, detector collimation 0.5 mm × 320 (isotropic voxels 0.5× 0.5×0.5 mm³), tube voltage 120 kV, tube current 400 mA. One infarcted dataset was acquired using x-ray tube current modulation of 10% of the maximum, with the maximum current at only the 75% time point of the R-R interval. Images were reconstructed at every 10% of the R-R interval in systole using a standard kernel (FC03), QDS+ noise reduction filter and a multisegment (3 to 5-beat) reconstruction algorithm. Electrocardiographic editing to account for arrhythmias was performed when necessary. In addition, a set of low-dose prospectively gated scans (120 kV and 20 mA at 0% and 50% of R-R) along with a high-dose (120 kV and 400 mA) retrospectively gated scan were acquired for one animal to assess the feasibility of tube current reduction and prospective gating for cardiac function analysis.

**CMR**

*In vivo* CMR images were acquired using a 3T MR scanner (Achieva, Philips, Best, The Netherlands) using a 32-element cardiac phased array. Myocardial viability was visualized using...
late gadolinium enhancement images, acquired 20-25 min after intravenous injection of a double
dose of gadolinium diethylenetriaminepenta-acetic acid (0.2 mmol/kg body weight, Magnevist,
Berlex, Wayne, New Jersey). A 3D ECG triggered, independent respiratory navigator gated,
breath-hold, phase-sensitive inversion recovery gradient echo imaging pulse sequence was
used. Imaging field of view (FOV) was 24×24×12 cm³, with an imaging matrix of
200×195×30, yielding an acquired voxel size of 1.20×1.23×4.0 mm³, reconstructed to
0.91×0.91×2.0 mm³. Other relevant imaging parameters were: flip angle 15°, TR/TE 5.3/2.6 ms,
and 289 Hz/pixel receiver bandwidth.

Image analysis. For each systolic cardiac phase the blood in LV is segmented from the
myocardium by thresholding the voxel intensities roughly between 200 HU and 650 HU. After
manually pruning the coronaries, aorta, and in some datasets the RV, (using MIPAV available
from NIH at: http://mipav.cit.nih.gov), a triangulated mesh representing the endocardial surface
is extracted from the boundary surface of the LV blood cast (Figure 1A-C, E). All computations,
unless specified otherwise, were done using Matlab (Mathworks Inc, Natick, MA).

To compare the results of the proposed algorithm to existing CT wall motion tracking software,
the datasets were analyzed using Vitrea fx software (Vital Images, Minnetonka, MN).

Motion tracking. We tracked the LV wall motion by calculating trajectories for the points on
the endocardial mesh. Each endocardial surface was represented by a triangular mesh. In order to
track the points on the meshes from end diastole (ED) to end systole (ES), the surfaces needed to
have the same number of triangles with a one to one correspondence between the triangle
vertices. This was accomplished by choosing a template mesh (in this case, the ED mesh) and

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warping it onto a target mesh (any systolic mesh e.g. the ES mesh) such that every triangle on the template mesh has a corresponding triangle on the target mesh (Figure 2D,E). We chose a non-rigid point registration algorithm called *coherent point drift* (CPD) for surface warping. Coherent point drift is a probabilistic method used for non-rigid surface registration in which surface points are forced to move *coherently* as a group to preserve the topological structure of the point sets\(^{15}\). The coherence constraint was imposed by regularizing the displacement field and using variational calculus to derive the optimal warping. A fast implementation of CPD, based on the fast Gaussian transform, was used to reduce the massive computational burden associated with high resolution CT data.

In order to match the anatomy via surface warping, the homologous anatomical features and their correspondences needed to be identified. Therefore, features engraved on the endocardial surface by fine anatomical structures such as trabeculae and papillary muscles, were encoded using a scale independent local shape measure, called *shape index* (SI) (Figure 1D, Figure 2), and incorporated in the warping algorithm to further improve its accuracy. Shape index is a curvature-based measure and for each point is defined by

\[
SI = \frac{\frac{2}{\pi} \arctan\left(\frac{k_1 + k_2}{k_1 - k_2}\right)}{k_1 - k_2}
\]  

(1)

where \(k_1\) and \(k_2\) are the principal (signed maximum and minimum) curvatures at that point. Figure 3 shows SI values for different surface shapes. For a saddle point \(k_1=-k_2\), thus SI=0; for a spherical surface \(k_1=k_2\neq 0\) and the SI= -1, if curvatures are negative and, SI=1 if they are positive, corresponding to a spherical cup and cap, respectively. For a valley \(k_1=0\), and \(k_2\) can have any negative value (by definition \(k_1 \geq k_2\)) thus as long as \(k_2\) is non-zero we have:
Same argument holds for a ridge which will have a SI value of 0.5. The intermediate SI values correspond to when these shapes are smoothly warped to each other.\textsuperscript{16, 17}

An important property of SI is that it is stretch invariant. As mentioned above, surface features e.g. ridges and valleys will have a certain SI value solely based on their shape and not on their curvatures i.e. steepness. Therefore, as long as the topology of the surface does not change under compression or stretch, the anatomical features such as ridges and valleys on the endocardial surface will retain their SI values. This property makes SI a useful tool for encoding endocardial features.

The output of the CPD algorithm is a displacement field that is used to calculate measures of local cardiac function. We propose a measure of local cardiac function called Stretch Quantifier of Endocardial Engraved Zones (SQUEEZ), defined as:

\[ SQUEEZ(v, t) = \frac{A(v, t)}{\sqrt{A(v, 0)}} \tag{2} \]

where \( A(v, 0) \) is the area of the small triangular patch \( (v) \) on the endocardial mesh at end diastole, and \( A(v, t) \) is the area of the same patch at time \( t \). SQUEEZ is calculated for each triangular patch on the surface, resulting in a high resolution local cardiac function map of the left ventricle.

**Statistical analysis.** For the data pool obtained from the 11 animals, two-tailed paired Student's t-test statistical analyses were performed on the SQUEEZ value and the slope of SQUEEZ versus time, to test the difference in the means of these parameters in healthy and infarcted regions. The accuracy of the registration algorithm was evaluated using the mean of the minimum pair-wise
Euclidean distance between the target and the warped datasets (i.e. for each point on the template mesh the Euclidean distance to every point on the warped mesh is calculated and the minimum is chosen). The mean±standard deviation of the minimum distances is reported.

Results
To evaluate resting LV function the blood pool of the LV was segmented in the end-diastolic and end-systolic phases in the 3D volume and end-diastolic volume, end-systolic volume, stroke volume, and ejection fraction were calculated for the LV (Figure 3). SQUEEZ values were measured in healthy and infarcted animals at different cardiac phases (Figure 4) and different locations of infarcted and remote myocardium as detected by contrast enhanced MRI (Figure 5).

Accuracy of the non-rigid registration algorithm (CPD)
The accuracy of the non-rigid registration algorithm was evaluated using the mean of the minimum Euclidean distance between the target and warped surfaces evaluated at all points. Over the 11 animals analyzed by our method there was a sub-pixel average error of 0.6±0.4 pixels (0.3±0.2 mm). All of the triangular patches on the meshes had sides ≥1 pixel.

Regional cardiac function
SQUEEZ was calculated for every point on the LV endocardial surface at each cardiac phase. All infarcted animals showed abnormal stretching in the LAD territory, which was consistent with the infarct model used in this work. One animal showed 2 distinct MI zones, and this was confirmed by examining the CMR image, which showed a secondary MI in the inferior wall.
Figure 4 shows SQUEEZ bull's-eye plots calculated for 5 consecutive phases from end diastole to end systole. Areas with yellow color (SQUEEZ>1) show abnormal stretch due to myocardial infarction.

Contrast enhanced MR images were used as the gold standard to verify the location of the infarcted regions detected in SQUEEZ maps (Figure 5A). Points were selected on regions of the endocardial surface near the MI zones as defined by the contrast enhanced CMR images. About the same number of points were selected in a remote region of the heart with no sign of MI (Figure 5B). The size of the selected regions roughly corresponded to that of one LV segment in the 17-segment AHA model 18.

The average SQUEEZ value was calculated for each zone and showed significant difference (p<0.0001) between MI and non-MI regions in infarcted animals (Figure 5B). For healthy animals, a region on the lateral wall was chosen corresponding to the remote non-MI region selected in infarcted animals. The SQUEEZ values for the non-MI in the infarcted hearts and the regions chosen in the healthy hearts were not significantly different.

In addition to SQUEEZ, the rate of change in SQUEEZ also showed a significant difference (p<0.0001) between MI and non-MI regions in the infarcted animals (Figure 5C) and no difference was found between the same lateral regions in healthy and non-MI regions. Non-MI regions showed an average SQUEEZ rate of approximately -0.6±0.2, whereas the MI zones had a rate of approximately 0±0.1, showing little or no stretch or contraction.

The SQUEEZ time plots for the tube current modulated dataset showed higher standard deviations due to increased noise levels; however, the difference between MI and non-MI regions was still significant, and the trend of the plots were similar to those of the high-dose datasets (Figure 5B).
The SQUEEZ map was calculated for the low-dose prospectively gated data set and compared to the SQUEEZ of the high-dose retrospectively gated data set at 50% of R-R interval. The difference between the SQUEEZ maps was computed (Figure 6). The results show low bias (0.01) with confidence interval (CI= [-0.12 0.15]) between the high dose retrospective and the low dose prospective scans. The differences could be attributed to the increased noise due to lower tube current, but also to heart rate variations between the acquisitions. More experiments are going be carried out to fully investigate the effects of CT noise on the accuracy of SQUEEZ. Use of the low dose prospective scan decreased the radiation dose by approximately ten-fold. The low bias and CI of the low-dose scan makes the use of low-dose prospectively gated CT for cardiac function very promising.

Regional ejection fraction (rEF) was calculated at ES for each cardiac segment using Vitrea fx software. The automatic segmentation of endocardial borders required manual correction which took approximately 150±15 minutes, as opposed to 4±2 minutes of operator interaction required in the proposed method. SQUEEZ values were averaged into the AHA 16 segments and compared to 1-rEF values obtained from Vitrea. There was good correlation (r=0.81, p<0.001) for the 6 mid-cavity segments (segments 7-12), but no correlation was found in basal and apical segments in any of the datasets.

Discussion

We have developed a new method for measuring regional cardiac function with high resolution from volumetric CT acquisitions which has proven to be effective in quantifying regional cardiac mechanics and detecting infarcted regions in a large animal model. Volumetric CT data used in this work can be reconstructed from the routine dose modulated coronary angiography CT scans.
Our method also eliminates the laborious human interaction required to segment the cardiac data for functional analysis that has plagued cardiac imaging for the past two decades. Current methods for CT regional cardiac function analysis involve time consuming manual segmentation, or manual correction of segmentation of the myocardium. These methods generally apply smooth contours to delineate epicardial and endocardial boundaries, thus failing to capture the fine anatomical endocardial structures visible in wide-range detector CT that can be used as landmarks to guide the motion tracking algorithm. Furthermore, these algorithms normally track the 3D motion by analyzing the displacements in stacks of 2D slices (usually oriented in the short axis). The longitudinal displacement of tissue into and out of a short axis slice can appear to be a change in the myocardial wall thickness in that short axis slice, but in fact is just bulk displacement of tissues in 3D space. This artifact is more prominent in basal and apical segments in which the position of the short axis contours may change significantly due to through-plane motion. This could explain the poor correlation between rEF and SQUEEZ in apical and basal segments. In addition, rEF calculation is based on distance from a centerline; if the centerline is not chosen correctly, there will be large errors in rEF calculations. This artifact is more prominent in apical slices, where a small change in the position of the centerline could result in large rEF values. Although the centerlines were chosen carefully, the irregular shape of the endocardial contour in apical slices, especially in hearts that have undergone significant LV remodeling, would still cause very large rEF values in some datasets.

**Comparison with Other Modalities**

Echocardiography is widely used in clinics for cardiac function and dyssynchrony analysis but does not produce a detailed map of the coronaries and is limited by the available acoustic
window. Although echocardiography has very high temporal resolution, the available window for transducer placement limits the orientation of the imaging plane. Furthermore, the variance of repeated echocardiographic measures is fairly high owing to dependence on operator experience, machine settings, available acoustic windows, and angle of incidence effects.

CMR is another highly attractive modality for regional cardiac function analysis. However, this method also has some practical drawbacks, including higher cost, occasional gating failures, more complex scanning protocols and longer scanning times. The inability to study the growing population of patients with implanted electronic devices, which is especially relevant in patients with previous myocardial infarction is another drawback. With its high isotropic resolution, CT decreases partial volume effects and accurately characterize the blood-myocardium interface, and eliminate through-plane motion artifacts.

Radiation and Iodinated Contrast

Radiation exposure and iodinated contrast agent dose are still primary concerns with the increasing use of CT technology in diagnostic cardiac imaging and have become a centerpiece of new hardware, software and imaging protocol improvements. Wide-area detector CT, with full cardiac coverage, does not need an overlapping radiation exposure and long scan times, as required in traditional helical CT imaging systems, and thus provides a significant radiation and contrast dose savings for cardiac imaging. Significant leaps have been made in the dose reduction algorithms parallel to advances in hardware in the past couple of years. Furthermore, we extended our validations to tube current modulation of 10% and prospectively-gated scans with tube-currents as low as 5% of the high-dose scans and the initial results were encouraging and confirmed the feasibility of using low-dose CT.
Iterative reconstruction algorithms\textsuperscript{20-22} could potentially improve the results of our method further; however they were not available at the time of these measurements. When available, these algorithms and numerous CT image noise reduction methods\textsuperscript{23, 24}, are expected to improve the results of SQUEEZ by reducing the noise at current x-ray tube settings, or reducing dose with tube current reduction. In this paper we demonstrated that SQUEEZ is capable of quantifying regional cardiac function with routine CT acquisitions; determination of the minimum number of photons for clinically acceptable images requires further investigation.

**Study Limitations**

Wide-range detector CT has limitations in temporal resolution intrinsic to CT imaging. This limitation has been reduced with improvements in multi-beat segmented image reconstruction and gantry rotation speed such that temporal resolution of under 60 ms is now achievable\textsuperscript{9}. Although it is possible to calculate SQUEEZ from single-beat CT acquisitions, especially during systole, multi-beat reconstructions will produce more robust SQUEEZ values with higher temporal resolution.

The reliance on SQUEEZ alone, rather than strain measures such as myocardial shortening, to characterize local function may be a limitation. Although SQUEEZ and myocardial strain both reflect mechanical contractile function of the heart, a simple mathematical relation between MRI mid-wall strain and SQUEEZ may not be found because they measure two different physical parameters. Strain measures shortening in the myocardium and is most reliable in mid-wall due to partial volume artifacts near the epi- and endocardial borders in MRI. SQUEEZ on the other hand, reflects endocardial deformation by measuring local changes in the area of the endocardial surface. Endocardial deformation metrics like SQUEEZ have an advantage in detecting the
myocardial ischemic cascade and the resulting transmural strain gradient. A recent study has shown that a significant correlation exists between surface deformation and 1-D strain metrics in 3D speckle tracking images. These results lead us to believe there will be a linear relationship between SQUEEZ and strain metrics. However, we have yet to determine the precise relationship between SQUEEZ and circumferential shortening under all circumstances. While the data obtained in this paper is promising, larger studies are needed to establish the precise diagnostic accuracy of SQUEEZ.

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Disclosures

None.
References


**Figure Legends**

**Fig. 1.** Steps of the proposed method. (A) cropped axial CT image of the LV. (B) the blood pool segmented from the volume by thresholding. (C) Endocardial surface extracted from the segmented images (inferolateral wall facing viewer). (D) shape index values calculated to encode the features engraved by the trabecular structures on the endocardial surface. Coherent point drift algorithm is used to find the correspondence between the endocardial features at end diastole (ED) (left), used as template, and other systolic phases (right) used as targets. (E) CPD warping results in endocardial meshes with corresponding triangles. A measure of regional cardiac function called SQUEEZ is calculated for each triangle on the ED endocardial surface mesh by tracking the corresponding triangle at different cardiac phases. $A(0)$ is the area of the triangle at ED, and $A(t)$ is its area at cardiac phase $t$. SQUEEZ is the square root of the ratio of the area of a triangle on the endocardial surface at a systolic phase to its area at end diastole. (F) SQUEEZ maps calculated for every triangle on the endocardial surface at five cardiac phases from end diastole to end systole.

**Fig. 2.** Local shape encoding using shape index. Left: Shape index values for the point at the center of the simple surfaces. From top: spherical cap, ridge, saddle point, valley, and spherical cup. Spherical cap: $k_1 = k_2 > 0$ thus $SI = +1$; ridge: $k_1 > 0, k_2 = 0$ and $SI = +0.5$; saddle point $k_1 = -k_2 
eq 0, SI = 0$; valley: $k_1 = 0, k_2 < 0$ thus $SI = -0.5$; spherical cup: $k_1 = k_2 < 0$ results in $SI = -1$; other SI values are caused by smooth deformation of these surfaces. Right: an example of shape index calculated for an ED endocardial surface.
Fig. 3. Global left ventricle function measures for healthy (n=3) and infarcted (n=8) pigs. From left to right: end diastolic volume (EDV): 87.8±17.7 (healthy) and 92.5±15.6 (infarcted); end systolic volume (ESV): 40.1±7.3 (healthy) and 50.4±6.6 (infarcted); stroke volume (SV=EDV-ESV): 47.6±10.5 (healthy) and 42.0±11.0 (infarcted); ejection fraction percentage (Ef= SV/EDV): 54.1±1.3 (healthy) and 44.9±5.6 (infarcted). The bars and whiskers indicate the mean and ± standard deviation of the quantities, respectively. (* indicates p<0.05)

Fig. 4. Bull's-eye plots of the SQUEEZ values for 3 typical infarcted (A), and 3 healthy animals (B) from end diastole (left) to end systole (right) at 10% R-R steps. Infarcted animals show abnormal stretching of the endocardium in LAD territory (anterior and anteroseptal segments) which is consistent with the infarction model (LAD occlusion after the second diagonal) used in this study.

Fig. 5. (A) Left: A short axis phase-sensitive inverted recovery (PSIR) MR image of an animal with an anterior/anteroseptal heterogeneously infarcted region. Infarcted region has characteristic high signal intensity. Right: End systolic SQUEEZ bull's-eye plot of the same animal. The short axis image in the left approximately corresponds to the SQUEEZ values along the dashed arc. The infarcted sub-regions in the MR image correspond to the regions detected in the SQUEEZ plot, depicted by the black arrows. Showing from left to right, a section with some loss of function, a section with complete loss of function that shows wall expansion, a small section with some contractility and a fourth sub-region with loss of function. (B) Time plots of the average SQUEEZ values for healthy, MI, and non-MI regions in systole for 3
healthy (top row) and 7 infarcted pigs (middle and bottom rows). The regions were chosen to be roughly the size of segments in the AHA 17-segment model. All infarcted pigs showed significant difference in SQUEEZ for MI and non-MI regions (p<0.0001). ( ** denotes the dose-modulated dataset) (C) Average SQUEEZ rate values calculated by averaging over the slopes of lines fitted to the curves in (B). SQUEEZ rate is significantly different between MI and non-MI regions in infarcted hearts (p<0.0001). There was no significant difference between non-MI regions in the infarcted hearts and the same regions chosen in the healthy hearts.

Fig. 6. Sample comparison between high dose and low dose scans: Bland-Altman plot of the SQUEEZ values calculated from high-dose retrospective and low-dose prospective scans shows low bias (mean=0.01) and standard deviation = 0.07. Dashed lines denote 95% confidence interval CI= [-0.12 0.15]. (N=2250)
\[ SQUEEZ(t) = \sqrt{\frac{A(t)}{A(0)}} \]
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