ASSESSMENT OF REGIONAL CARDIAC FUNCTION
FROM 4D COMPUTED TOMOGRAPHY

by
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Abstract

The current method for diagnosing Coronary Heart Disease (CHD) often begins with a nuclear medicine stress SPECT exam. This exam is expensive in multiple ways: 1) it is time consuming and costly, 2) it exposes the patient to relatively high levels of radiation, 3) it has limited sensitivity and specificity for the existence of CHD. This proposal seeks to develop a technology to replace SPECT scanning as the first step in diagnosing CHD with a comprehensive cardiac CT exam. Many of the patients who have a narrowing of the coronary artery do not suffer a sufficient reduction in blood flow to produce hypoxia in the myocardium. It is becoming clear that these vessels should not be treated mechanically with stents or balloon angioplasty, and these patients do not need to go to the catheterization lab.

In order to replace SPECT as the first diagnostic test for CHD, coronary CT must be accompanied by an additional test that determines if the stenosis is functionally significant.

This highlights a current unmet clinical need: A CT based test to discriminate significant coronary heart disease in patients who have a stenosis detected on Coronary CT Angiography.

The innovation introduced in this dissertation is the development of a CT test that accurately measures the change in regional ventricular wall function. We call this method Stretch Quantification of Endocardial Engraved Zones (SQUEEZ). It extracts the endocardial surface of the left ventricle and tracks the motion of the endocardial wall in 3D with minimal user interaction. We tested the performance of this method in noisy CT acquisitions in order to find the minimum possible dose to produce SQUEEZ values with a specified precision. The results showed that dose reductions of ~10 fold are achievable, with respect to the dose required for diagnostic coronary CT angiography, using the current technology. We also investigated the agreement of SQUEEZ vs. the gold standard tagged MRI
in estimating metrics of regional cardiac function in acute myocardial infarction. The results indicate very good correlation between SQUEEZ and circumferential strain from tagged MRI in regional myocardial mechanics.

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Chapter 1. Introduction

1.1. Background

The current method for diagnosing Coronary Heart Disease (CHD) often begins with a nuclear medicine stress SPECT exam; over 17 million such exams are done each year in the US alone. Unfortunately, this exam is expensive in multiple ways: 1) it is time consuming and costly, 2) it exposes the patient to relatively high levels of radiation, 3) it has limited sensitivity and specificity for the existence of CHD. In this dissertation we explain how to develop a technology to replace SPECT scanning as the first step in diagnosing CHD with a comprehensive cardiac CT exam. This new method has the opportunity to decrease the number of patients who go on to have a negative x-ray coronary angiography, thus benefiting patients and reducing healthcare costs.

Coronary Heart Disease is a dominant health care problem in both the developed and developing world: in the US alone there are 1.2 million heart attacks each year and 9 million patients who have angina pectoris. With the US prevalence of high blood pressure at 76 million people, 135 million people classified as overweight, and 45 million smokers, this problem will continue to burden the health care system.

Technical advances in CT over the past 5 years have lead to a ~20-fold reduction in radiation exposure during a cardiac exam, bringing the total dose of the exam to well below than the average annual dose from natural radiation. Coronary CT angiography (CCTA) is emerging as the method of choice for diagnosing the large number of patients with "low to medium risk" for Coronary Heart Disease (CHD), patients who have chest pain coupled with normal electrocardiogram (EKG) and normal blood enzymes. If the coronary vessels are
clear of stenosis on a CCTA imaging study this virtually ensures that the patient’s symptoms are not from CHD (negative predictive value > 99%). Multiple studies have lead to the statement that clear vessels on CCTA gives the patient “a two year warranty period for freedom from major cardiac events (MACE)”\textsuperscript{5,6}. Recent clinical trials have consistently shown the safety, efficiency and cost-savings associated with a negative CCTA to identify patients for discharge from the emergency department\textsuperscript{7}.

However, for those patients that have stenosis present on CCTA, almost all of them go on to further exams such as nuclear medicine, echocardiography (echo) or X-ray coronary catheterization, with a high fraction of those exams yielding negative results.

The problem is quite simple. Many of the patients who have a narrowing of the coronary artery do not suffer a sufficient reduction in blood flow to produce hypoxia in the myocardium. It is becoming clear that these vessels should not be treated mechanically with stents or balloon angioplasty, and these patients do not need to go to the catheterization lab.

In order to replace SPECT as the first diagnostic test for CHD, coronary CT must be accompanied by a test that determines if the stenosis is functionally significant. This highlights a current unmet clinical need:

**A CT based test to discriminate significant coronary artery disease in patients who have a stenosis detected on Coronary CT Angiography.**

Measuring resting left ventricular (LV) function in the setting of acute pain has been shown to improve the diagnosis of acute coronary syndrome (ACS) by detection of regions affected by functionally significant stenoses. Seneviratne et al. demonstrated a 10% increase in sensitivity to detect ACS by with the addition of resting regional left ventricular function over coronary assessment alone, leading to significantly improved the overall accuracy\textsuperscript{8}. Schlett et al. also showed that the addition of regional wall motion abnormality (RWMA)
analysis in *resting* patients increases the sensitivity of CCTA in predicting major adverse cardiac events (MACE)\(^6\).

The RWMA analysis has been traditionally performed by visually inspecting 2D movies of the left ventricle or by laborious delineation of epi- and endocardial contours of the LV for quantitative wall thickening calculations; however, these techniques are prone to error from through-plane motion and require long analysis times.

We have developed a method for assessment of regional cardiac function, and wall motion abnormality, called Stretch QUantification of Endocardial Engraved Zones (SQUEEZ). The method is capable of measuring endocardial contraction with high spatial resolution in 3D using CT images acquired during a few heartbeats\(^9,10\).

This dissertation outlines our new technique, and the critical milestones required to implement and validate it.

**1.2. Outline Of The Technique**

Our technique uses the change in local muscle shortening to detect functionally significant stenoses; while this is the same method used by echocardiography\(^11\), we can obtain the diagnosis *in a few heartbeats while the patient is still in the CT scanner* (as opposed to \(1/2\) day for SPECT or stress-echo). We quantify the change in local wall motion associated with ischemia by obtaining 3D movies of the left ventricle and tracking the wall motion. If the heart motion is not affected, the stenosis is not significant and the patient can be treated medically.

The CT images are obtained at a few time points in the heart cycle from end-diastole through end-systole. For each time point the bright left ventricle (LV) blood pool is extracted using simple automatic thresholding yielding a set of 3D "casts" with the details of
the LV endocardium engraved on the each cast. A 4D non-rigid deformation algorithm is used to warp the end-diastolic cast into the shape of the subsequent casts in the heart cycle. The resulting deformation fields are used to precisely calculate the local wall motion at all points on the LV endocardium \(^9\). For normal muscle we observe local contraction; for abnormal muscle we observe either no contraction or local stretch during the heart cycle. The quantification of the wall motion can be expressed as a number reflecting the amount of local stretch. We call this method “Stretch QUantification of Endocardial Engraved Zones” or SQUEEZ. For example, a SQUEEZ value of 0.75 means the tissue has contracted 25%, a value of 1.0 means the tissue is static, and a value of 1.25 means the tissue has stretched by 25%.

1.3. Innovation And Significance

1. **A new method for tracking local ventricular function.** The basic principle of the method is made possible by new high-resolution cardiac CT data from wide area detectors that capture the details of the endocardial trabecular tissue. A major contribution of this work is the recognition that these trabecular features on the endocardium can be used as landmarks to track the relative motion of different regions of the endocardial surface in 3D. The tracking results can then be used to estimate local myocardial function.

2. **A new “contour free” metric for regional LV function: SQUEEZ.** Classic metrics such as ejection fraction (EF), wall thickening, and circumferential shortening from MRI tagging suffer from numerous drawbacks including artifacts from through plane motion and the necessity for segmenting LV contours. We introduce a new parameter that characterizes local ventricular function which: can be measured in a few heartbeats, does not suffer the same drawbacks, and is entirely “contour free”. No LV contours are required, and the tracking is done from true isotropic 3D data eliminating any through-plane artifacts in the
assessment of myocardial function. This is a huge step towards fully automated operator independent analysis of LV function.

3. A new method for precise measurement of dyssynchrony of LV mechanical activation.

We introduce a new method for calculating the mechanical delay between early activation and late activation in the LV; it improves upon previous methods in that it does not require user intervention, it is possible to use it in patients with pacemakers, and it can be obtained in a few heartbeats. This approach has the opportunity to deliver an unambiguous and sensitive image-based metric to identify appropriate candidates for Cardiac Resynchronization Therapy $^{12,13}$.

1.4. Specific Aims

1.4.1. Aim.1: Develop and validate a method for tracking cardiac wall motion and quantifying regional myocardial contractility.

In this aim we extract the endocardial surface of the left ventricle at every cardiac phase and detect and track the impressions of trabecular structures on the extracted surface, as summarized in section 1.2. We will use a fast and accurate non-rigid surface registration algorithm to track the endocardial features.

Next, we calculate an index of regional cardiac function using the endocardial motion trajectories. This metric is computed from the fractional change in the local surface of the left ventricle. It is computed over the whole endocardial surface. Aim.1 is discussed in detail in Chapter 2.
1.4.2. **Aim.2:** Characterize the Accuracy and Precision of SQUEEZ in noisy acquisitions to achieve best regional ventricular function with the lowest radiation dose possible.

CT imaging has complex noise and signal detection characteristics\textsuperscript{14,15} and these are becoming even more complex with the introduction of iterative reconstruction algorithms\textsuperscript{16,17}. We plan to measure the accuracy and precision of SQUEEZ using measurements made directly from the CT scanner in animal models in order to incorporate all of the variables that are of importance such as motion, temporal resolution, and radiation dose. Our basic goal in this aim is to create high quality data sets from very high dose, high time resolution scans to obtain a “gold standard” mesh representation of the LV, and a “gold standard” SQUEEZ map. In Chapter 3 we evaluate the precision and accuracy of low-dose, clinically viable protocols by comparing their performance to the gold standard as a function of imaging parameters.

1.4.3. **Aim.3:** Evaluate the agreement of CT-based SQUEEZ regional cardiac function with myocardial strain calculated from tagged MRI.

We can accurately measure local myocardial function such as circumferential shortening ($E_{cc}$) with previously validated MRI tagging methods\textsuperscript{18–20}. These quantities have been used in numerous studies\textsuperscript{21} to evaluate ischemia\textsuperscript{22–25}, heart failure\textsuperscript{26}, the effects of pacing\textsuperscript{27–33}, pulmonary hypertension\textsuperscript{34}, and dyssynchrony\textsuperscript{28,35–37}. If it is possible for SQUEEZ to be used in place of these metrics, it will significantly reduce the imaging and analysis time and make a significant impact on our ability to bring these quantitative techniques into standard clinical practice. SQUEEZ is derived from the motions of trabecular tissues and other features on the endocardium. These features do not participate in actual myocardial shortening but are in fact “flags” on the surface of the endocardium that move in response
to that shortening. This brings us to an important question: *What is the relationship between the values obtained by SQUEEZ and the underlying myocardial shortening?* We have plenty of experience with MRI tagging that tells us there is an “amplification” of shortening observed in the endocardial region of the LV\textsuperscript{38,39}. In Chapter 4 we map the relationship between SQUEEZ and myocardial shortening by measuring SQUEEZ and MRI tagging in the same animal in back-to-back acquisitions. We also created a variable amount of shortening in the LV by creating a zone of infarction. In particular we test the hypothesis: *There exists a highly correlated and linear relationship between SQUEEZ and circumferential shortening.*
Chapter 2. Method for tracking cardiac wall motion and quantifying myocardial contractility

This method tracks the relative motions of the trabecular tissues on the endocardium, as measured from the LV blood pool signal, to obtain a local estimate of LV function. Figure 2-1(a) is a frame from a video of the human LV endocardium showing the complex meshwork of trabecular tissue. These features are also readily visible in modern high temporal resolution CT images used for coronary CT angiography (CCTA), an example of which is shown in Figure 2-1(b) (Single heartbeat CT image from 320-row detector CT scanner with prospective ECG-triggering: 175ms exposure time, 100 kV and 280mA, dose ~ 2.8mSv).

Figure 2-1- The image in (a) is from an endoscopic video of the LV trabecular tissue on the endocardial surface. (From www.visibleheart.com - Human Anatomy - Left Ventricle Apex) The single heartbeat CT image in (b) also shows the trabecular indentations in the “cast” of the endocardial surface created by the bright LV blood pool signal. This is a single frame from a movie of the beating heart obtained in one heartbeat on an Aquilion ONE Toshiba CT scanner.
A 4D non-rigid deformation algorithm is used to warp the end-diastolic cast into the shape of the casts found at later time points in the heart cycle. We use the coherent point drift (CPD) non-rigid registration algorithm; however, it is important to note that many possible deformations algorithms can be used for this step such as 4D b-splines, large deformation diffeomorphic metric mapping (LDDMM), and deformable demons. The resulting deformation fields are used to precisely estimate the local deformation at all points on the LV endocardium.

In the following sections of this chapter we summarize our findings previously published in by Pourmorteza et al. First we describe the SQUEEZ method in detail followed by its validation with delayed enhanced MRI for detection of infarcted regions. Next, the results of comparison between SQUEEZ and a commercial CT analysis software is reported. Lastly, we show preliminary results of application of SQUEEZ in assessment of dyssynchrony in animals with dyssynchronous heart failure.

2.1. Stretch Quantification of Endocardial Engraved Zones (SQUEEZ)

2.1.1. Background

Most mechanical analysis in clinical setting is based on echo methods derived from two-dimensional motion data. 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.
Few tomographic imaging modalities are capable of producing data with adequate temporal and spatial resolution for detailed regional function assessment. One difficulty with quantitative methods to estimate myocardial function is inability to obtain adequate landmarks in the heart. MR tissue tagging 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, the rapidly growing population of patients with implanted pacemakers or implantable cardioverter defibrillators (ICD) are still contraindicated.

Recent dramatic advances in CT imaging techniques allow for volumetric functional imaging of the entire heart with a few gantry rotation. The high temporal resolution 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 the 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; however, the low spatial resolution of the images was a limitation. Other limitations of current methods are their dependence on manual segmentation of the endocardial and epicardial surfaces and long computation time associated with the surface registration algorithms.
In the following section we introduce a method of tracking the LV wall motion and assessing regional 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. The method is tested on a group of animals with myocardial infarctions (MI) and results are then validated against phase sensitive contrast enhanced MRI to localize the MI regions.

2.1.2. Methods and Material

2.1.2.1. 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 55. In short, 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 deflating the balloon terminated the occlusion of the vessel, 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.

2.1.2.2. 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.

2.1.2.3. Phase-sensitive inversion recovery MRI

In vivo MR 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 EKG triggered, independent respiratory navigator gated, breath-hold, phase-sensitive inversion recovery (PSIR)
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.

**Figure 2-2** - 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 (inferior 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). (E) 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. (F) SQUEEZ maps calculated for every triangle on the endocardial surface at five cardiac phases from end diastole to end systole. (Figure originally published in [9]).
2.1.2.4. 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 2-2 A-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). This is described in detail in section 2.2.

Figure 2-3 - Local shape encoding using shape index. Left: Shape index values for the point at the center of the simple surfaces. From the 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 \( k_1 = -k_2 \neq 0, SI = 0 \); 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. (Figure originally published in *).

2.1.2.5. Endocardial Wall Motion Tracking

We tracked the LV wall motion by calculating trajectories for the points on the endocardial mesh. A triangular mesh represented each endocardial surface. 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 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 2-2 D,E).

We chose a non-rigid point registration algorithm called coherent point drift (CPD) \(^{40}\) 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.

The registration is formulated as a Maximum Likelihood estimation problem, where one point set (template mesh) represents centroids of a Gaussian mixture model (GMM) and the other point set (target mesh) represents the data. CPD algorithm regularizes deformation by penalizing high frequency contents of the deformation field using a Gaussian high-pass filter. In other words, the algorithm penalizes all high order derivatives of the deformation field, whereas thin-plate spline (TPS) algorithms only regularize first and second-order derivatives of the field. This results in a smoother and more coherent deformation.

Compared to similar non-rigid surface registration methods based on TPS deformations \(^{57-59}\), the CPD regularization can be generalized to nD, whereas for 4D or higher, the TPS kernel solution does not exist. This is especially important when surface features such as curvature metrics or shape measures need to be incorporated as additional dimensions to improve the performance of the algorithm. Furthermore, changing the Gaussian filter width can control the locality of spatial smoothness, whereas TPS does not have such flexibility.

The choice of Gaussian filters and kernels also allows for reduction of the massive computational burden, associated with high resolution CT datasets, by taking advantage of
the fast Gaussian transform \(^{10}\). A detailed description of the CPD algorithm and comparison with other point set registration algorithms can be found in \(^{40}\).

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 \textit{shape index} (SI) (Figure 2-2 D, Figure 2-3), 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

\[
SI = \frac{2}{\pi} \arctan \frac{k_1 + k_2}{k_1 - k_2}
\]

\textit{Equation 2-1}

where \(k_1\) and \(k_2\) are the principal (signed maximum and minimum) curvatures at that point. Figure 2-3 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:

\[
SI = \frac{2}{\pi} \arctan \frac{+k_2}{-k_2} = -0.5
\]

\textit{Equation 2-2}

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 \(^{60,61}\). 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 regional cardiac function. The regional myocardial function can be expressed as a number reflecting the amount of local stretch. A triangle mesh is used to represent the cast of the endocardium; for each triangle on the end-diastolic mesh, \( \xi \), the change in area from end-diastole \( A(\xi,t=ED) \), to a later phase \( A(\xi,t=T) \) is computed; the ratio of the change of area is computed, and the square root is taken to make the dimensions the same as 1D contraction or stretch:

\[
SQUEEZ(\xi,T) = \sqrt{A(\xi,T)/A(\xi,ED)}
\]

Equation 2-3

We call this function “Stretch Quantifier of Endocardial Engraved Zones” or SQUEEZ. SQUEEZ is calculated for each triangular element on the ED surface, resulting in a high-resolution regional cardiac function map of the left ventricle.

2.1.2.6. Statistical Analysis

For the data pool obtained from the 11 animals, two-tailed 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 pairwise 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.

2.1.3. Results

To evaluate resting LV function the blood cast 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 2-4). SQUEEZ values were measured in healthy and infarcted animals at different cardiac phases (Figure 2-5) and different locations of infarcted and remote myocardium as detected by contrast enhanced MRI (Figure 2-6 A).

![Figure 2-4](image)

*Figure 2-4 - 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); all in milliliters, and 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. (Figure originally published in 9).
2.1.3.1. 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.

2.1.3.2. 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 MR image, which showed a secondary MI in the inferior wall. Figure 2-5 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 2-6 A). Points were selected on regions of the endocardial surface near the MI zones as defined by the contrast enhanced MR images. About the same number of points were selected in a remote region of the heart with no sign of MI (Figure 2-6 B). The size of the selected regions roughly corresponded to that of one LV segment in the 17-segment AHA model 62.

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 2-6 B). 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.

Figure 2-5 - Bull’s-eye plots of the SQUEEZ values for 3 typical infarcted (A), and 3 healthy pigs (B) from end diastole (left) to end systole (right) at 10% R-R steps. Infarcted subjects show abnormal stretching of the endocardium in LAD territory (anterior and anteroseptal segments) consistent with the infarction model (LAD occlusion after the second diagonal) used in this study and the locations observed with contrast enhanced MR. (Figure originally published in 9).
Figure 2-6 – (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. (Figure originally published in 9).

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 2-6 C); 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.

Figure 2-7 - 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)

2.1.3.3. Effects of dose reduction on SQUEEZ

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 2-6 B). The SQUEEZ map was calculated for the low-dose prospectively gated dataset and compared to the SQUEEZ of the high-dose retrospectively gated data set at 50% of R-R interval. The correlation and difference between the SQUEEZ maps were computed (Figure 2-7). The results show significant correlation (r=0.91, p<0.001) and 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. Use of the low dose prospective scan decreased the radiation dose by approximately a ten-fold. The good correlation with the high-dose scan and low bias and CI of the low-dose scan
makes the use of low-dose prospectively gated CT for cardiac function very promising. The effects of noise on the accuracy and precision of SQUEEZ are discussed in detail in 2.5.4.

2.2. **Comparison with commercial CT function analysis software**

To compare the results of the proposed method with existing CT cardiac function analysis methods, we analyzed the datasets using Vitrea fX software (Vital Images, Minnetonka, MN), available through Toshiba Medical Systems. Vitrea provides an automatic segmentation that requires manual correction of the endo- and epicardial borders. It produces high-resolution bull’s-eye plots but only provides quantitative values for 16-segment AHA plots. Vitrea software measures the regional ejection fraction (rEF) defined by

\[
\text{rEF}\% = \frac{r_1 - r_2}{r_1} \times 100
\]

*Equation 2-4*

where \( r \) is the distance of a point on the endocardial contour from a manually selected centerline in a short axis slice at ES \( (r_2) \), and ED \( (r_1) \). For a small arc of angle \( d\theta \) and length \( c = rd\theta \) on the contour, the circumferential shortening can be approximated by

\[
\frac{c_1 - c_2}{c_1} = \frac{r_1 d\theta - r_2 d\theta}{r_1 d\theta} = \text{rEF}
\]

*Equation 2-5*

Assumed that, in a small surface element, shortening in an arbitrary direction is almost equal to circumferential shortening.
\[ 1 - \frac{c_2}{c_1} \approx 1 - \frac{\sqrt{A_2}}{\sqrt{A_1}} = 1 - SQUEEZ \]

*Equation 2-6*

We investigated the following relationship between our SQUEEZ results and the rEF calculated from Vitrea in the 16-segment measurements:

\[ SQUEEZ \propto 1 - rEF \]

*Equation 2-7*

Paired two-tailed Student's t-test statistical analysis was performed on the SQUEEZ values to test the difference in the means of the measurements in healthy and infarcted regions. All results are reported in mean ± standard deviation.

**2.2.1. Results**

SQUEEZ was calculated for every point on the LV endocardial surface at each cardiac phase (Figure 2-5). All infarcted animals showed abnormal stretching in the LAD territory, which was consistent with the infarct model used in this work, and was confirmed by the PSIR MR images.

Regional ejection fraction was calculated at ES for each cardiac segment using Vitrea. The automatic segmentation of endocardial borders required manual correction, which took approximately **150±15 minutes** in Vitrea when we ran at full slice resolution, whereas manual operator interaction needed for SQUEEZ was limited to bulk cropping of the blood-cast in 3D which took **4±2 minutes**.

SQUEEZ values were averaged into 17 segments and plotted against the 1-rEF values obtained from Vitrea. The regression plots show good correlation \( r=0.81, p<0.001 \) for the
6 mid-cavity segments, but no correlation was found in basal and apical segments in any of the datasets (Figure 2-8).

![Figure 2-8](image)

**Figure 2-8** - Scatter plots for linear regression analysis between SQUEEZ and rEF measurements for the 16-segment AHA model. From left to right: Basal segments, mid-cavity segments, and apical segments. (Figure originally published in\textsuperscript{10}).

![Figure 2-9](image)

**Figure 2-9** - (A) PSIR image of an animal with an anterior/anteroseptal and an inferolateral infarcted region. The anterior/anteroseptal infarct can be divided into smaller infarcted sub-regions with various levels of transmurality. B and C: End systolic SQUEEZ plots of the same animal, in original SQUEEZ color map (B) and SQUEEZ values in Vitrea color map (C). The short axis slice in (A) corresponds to a concentric circle in the polar plots. The four different levels of transmurality in the small sub-regions are distinguishable in both plots as depicted by the black arrows. D: End systolic regional ejection fraction plot from Vitrea. The small infarcted sub-regions are not visible in this map. Furthermore, the streaks of colors in circumferential direction, especially in anterolateral segments, shown as stair-step artifacts, show the 2D nature of the rEF calculation algorithm. (Figure originally published in\textsuperscript{10}).

Vitrea did not provide access to the numerical values of the high-resolution bull's-eye plots, therefore we could only compare them to SQUEEZ maps by visual inspection. Although in general the maps look similar, SQUEEZ maps seem to be able to detect wall motion differences at a much higher spatial resolution. This could be attributed to the fact that in Vitrea the number of points on the contours is limited and the segmentation process
smooths the contours, therefore they cannot capture the true shape of the endocardial surface. This is especially evident in the dataset shown in Figure 2-9 where the heterogeneous anterior/anteroseptal infarcted region has sub-regions with different levels of transmurality. SQUEEZ can detect the small heterogeneous sub-regions, whereas the rEF map does not seem to be able to differentiate between different levels of infarct transmurality. Contrast enhanced MR images were used as the gold standard to verify the location of the infarcted regions detected in SQUEEZ maps. Points were selected on regions of the endocardial surface near the MI zones as defined by the contrast enhanced MR images. About the same number of points was selected in a remote region of the heart with no sign of MI (Figure 2-9). The size of the selected regions roughly corresponded to that of one LV segment in the 17-segment AHA model. 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. 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.

2.2.2. Discussion

After Volumetric CT data used in this work can be reconstructed from the routine dose modulated coronary angiography CT scan that is acquired in less than 5 heartbeats. 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 (150±15 min for
Vitrea vs. 4±2 min for SQUEEZ). The rEF calculation, by definition, is sensitive to the parameters discussed below.

![Figure 2-10](image)

**Figure 2-10 - Sensitivity of rEF to center point selection:** Solid and dashed concentric circles represent endocardial contours at ED and ES, respectively. Assuming uniform radial motion; if the center point is chosen on the center of the circles (A), every point on the contour will have similar rEF values; however, if the center point is misplaced (B) regional function will be underestimated in P1 and overestimated in P2. (Figure originally published in[10]).

**Initial distance from centerline:** Since rEF = Δr/r, for a constant Δr the regional function is dependent on the initial distance of the point from the centerline. Hence rEF is less sensitive to wall motion in short axis slices in which endocardium has a large radius e.g. basal segment.

**Through-plane motion:** The longitudinal displacement of tissue into and out of the short axis slice, looks like a change in the endocardial wall position in the short axis slice due to myocardial thickening or stretching, but it in fact is just bulk displacement of tissues in 3D space. The overestimation of regional function in mid-cavity segments (slope=1.2) could be attributed to this artifact (Figure 2-8). However this artifact is more prominent in basal and apical segments in which the topology of the short axis contours may change significantly due to through-plane motion.

**Centerline location:** Regional EF 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 very large rEF values (Figure 2-8-apical). Although the centerlines were chosen carefully, the irregular shape of the contour in apical slices, especially in hearts with chronic infarcts, which have gone under significant LV remodeling, would still cause unrealistically large rEF values in some datasets (Figure 2-10).

### 2.3. CPD vs. LDDMM

As a preliminary test of consistency of CPD against a well-established deformation algorithm we compared its performance against Large Deformation Diffeomorphic Metric Mapping (LDDMM) \(^4\). The LDDMM surface matching algorithm computes an optimal diffeomorphism between a template and a target surface, and it has been extensively validated for cardiac motion and cardiac shape \(^4\). For this preliminary study the mean minimum Euclidean distance between the target and the warped meshes was: LDDMM: 0.71±0.25 mm, and CPD: 0.86±0.42 mm (Figure 2-11). SQUEEZ was then calculated for each triangular element of the endocardial meshes (Figure 2-12 A, B). The mean absolute difference in SQUEEZ calculated from the LDDMM and CPD meshes was 0.06±0.05 (Figure 2-12 C); however, most of the significant difference was isolated to a few local positions. The LDDMM fitting required \textbf{two hours} of compute time to match only two meshes of roughly 10000 vertices and 20000 faces (this was subsampled by a factor of 3×3×3 compared to the native resolution of the CT data in order to obtain a reasonable analysis time with LDDMM). CPD on the other hand provided surface matching with sub-millimeter accuracy in less than \textbf{3 minutes}. CPD results appear smoother in general; this is mainly due to the fact that CPD uses singular value decomposition (SVD) to reduce the dimension of the registration problem. Although this considerably speeds up the registration, it trades off
speed with spatial resolution. However, it is possible to tune the regularization coefficient in LDDMM to achieve a similar level of smoothness of the deformation field.

Mean Minimum Euclidean Distance Between Two Meshes

Figure 2-11 – Mean minimum Euclidean distance between two meshes: (A) Distance between the target mesh and the mesh warped by CPD. (B) Distance between the target mesh and the mesh warped by LDDMM. (C) Distance between the two meshes warped by CPD and LDDMM.

SQUEEZ Estimated Using Different Warping Algorithms

Figure 2-12 – SQUEEZ maps of a single animal with a chronic infarct estimated using different non-rigid registration algorithms: (A) Coherent Point Drift (CPD), (B) Large Deformation Diffeomorphic Metric Mapping (LDDMM), and their difference (C) LDDMM-CPD.
In conclusion, although LDDMM was slightly more accurate in non-rigid registration, CPD was substantially faster and therefore more suitable for SQUEEZ calculation in clinical settings. Furthermore, there are multiple parameters to be set in both algorithms; it may be possible to tune the parameters in each method such that the agreement between them would improve.

2.4. SQUEEZ and Threshold Selection

The uniform intensity of the bolus of contrast in the LV makes it easy to segment the endocardial border just by thresholding the CT volume at a certain image intensity. The threshold value can be manually selected by the user to ensure maximum separation between blood and myocardium. This task is fairly simple and in our initial experiments takes less than 30 seconds. However, it is beneficial to have an automatic and robust method for calculating the threshold value; this will ensure consistency and removes one extra step of operator interaction.

In this section we investigate the effects of choosing and deviating from the threshold value. Our goal is to segment the blood cast of the LV and then extract the outer surface of the cast.

2.4.1. Image Acquisition

Ten pigs with chronic myocardial infarctions (MI) were created as described \(^{55}\). The left anterior descending (LAD) coronary artery was engaged with a catheter under fluoroscopic guidance. The LAD was occluded just distal to the second diagonal branch by inflating an angioplasty balloon. After 120 minutes, the occlusion was terminated and the restoration of flow was confirmed by angiography. The CT studies were performed between 5 to 11 months after MI induction.
The animals received intravenous metoprolol (2 to 5 mg) and/or amiodarone (50 to 150 mg) prior to the scan to achieve a heart rate < 100 beats/min. The CT scans were performed using a 320-detector scanner (Aquilion ONE, Toshiba Medical Systems Corporation, Otawara, Japan). After scout acquisitions a 60-100 ml bolus of ioxixanol (Visipaque, 320 mg iodine/ml, Amersham Health, Amersham, United Kingdom) was injected intravenously at a rate of 4 ml/s and a first-pass cardiac function scan was performed. The scan was triggered to start when the intensity of the contrast agent in the left ventricle exceeded 200 HU. The acquisitions were performed using a 5-beat retrospectively gated CT protocol with the following parameters: gantry rotation time 350 ms, detector collimation 280 to 320 × 0.5 mm, and x-ray tube voltage/current 80 kVp / 500 mA.

Images were reconstructed every 5% of the R-R interval in systole using the FC08 reconstruction kernel at 0.39 × 0.39 × 0.50 mm³ voxel size. Two reconstruction algorithms were used: a) filtered back-projection (FBP) with Quantum Denoising Software (QDS+) and b) the standard setting of Toshiba’s iterative algorithm named Adaptive Iterative Dose Reduction 3D (AIDR 3D) 63. When necessary, EKG editing was performed to account for arrhythmias.

2.4.2. Method

We propose the threshold value selection as follows. The probability distributions of image intensities in myocardium and blood are estimated by selecting regions of interest (ROI) on the image (Figure 2-13 A). The intensity distribution can be approximated with a Gaussian of mean \( \mu \) and standard deviation \( \sigma \).

\[
P(\mu, \sigma) = \frac{1}{\sigma \sqrt{2\pi}} \exp \left( -\frac{(x - \mu)^2}{2\sigma^2} \right)
\]

Equation 2-8

The segmentation task can now be performed as a 1-D Bayesian classification.
The threshold $x$ is selected such that

$$x_0 = \{ x : P(\mu_{myo}, \sigma_{myo} | x) = P(\mu_{blood}, \sigma_{blood} | x) \}$$

Equation 2-9

i.e. the intensity value at which there is equal chance that a voxel belongs to class 1 (myocardium) or class 2 (blood) (Figure 2-13 B).

Sensitivity of squeeze to the threshold value was evaluated over the range $[-4 \sigma_{myo}, 8 \sigma_{myo}]$ around $x_0$. For each threshold value, end-systolic SQUEEZ was calculated as previously described in section 2.1.2.4. The SQUEEZ map calculated from the FBP reconstruction at $x_0$ was used as the reference.

Figure 2-13 – (A) sample CT image with ROIs selected on the myocardium (blue) and LV blood (red). (B) Schematic of the distribution of the intensities of pixels in the selected ROIs. The dashed line represents the selected threshold.

2.4.3. Results

The mean and standard deviation of error in SQUEEZ due to threshold selection was then calculated. Figure 2-14 depicts the error in SQUEEZ in a single animal. The interval where
the error in SQUEEZ was less than 0.03 was 159±73 for FBP and 169±86 for images reconstructed with AIDR. This suggests that there is an interval of at least 80 HU around the automatically selected threshold where the error in SQUEEZ due to segmentation is less than 0.03.

![Error in SQUEEZ as a function of threshold value](image)

**Figure 2-14** – Mean ± standard deviation of error in SQUEEZ as a function of threshold value in a single animal. Top: results from FBP reconstruction; bottom: results from AIDR reconstruction.

### 2.5. Determining LV Dyssynchrony Using SQUEEZ

#### 2.5.1. Background

Using non-invasive imaging to evaluate the mechanical dyssynchrony of the left ventricle has been an active area of research for a decade; however, the role of imaging remains controversial. Accurately identifying responders to Cardiac Resynchronization Therapy (CRT) remains an unmet clinical need because only 50% of patients change NY class after
CRT treatment. Cardiac CT offers a number of benefits for these patients because many key parameters can be measured from a single exam: the location of scar will appear as a region of low deformation and low SQUEEZ values in resting CT; the ejection fraction can be computed with extraordinary precision; coronary vein morphology and location can be determined from the CT angiograms. The addition of a CT based method for estimating local mechanical dyssynchrony would round out this exam such that all key parameters would be available after a simple CT exam for CRT procedure planning. The mechanical dyssynchrony of LV activation has been characterized successfully in previous studies with MRI tagging followed by computation of the CURE index. However, MRI tagging studies require long imaging times, with long patient breath-holds, and the image analysis requires extensive user interaction and time. Follow up MRI studies while possible, are much more difficult due to the presence of the pacemaker. Cardiac CT coupled with SQUEEZ could provide excellent estimates of the CURE index and measuring patient response to CRT will be simple and highly accurate with follow up CT studies.

2.5.2. Method and Material

Left bundle branch block was induced in two adult dogs with ischemic dyssynchronous heart failure (DHF). Volumetric 320-slice CT was done at animals’ intrinsic heart rates ~100 bpm. The data were reconstructed at every 5% of the R-R cycle at 0.5×0.5×0.5mm³ using multi-beat reconstruction. Left ventricle (LV) regional function maps were computed by SQUEEZ. A circumferential uniformity ratio estimate (CURE)

\[ CURE = \frac{S_0}{(S_0 + 2S_h)} \]

Equation 2-10
was calculated using SQUEEZ from CT, instead of MRI-based strain; $S_0$ and $S_h$ are sums of zero and higher-order Fourier coefficients of short-axis SQUEEZ over time and slices.

### 2.5.3. Results

CURE values were calculated for each animal group, $0.58\pm0.07$ (2 DHF) and $0.81\pm0.02$ (4 healthy pigs) ($p<0.01$, two-tailed t-test). Figure 2-15 shows bull's-eye plots of SQUEEZ for a healthy and a DHF animal (time interval ~60ms). Septal shortening (blue) and LV free-wall stretch (orange) followed by lateral shortening is visible in the DHF data. In each case the latest activated myocardial segment could be identified.

![SQUEEZ plots of 3 animals in time. Top: Healthy animal, Middle: animal with chronic myocardial infarction (MI) in the LAD territory, Bottom: animal with ischemic dyssynchronous heart failure (DHF).](image)

### 2.5.4. Discussion

We demonstrated a promising application of CT in characterizing dyssynchronous wall motion in animals with ischemic dyssynchronous heart failure. Combined with CT-based coronary vein and scar imaging, SQUEEZ could facilitate pre-procedure planning of cardiac
resynchronization therapy (CRT) lead placement. For patients with dyssynchronous heart failure, SQUEEZ could fill a clinical need in identifying patients who will respond to CRT.

In follow-up studies, these patients will have CRT implants, and cannot be imaged reliably in MRI. Echocardiography is possible but is shown to have modest performance in multicenter studies (see section 5.1.1 for more details). Therefore, CT-based techniques like SQUEEZ would be the method of choice for follow-up studies to assess the effectiveness of CRT in reducing major adverse cardiac events (MACE) in patients. Our future plans include investigating the power of SQUEEZ in predicting MACE in a group of patients as well as its application in CRT candidate selection and surgical planning.

However, first we need to optimize the CT acquisition protocol with respect to radiation dose to ensure patients’ safety. In the next chapter we investigate the performance of SQUEEZ in low-dose acquisitions, in order to find the minimum amount of radiation dose needed to acquire reliable estimates of SQUEEZ.
Chapter 3. Performance of SQUEEZ in noisy acquisitions

Cardiac CT images have very complex noise properties due to the reconstruction over time and 3D space. Large array detectors coupled with new iterative reconstruction techniques introduce correlations in image noise that are not easily simulated without access to proprietary reconstruction and calibration techniques from the manufacturer. Therefore, to fully characterize the performance of SQUEEZ as a function of spatial resolution and radiation dose using scanner equipment and reconstruction software approved for humans, we are required to perform experiments over a range of these parameters in the same heart. This is only possible in computer simulations or in an animal model in which total radiation dose is not a limitation.

The contrast-to-noise ratio (CNR) between the LV blood pool signal and the myocardium is the primary factor for robust automatic segmentation of the LV blood pool. We used the vendor provided filtered back projection (FBP) algorithm and the 3D Adaptive Iterative Dose Reduction (AIDR3D)\textsuperscript{63}, and the Iterative Model Reconstruction (IMR)\textsuperscript{72} algorithms, all of which are approved by the FDA for use in humans.

The goal is obtain images of very high quality (low noise, low artifact) to use as the reference for the performance of SQUEEZ in noisy acquisitions. Even in animal models, consecutive scans may be slightly different due to respiratory motion, and the variability in heart rate or stroke volume.

We tested the accuracy and precision of SQUEEZ in presence of noise in two ways:

**Section 3.1:** Using a simulated moving heart phantom, we compared the performance of SQUEEZ in noisy acquisitions reconstructed with FBP and IMR (Philips Healthcare)
Section 3.2: In a cohort of animals, high-dose data was acquired and then noise was added to the projection data using a noise simulator (Toshiba Medical Systems). The raw data was then reconstructed using FBP and AIDR.

3.1. Phantom Simulations

3.1.1. Purpose

To investigate the effect of a new Iterative Model Reconstruction (IMR) (Philips Healthcare) on estimating regional cardiac function (SQUEEZ) from ultra-low dose cardiac CT scans.

3.1.2. Materials and Methods

A modified version of the Utah Center for Advanced Imaging Research (UCAIR) analytic beating heart phantom was used to simulate cardiac acquisitions at low dose settings on a 256-slice iCT scanner (Philips Healthcare). Images were reconstructed using traditional filtered back-projection (FBP) and the new IMR algorithms for end-diastolic and endsystolic cardiac phases. IMR is a reconstruction algorithm that recovers the object from the attenuation data by solving an optimization problem using statistical models. The IMR reconstructions were performed on a prototype GPU-based reconstruction system. Finally, SQUEEZ was calculated for each point on the endocardium.

3.1.3. Results

Noisy images were simulated using a CT noise simulator and reconstructed using FBP and IMR (Figure 3-1). SQUEEZ values from noisy FBP and IMR reconstructions were compared with values from noiseless data. Bland-Altman plots (Figure 3-2) showed error bias and standard deviation in SQUEEZ values of 0.005±0.064 at 50 mAs, whereas with IMR the error
was -0.004±0.060 at 5 mAs. The algorithm was unable to track the endocardial surface in 5 mAs FBP datasets due to excessive noise.

Conclusion

These results indicate that it is possible to achieve comparable accuracy in estimates of SQUEEZ using the IMR reconstruction algorithm with a ten-fold reduction in dose compared to traditional FBP.

![Figure 3-1](image1.png)

**Figure 3-1** - Simulated noisy images of the heart phantom. The hyperintense region is the left ventricle. (A) FBP reconstruction of an acquisition simulated at 50 mAs. (B) IMR reconstruction of the same acquisition simulated at 10x lower dose (5 mAs).

![Figure 3-2](image2.png)

**Figure 3-2** - (A) the Utah Center for Advanced Imaging Research (UCAIR) analytic heart phantom. (B) Bland-Altman plots of SQUEEZ values from noisy reconstructions with respect to the SQUEEZ calculated from noiseless data. (Figure originally published in 73)
3.2. Accuracy and Precision of SQUEEZ in noisy acquisitions: an animal study

The purpose of this study was to determine the low radiation dose threshold for calculating SQUEEZ with sufficient accuracy and precision to assess regional wall motion abnormalities automatically.

Toward this end, we obtained “reference” CT images in animals with normal radiation dose, and then simulated low dose acquisitions by creating lower contrast-to-noise (CNR) images from the raw data using a noise addition tool. We measured the reduction in precision of SQUEEZ as a function of reducing image quality and radiation dose.

3.2.1. Material and Methods

3.2.1.1. 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).

Ten pigs with chronic myocardial infarctions (MI) were created as previously described by Schuleri et al. and also in section 2.4. The left anterior descending (LAD) coronary artery was engaged with a catheter under fluoroscopic guidance. The LAD was occluded just distal to the second diagonal branch by inflating an angioplasty balloon. After 120 minutes, the occlusion was terminated and the restoration of flow was confirmed by angiography. The CT studies were performed 5 to 11 month after MI induction.
3.2.1.2. Image Acquisition

The animals received intravenous metoprolol (2 to 5 mg) and/or amiodarone (50 to 150 mg) prior to the scan to achieve a heart rate < 100 beats/min. The CT scans were performed using a 320-detector scanner (Aquilion ONE, Toshiba Medical Systems Corporation, Otawara, Japan). After scout acquisitions a 60-100 ml bolus of iodixanol (Visipaque, 320 mg iodine/ml, Amersham Health, Amersham, United Kingdom) was injected intravenously at a rate of 4 ml/s and a first-pass cardiac function scan was performed. The scan was triggered to start when the intensity of the contrast agent in the left ventricle exceeded 200 HU. The high quality breath-hold “reference” CT acquisitions were performed using a 5-beat retrospectively-gated CT protocol with the following parameters: gantry rotation time 350 ms, detector collimation 280 to 320 × 0.5 mm, and x-ray tube voltage/current 80 kVp / 500 mA.

Images were reconstructed every 5% of the R-R interval in systole using the FC08 reconstruction kernel at 0.39 × 0.39 × 0.50 mm³ voxel size. Two reconstruction algorithms were used: a) filtered back-projection (FBP) with Quantum Denoising Software (QDS+) and b) the standard setting of Toshiba’s iterative algorithm named Adaptive Iterative Dose Reduction 3D (AIDR 3D). When necessary, ECG editing was performed to account for arrhythmias. Figure 3-3 shows a typical outcome of the reconstruction algorithms.

Figure 3-3 - Multiple cardiac phases of a single slice of the 4D reference CT data used to obtain SQUEEZ.
3.2.1.3. Noise Simulation

In order to simulate the effects of low-dose acquisitions for each scan, 8 lower dose acquisitions were simulated using the CT manufacturer supplied noise addition toolbox\textsuperscript{76}. The toolbox models specific system noise empirically with water phantom scans at various acquisition settings and a compound noise distribution based on photon statistics (Poisson distribution) and electronic noise (Gaussian distribution). The simulated noise is then added into the raw projection data based on the desired reduction in tube current.

The reference datasets were acquired at tube current-time product of 111-127 mAs; The effective mAs levels of the lower dose simulations were set at the following descending values: 100, 80, 60, 50, 40, 30, 20, 10, and 5.

Each simulation was reconstructed using FBP and AIDR3D as described in the previous section. The LV blood pool vs. myocardium CNR decreased and image quality visibly decreased as the simulated current-time product was decreased, as shown in Figure 3-4. This series of images produced an LV signal that could be automatically segmented from the myocardium for all mAs values of greater than ~20-30 depending on the intensity of blood and existence of low-dose ring artifacts in the LV.

3.2.1.4. Effect of Decreasing CNR

End systolic SQUEEZ was calculated as a measure of regional wall motion for all noise levels. For each animal, the SQUEEZ map calculated from the reference image was used as the reference values in Bland-Altman analysis of SQUEEZ values measured from the simulated images that had increasing levels of noise.
Figure 3-4 - The original "reference" images (left column, 127 mAs) compared with simulated images at lower mAs values created from the same raw data. The top row shows images reconstructed with FBP and the bottom row AIDR3D ("standard" setting). Low-dose ring artifacts appear at 20 mAs and are very prominent at 10 and 5 mAs.

3.2.1.5. Effect of Reducing Spatial Resolution

Spatial smoothing is a simple method of noise reduction. We assessed the effect of spatial smoothing on SQUEEZ in noisy acquisitions. For each noise level the reconstruction the 3D CT volumes were smoothed by a series of 3D Gaussian kernels with increasing standard deviation (σ) from 0.5 to 5 voxels. The smoothed 3D data was then used for SQUEEZ analysis.

The unsmoothed original FBP reconstruction was used as the reference and the error was calculated as the difference between the SQUEEZ maps of the unsmoothed reference and those smoothed with Gaussian kernels.

3.2.1.6. Statistical Analysis

Continuous data were expressed as mean ± SD. The distributions were tested for normality using the Lilliefors test\textsuperscript{77}. Significance of difference between the means and standard deviations of variables were tested using the Students t-test and the F-test, respectively.
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Table 3-1 - LV blood pool vs. myocardium CNR values for the original reference images ("Full Dose" column) and lower CNR images after addition of noise with the noise tool software. Each column gives the mAs value used in the noise simulation tool. FBP: Filtered Back Projection, AIDR: Adaptive Iterative Dose Reduction.

3.2.2. Results

The contrast-to-noise ratio (CNR) between the LV blood signal and the myocardial signal was calculated as a measure of image quality for the reference image and higher noise simulated images (Table 3-1). The highest CNR values were approximately 30, and the lowest values were approximately 1 in images that had recognizable features. The difference in the CNR values in the Full Dose images was due to differences in x-ray contrast concentration in the LV blood pool at the time of image acquisition; this gives the data a very broad coverage of CNR values. The LV blood in images with CNR<4 could not be automatically segmented due to low-dose ring artifacts in the images; the images containing these artifacts included the 5, 10, and some 20 mAs simulations (see Figure 3-4). Global ejection fraction percentages for each of the ten animals were calculated from the 3D blood
casts of the LV at end diastole and end systole. The average EF was 43% ± 12% and the average heart rate was 74±13 bpm. The range of SQUEEZ values observed in the animals was 0.5 (normal contraction) through 1.2 (stretch in the infarct zone); all infarct regions were well resolved in every case. A good range of SQUEEZ values was seen in each individual animal due to the presence of the infarct.

3.2.2.1. Dependence of SQUEEZ precision on image noise level

Figure 3-5 shows the SQUEEZ plots obtained from images with decreasing mAs values (and also decreasing CNR) in one animal. We calculated the error in SQUEEZ due to the simulated noise using the full-dose FBP reconstruction as the reference (Figure 3-5, top row, 111mAs, shown in the red box). The standard deviation of the error for both FBP and AIDR reconstructions increased as the simulated mAs values decreased.

Figure 3-6 shows the standard deviation of the error in SQUEEZ with respect to CNR in the lower dose images for all animals. These results indicate that for acquisitions with CNR>4, SQUEEZ can be estimated with a precision of ±0.04 (p<0.001). The low-dose SQUEEZ maps calculated from AIDR reconstructions seem to show slower deterioration as the CNR decreases compared to the FBP SQUEEZ maps; however this difference was not statistically significant.

3.2.2.2. Dependence of precision of SQUEEZ on spatial smoothing

In order to evaluate the dependence of SQUEEZ on spatial resolution the lower dose reconstructions were smoothed by Gaussian kernels with σ = 0.5 through 5 voxels. The error in SQUEEZ maps was calculated using the original highest dose FBP reconstruction as the reference (Figure 3-7,Figure 3-8). A Lilliefors test (α=0.001) was used to assess the
normality of the error distributions. The null hypothesis was not rejected, meaning that the error values for all $\sigma$ follow a Gaussian distribution.

Figure 3-5 - Top two rows: SQUEEZ plots in a single animal (#5) obtained from the reference image and simulated images with decreasing mAs. The SQUEEZ plot in the top left corner (FBP, 111 mAs) was used as the "reference". Bottom two rows: Gray scale plots showing the difference between the SQUEEZ plots at each mAs value and the full-dose SQUEEZ plot calculated from the reference FBP reconstruction.

Figure 3-6 - Standard deviation of error in SQUEEZ vs. CNR for images reconstructed with FBP (left) and AIDR 3D (right) for simulated acquisitions (20-100 mAs) over all 10 animals.

A Student's t-test and F-test were then used to compare the means and variances of the errors, respectively. For these data, the $\sigma=1$ kernel provided the optimal spatial smoothing
for obtaining maximum precision in SQUEEZ as shown in Figure 3-9. The precision of SQUEEZ monotonically decreased for $\sigma$ values greater than the optimal $\sigma$; however, the resultant increase in error of the SQUEEZ map remained below 0.06 for $\sigma \leq 5$ pixels.

![Figure 3-7](image-url) - (A) SQUEEZ plots obtained from images with simulated 30 mAs (top two rows) and original acquisitions (bottom two rows) as the width of the Gaussian smoothing kernel was increased. (B) Error in SQUEEZ with respect to the full-dose FBP acquisition.

The precision of SQUEEZ from the unsmoothed AIDR images was identical to the $\sigma = 1$ data for the FBP reconstructed images (Figure 3-9). This would indicate that the AIDR reconstruction produced images that contained inherent smoothing. The standard deviation of error in AIDR unsmoothed volumes and volumes with $\sigma = 1$ were not significantly different, suggesting that the "effective" spatial smoothing of standard AIDR is the same as the spatial smoothing of a Gaussian kernel with $\sigma = 1$. Furthermore, the standard deviation of error for FBP volumes smoothed with $\sigma = 1$ was not significantly different from that of unsmoothed AIDR volumes.
Figure 3-8 - 3D plots of SQUEEZ as a function of increasing width (σ) of the smoothing kernel for the 30 mAs noisy simulations (top two rows) and original acquisitions (bottom two rows) reconstructed with FBP and AIDR. The surface rendering shows the effect of progressively more smoothing. The green arrow marks an ridge on the endocardial surface (far left) that is as the surface is smoothed (far right).

Figure 3-9 - Error in SQUEEZ values between the reference (unsmoothed full-dose FBP) and the smoothed volumes reconstructed with FBP (left) and AIDR (right), for the 30 mAs noisy simulations (top row) and the full dose acquisitions (bottom row). Dots and whiskers indicate the mean and standard deviation of error, respectively.
3.2.3. Discussion

In this section we evaluated the precision of SQUEEZ in simulated low-dose acquisitions for the assessment of regional wall motion abnormalities. LV volumes with CNR>4 between the blood pool and the myocardium could be used to estimate SQUEEZ with a precision of ±0.04. The results also suggest that increasing CNR can improve the precision of SQUEEZ (Figure 3-6). The CNR may be improved by increasing the amount of x-ray contrast agent in the LV blood pool, increasing the radiation dose, or both. Also, the CNR can be optimized by careful timing of the scan with respect to the arrival of the x-ray contrast agent into the LV. Most commercial scanners have a simple user interface for setting the target contrast and dose levels.

At very low radiation dose image quality can be compromised by the presence of ring artifacts\(^7\) (Figure 3-3) caused by mis-calibrated or defective detector elements or photon starvation. Although it is theoretically possible to completely remove ring artifacts by careful recalibration of the scanner, most commercial scanners cannot be easily calibrated for mAs levels below 10. This imposes a lower bound for dose reduction in SQUEEZ with the current technology; however, we believe with standard technology a 5 to 6-fold dose reduction vs. the dose required for standard CT coronary angiography can produce data with sufficient quality to perform SQUEEZ.

3.2.4. Conclusion

If the CNR between LV-blood and myocardium is greater than 4, then SQUEEZ can assess regional wall motion abnormality with minimal user input with a precision of ±0.04 (representing 6% of the dynamic range of SQUEEZ values [0.5-1.2]). In the absence of ring artifacts, reliable SQUEEZ values were estimated from images with mAs values as low as 20
and a radiation dose reduction of a factor of 5-6 over the 111-127 mAs original reference acquisitions.
Chapter 4. Agreement of SQUEEZ with myocardial strain calculated from tagged MRI

4.1. Background

Accurate detection and estimate of the extent of regional myocardial dysfunction is important in the diagnosis and management of patients with myocardial ischemia.

Tissue Tagged Magnetic Resonance Imaging is a highly attractive tool for myocardial viability and cardiac function analysis due to the absence of ionizing radiation and high temporal resolution. It has been validated, is accurate, and is currently the gold standard for noninvasive local myocardial function analysis. However, tagged MRI has some practical drawbacks compared to CT, including higher cost and significantly more complicated image acquisition and analysis steps, each of which requires lengthy, skilled, human operator interaction. Long scan times (hundreds of heartbeats) that require multiple reproducible breath-holds are especially difficult for cardiac and/or claustrophobic patients.

Furthermore, for tagged MRI the heart is scanned in a series of 2D slices and the position of the heart often changes between different breath-holds. Deterioration of EKG signal due to the magnetic field and magneto-hemodynamic distortions are also a potential cause of exam failure.

Most recent coronary CT angiography (CTA) technologies provide exceptional high sensitivity for detection and high negative predictive value for exclusion of obstructive coronary artery disease (CAD). These techniques are extremely robust and require only 1-3 heartbeats.
More importantly, resting left ventricular function (LVF) metrics data has been shown to improve diagnosis of acute coronary syndrome (ACS). Seneviratne et al. showed that adding regional LVF in resting patients resulted in a 10% increase in sensitivity to detect ACS by cardiac CT and significantly improved the overall accuracy.

Present CT-based methods of regional LVF assessment rely on manual contouring of the endo- and epicardial borders of the left ventricle or are based on subjective visual scoring of the motion and/or shortening of the LV wall. 2D analysis methods are also susceptible to through-plane motion artifacts and cannot readily distinguish the rigid translation of the heart muscle from its non-rigid contraction. Cardiac CT data is intrinsically 3D; the analysis of LV function should take advantage of the ability to track the heart in 3D.

In this section we assess the agreement between SQUEEZ calculated from CT and myocardial strain calculated from tagged MRI to measure regional myocardial function in the LV. To this end, we created an acute model of myocardial infarction in a cohort of canines, and acquired cardiac function CT and tagged MRI scans from each animal. The resulting end-systolic state of the LV in each case contained regions of both normal contraction and abnormal contraction due to ischemia.

4.2. Material and Methods

4.2.1. Animal Model

Nine dogs weighing 10 to 15 kg were studied with institutional approval. Anesthesia was induced by subcutaneous acepromazine (0.2 mg/kg), followed by intravenous thiopental sodium (15 mg/kg). Anesthesia was sustained by inhaled isoflurane (0.5% to 2.0%).

To make a model of acute myocardial infarction, the animals were intubated and surgical preparation included median sternotomy, venous catheters, arterial lines, and a snare
around the left anterior descending (LAD) coronary artery, typically positioned distal to the first diagonal branch. The LAD was occluded for 2 hours followed by 2-hour reperfusion prior to commencing imaging. Tagged and cine MRI scans were performed during the reperfusion phase (Figure 4-1).

The animals were then transported to CT suite and the LAD was re-occluded. First-pass contrast enhanced CT scans were acquired after at least 2 hours of reperfusion and approximately 5 minutes after LAD re-occlusion (Figure 4-2). The average delay between the CT and MRI scans was less than 1 hour.

After the CT scans, animals were euthanized with potassium chloride following heparin administration.

![Experiment Design](image)

Figure 4-1 – Experiment design for comparing the performance of SQUEEZ and tagged MRI in dogs with acute myocardial infarction.

4.2.2. MR Imaging

LV geometry and function were evaluated with a cine true fast sequence. In addition, short axis tagged cine MRIs were acquired and used to derive circumferential myocardial strains ($E_{cc}$)\textsuperscript{19}. The LV was manually segmented from the cine MR images using the Osirix Imaging Software to calculate the global ejection fraction (EF). Circumferential myocardial strain ($E_{cc}$) was estimated by manual segmentation and analysis of the tagged images using
FindTags\textsuperscript{82} and Tagged Tissue Tracking (TTT)\textsuperscript{19} software packages developed at the Johns Hopkins University.

FindTags was used to automatically contour the endocardial and epicardial boundaries and segment the tags. The automatically created contours and tags were manually edited. Next, a B-spline-based motion tracking technique was used to track the tags and calculate subendocardial circumferential strains by TTT.

\begin{figure}[h]
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\caption{Visualization of the myocardium with perfusion deficit due to LAD occlusion: One minute delayed contrast enhanced CT images of a single animal after occlusion of the left anterior descending (LAD) coronary artery. The red arrows show hypointense area in the myocardium with perfusion deficit induced in the LAD territory. (A): short-axis view, (B,C): long-axis view. Imaging parameters: 80 kVp, 600 mA, reconstructed with AIDR standard, FC08.}
\end{figure}

4.2.3. CT Acquisition

Animals were scanned with electrocardiographic (EKG) monitoring using a 320-row detector scanner (Aquilion ONE ViSION; Toshiba Medical Systems Corporation). First-pass contrast enhanced CT scans were acquired while respiration was suspended using a 3 to 5-beat retrospectively gated protocol with the following x-ray tube parameters: 80 kVp and 600 mA. Gantry rotation speed (275 ms - 350 ms) was set based on the animal’s heart rate to ensure optimal temporal resolution (40-60 ms). Real-time bolus tracking was performed using Toshiba’s SUREstart following a bolus injection of 35 to 60 ml of Iodixanol (Visipaque
320) at a rate of 1 ml/sec. The scan was triggered when the intensity of the blood in the LV exceeded 800 HU.

CT volumes were then created using the standard setting of the 3D Adaptive Iterative Dose Reduction (AIDR3D) reconstruction algorithm with FC08 kernel at 0.5 mm slice thickness and 0.29 to 0.45 mm in-plane pixel size. A total of 20 volumes were reconstructed at 5% intervals of the R-R cycle. EKG editing was performed when necessary to account for arrhythmias.

4.2.4. Myocardial Function Estimation

Global ejection fraction was calculated from both CT and MRI acquisitions. In some cases, the physiological state of the animal changed in the time between the CT exam and the tagged MRI exam. Animals with more than 10% difference in EF between the CT and MRI scans were excluded from the study due to the difference in the hemodynamic state of the hearts. The MR circumferential strain (£cc) curves were calculated as explained in the previous section using the FindTags and TTT packages.

For each systolic cardiac phase in the CT volumes, regional myocardial function was calculated with SQUEEZ. A SQUEEZ value of 0.75 means the tissue has contracted 25% (normal), a value of 1.0 means the tissue is akinetic, and a value of 1.25 means the tissue has stretched by 25% (dyskinetic). On the other hand, strain metrics derived from tagged MRI, such as circumferential shortening (£cc) are represented as percentage of stretch (for example, £cc=-0.25 in normal tissue, £cc=0 in akinetic tissue, and £cc=0.25 in dyskinetic tissue). Since there is an offset of 1 between the SQUEEZ and £cc metrics, we compared Ecc to SQUEEZ-1 throughout this paper. The SQUEEZ vs. time and Ecc vs. time curves were computed in 18-segment bull's-eye plots of the left ventricle (Figure 4-3 A, B). Peak systolic
SQUEEZ and $E_{cc}$ contraction values were then calculated for each segment of the bull’s-eye plots.

### 4.2.5. Statistical Analysis

Comparisons between peak systolic LV contraction values by SQUEEZ and tagged MRI were performed by linear regression analysis between (SQUEEZ-1) vs. $E_{cc}$. Differences between myocardial peak systolic strains were assessed and the agreement between the two methods (peak systolic strain by MRI and SQUEEZ) was expressed as 95% limits of agreement, as recommended by Bland and Altman\textsuperscript{83}. Statistical significance level was set at $p < 0.05$.

<table>
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Table 4-1 - Ejection Fraction calculated from CT and MRI acquisitions for all animals. Numbers in red indicate difference in EF of over 10%. (* Animal 5 was excluded due to motion artifacts in CT).

### 4.3. RESULTS

Table 4-1 gives the global ejection fraction (EF) values each animal computed from the CT and MRI acquisitions. Three animals were excluded from further analysis due to the large difference between the EF values during the CT and MRI acquisitions; in each case the physiological state of the animal deteriorated markedly between in the time between the CT
exam and the MRI exam. Another animal was excluded due to motion artifacts in the CT acquisition caused by spontaneous respiratory motion and an increase in the heart rate, which caused a mismatch between the gantry rotation speed, and the heart rate.

In the remaining 5 animals, SQUEEZ and E_{cc} were calculated at all systolic phases and the peak contraction values were extracted from the time plots (Figure 4-3 C). The ranges of these values were -0.29 to -0.01 and -0.26 to -0.01 for SQUEEZ -1 and E_{cc}, respectively. The peak contractions from SQUEEZ were then compared to the peak E_{cc} from MRI as the reference (Figure 4-4). The linear regression analysis showed good correlation between (SQUEEZ-1) and E_{cc}: r=0.79, p<0.001, slope=0.88, intercept= -0.03. The Bland-Altman analysis of the results yielded bias of -0.015 and 95% confidence interval ±0.08.

Figure 4-3 – (A) Tagged MRI images of a short axis slice of a single animal in end-diastole and end-systole. (B) First-pass CT images of the same animal. The dotted lines divide each short axis slice into 6 myocardial segments. (C) Time plots of the regional function of each segment in A (top 3 rows) and B (bottom 3 rows); x-axis is normalized time in systole.
4.4. Discussion

We found very good agreement between the estimates of circumferential strain ($E_{cc}$) from tagged MRI and SQUEEZ-1 from CT. There was some residual uncertainty between the estimates in our experiments as shown in Figure 4-3. There are a few possible sources of these differences:

1. Although both SQUEEZ and $E_{cc}$ measure local cardiac wall motion, they are different physical entities; $E_{cc}$ is a measure of myocardial contraction in the circumferential direction, whereas SQUEEZ is a directionless measure of the geometric mean of contraction on the endocardial surface. We would anticipate SQUEEZ to measure a higher amount of contraction and this was observed.
2. Modern CT scanners can resolve images at a slice thickness of 0.5 mm; however, tagged MRI is usually acquired at 6-8mm slice thickness, which makes the endocardial boundary blurred due to the partial volume effect. Therefore, the \( E_{cc} \) measurements are not conducted on the endocardial surface, but rather in a subendocardial-midwall shell of myocardium. Consequently, the underlying true relationship between \( E_{cc} \) and SQUEEZ-1 may not be linear with a slope of 1, because of the transmural decrease of local shortening from endocardium to epicardium in the LV \(^{84}\).

3. Another reason for the mismatch in global function and peak shortening could be that the heart was in different states during imaging: LAD reperfusion during MRI, and re-occlusion during CT. This was due to restrictions in the study design, since the study was originally planned to test a different hypothesis unrelated to testing the correlation of myocardial function in CT and MRI. Careful experiment design with smaller infarct size and more control over the heart rate and global function of the left ventricle is desired to better examine the agreement of CT and MRI in estimating myocardial function.

4. Cardiac CT images are typically acquired in 1-5 heartbeats in a single breath-hold; tagged MRI, however, requires \( \sim 12 \) heartbeats in each of 8 short axis slices and 4 long axis slices (12 breath-holds). Therefore tagged MRI provides measurements that are averaged over 10-20 minutes; SQUEEZ on the other hand is less susceptible to the intrinsic beat-to-beat variability in stroke volume and heart rate.

5. The open chest animal model used in these experiments provided ease of access to the LAD in order to perform multiple occlusions and re-perfusions; however, since the heart was not attached to the sternum, its position during the MRI and CT scans was not exactly the same.
Radiation dose is always a concern with CT. Recent advances in CT technology have made it possible to take “snapshots” of the heart with effective dose of less than 1 mSv \(^85,86\) and as low as 0.1 mSv \(^87\) for coronary angiography. The image quality necessary for wall motion tracking can be far lower than that for characterizing the coronary vessels. In the previous chapter we showed that by lowering the x-ray tube current and voltage (to \(\sim30\) mA and 80 kVp) and using advanced reconstruction algorithms it is possible to calculate reliable SQUEEZ values and reduce the radiation dose 6 to 10-fold \(^9,73\).

Despite the fact that there are some differences in regional function metrics obtained from MRI and SQUEEZ, the limits of agreement between the techniques were relatively small, indicating that the impact of these potential errors is likely to be modest. Therefore, the present study gives foundation for the use of SQUEEZ to measure regional cardiac function in humans.

### 4.5. Conclusion

There is excellent agreement between the estimates of local myocardial deformation obtained from CT SQUEEZ and tagged MRI endocardial circumferential strain (\(E_{cc}\)) in a heart with variable end-systolic strain due to ischemia. For myocardial regions with \(E_{cc}\) values in \([-0.3, 0]\) the line relating SQUEEZ-1 to \(E_{cc}\) was \((SQUEEZ-1) = 0.88(E_{cc}) - 0.03\).
Chapter 5. Discussion and Future Directions

We have developed a new 3D method for measuring regional cardiac function from volumetric CT images that, in our preliminary results, proved to be effective in quantifying regional cardiac mechanics and detecting infarcted regions. The CT data used in this work can be acquired during routine coronary CT angiography (CCTA) scan in less than 5 heartbeats with little extra radiation. 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.

Acquiring mechanical function during CCTA, with minimal extra radiation may have particular clinical value in patients with dyssynchronous heart failure (DHF) to identify their candidacy for CRT as well as to help guide the optimal placement of the CRT lead. It may also be helpful for assessing myocardial dysfunction in patients with myocardial ischemia, especially when used in tandem with CT coronary imaging.

In addition, automated cardiac function analysis with CT will eliminate the need to assess function with other modalities such as echocardiography, SPECT, or MRI, increasing patient throughput and decreasing overall cost for patients and payers.

Current methods for CT regional cardiac function analysis involve time-consuming manual segmentation, or manual correction of segmentation of the myocardium. Furthermore, the high homogeneous contrast between the blood pool and the myocardium in the wide-range detector CT data allows for simple automated segmentation algorithms to be used and eliminates the need for lengthy human interaction. We believe this will make the inclusion of myocardial function in the cardiac CT examinations very simple.
5.1. Comparison with Other Modalities

Before the advent of wide-range detector CT, using Dynamic Spatial Reconstructor (DSR) data, Amini and Duncan proposed a framework for motion tracking of curves and surfaces, based on elastic models and bending energy of a 3D surface, with specific applications to the LV endocardial surface. DSR has good spatial and temporal resolution; however, the scanner is not widely available.

5.1.1. Echocardiography

Echocardiography, on the other hand, is widely used in clinics for cardiac function and dyssynchrony analysis. Most mechanical dyssynchrony analysis is based on echo-Doppler methods, which in turn are largely derived from only two dimensional longitudinal motion data and are susceptible to through-plane motion. The choice of imaging orientation is mainly based on practical grounds given available windows for transducer placement. However, cardiac contraction is principally circumferential, and thus echo-based Doppler methods may not provide the most accurate and comprehensive assessment of cardiac motion. Furthermore, the variance of repeated B-mode and Doppler two-dimensional echocardiographic measures is fairly high owing to dependence on operator experience, machine settings, available acoustic windows, and angle of incidence effects. In spite of their high temporal resolution, fairly high variance of echocardiographic and Doppler measures owing to dependence on operator experience, machine settings, available acoustic windows, and angle of incidence effects have lead to echocardiography's modest performance in multicenter studies.
5.1.2. Cardiac Magnetic Resonance Imaging

Tagged MRI is a highly attractive research modality for regional cardiac function analysis. However, this method also has some practical drawbacks compared to CT, including higher cost, occasional gating failures, more complex scanning protocols and longer scanning times.

As the clinical indications for implantable cardiac defibrillators and biventricular pacing therapy continue to expand, development and validation of alternative imaging modalities with similar anatomic, functional, and viability imaging capabilities are needed to accommodate this growing population of patients who are not candidates for MRI. In 2006 alone, an estimated 114,000 patient implantable defibrillators and 418,000 pacemaker procedures were performed in the United States.

With its high isotropic resolution, CT has the potential to greatly decrease partial volume effects and accurately characterize the blood-myocardium interface, which allows for true 3D data and the ability to reconstruct any arbitrary slice orientation from the original stack of axial slices. This is especially important in motion tracking, since the heart motion is not limited to displacements in the short axis plane.

3D tagged MRI can be performed as stack of orthogonal 2D images acquired over a relatively long period of time. The 2D MRI slices are much thicker than those in CT and the images suffer from partial volume artifacts. Furthermore, since the 2D slices are acquired over tens of heartbeats, the beat-to-beat variability in heart rate and stroke volume could cause mismatch in heart’s location and cardiac phase during a single acquisition.
5.1.3. Single Photon Emission Computerized Tomography (SPECT)

Cardiac SPECT is used to uncover myocardial perfusion deficits under stress and over 17 millions of these scans are performed in the US, annually \(^1\). Initial studies have demonstrated that wide-range detector CT enables comprehensive coronary arterial and perfusion imaging in a single examination. Adenosine stress CT can identify stress-induced myocardial perfusion defects with diagnostic accuracy comparable to SPECT, with similar radiation dose and with the advantage of providing information on coronary stenosis \(^{90-93}\). In addition, recent studies suggest that CT can provide anatomical visualization of heart valves, pulmonary veins and cardiac venous system that could be valuable in cardiac electrophysiological procedures\(^{94}\). The competitive advantage of CT-SQUEEZ over SPECT is multifold:

**Radiation dose:** SPECT exposes the patient to 10-30 mSv per exam \(^{90,95}\) whereas the proposed method can be performed at much lower doses (1-5 mSv depending on the scanner, with room for more dose reduction). This could reduce the radiation dose by \(~20x\).

**Higher spatial resolution** in CT (20-200x smaller voxel size) could lead to detection of smaller myocardial abnormalities that may not be visible in SPECT.

**Scan time:** A typical CT scan takes approximately 20 minutes, including preparation time, whereas SPECT takes about half a day of the patient’s time.

**Sensitivity and specificity** of SPECT is lower than CT (coronary angiography alone) in detection of coronary artery disease: 86% and 74% for SPECT \(^{96-98}\); 91% and 93% for CT \(^7\). Given the high number of patients who suffer from CHD, this change in accuracy would effect tens of thousands of patients each year.
5.2. Future Directions

5.2.1. Validate the use of SQUEEZ for measuring regional myocardial function using low radiation dose in patients undergoing clinically indicated CT studies.

The preclinical studies from Aims 1-3 allowed us to refine the acquisition parameters and test the accuracy, and precision of SQUEEZ in ways that are not possible in human volunteers. However, the clinical translation of this method requires testing in a relevant patient population that can benefit from the development of this technology. There is a large number of cardiac procedures performed that could benefit from fast cardiac function imaging including, but not limited to: device implantation (Implantable Cardioverter-Defibrillators, Pacemakers, and Bi-ventricular Pacemakers) and arrhythmia ablation procedures (Atrial Fibrillation/Flutter - AF, Supraventricular Tachycardia - SVT, and Ventricular Tachycardia - VT). The vast majority of patients undergoing implantation of bi-ventricular pacemakers or ablations for AF, SVT, or VT have a pre-procedural cardiac CT or MR scans performed. These studies are performed to map scar and coronary venous anatomy in the cases for bi-ventricular pacemaker implantation and electro-anatomical mapping of AF, SVT, and VT. We could leverage this readily available population of patients with a wide range of LV systolic function to test the clinical application of SQUEEZ and compare these results to MR tagging analyses. The patient groups that would benefit from this technology include: cardiac resynchronization therapy candidates, patients with acute chest pain syndrome (ACS) admitted to the emergency department, coronary heart disease (CHD) patients with low to medium size stenoses.
5.2.2. Integration of motion compensation and novel task-based statistical reconstruction techniques

5.2.2.1. Motion corrected reconstruction

Due to the motion, cardiac images may contain artifacts, blurring from limited temporal resolution, or excessive noise because current ECG-gated 3D image reconstruction methods assume the object is stationary. This will degrade the accuracy of SQUEEZ estimates of LV function. This limitation has been reduced with improvements in multi-beat segmented image reconstruction and gantry rotation speed such that temporal resolution of under 50 ms is now achievable.

We can take advantage of a fully 4D iterative image reconstruction method that alternates between Motion Estimation (ME) and Motion Corrected Reconstruction (MCR), ME-MCR, to estimate and compensate for the motion of the entire heart during the reconstruction process. ME-MCR could improve the effective temporal resolution of images and decreases motion artifacts. ME-MCR can also decrease image noise by using more projection data while not introducing motion artifacts. ME-MCR can provide time-resolved images from which more accurate and precise SQUEEZ values can be calculated. The improved temporal resolution could make SQUEEZ suitable for LV function estimation at higher heart rates necessary for cardiac stress test.

5.2.2.2. Task-based and Statistical reconstruction methods

While ME-MCR excels at estimating cardiac motion and improving spatial resolution, the method does not explicitly model noise, whereas statistical approaches like PIRPLE (Prior Image with Registration, Penalized Likelihood Estimation) can have distinct advantages in reducing noise. We could integrate the motion compensation of ME-MCR with
PIRPLE. It is also possible to use a sequence of prior cardiac volumes (e.g., the rest-state CT volumes from the CTA, and CT volumes at different times in the cardiac cycle) via a generalization the prior-image penalty term. This will allow us to use all of the data obtained during the coronary imaging protocol toward constructing the LV endocardium accurately.

5.2.3. Derive “directional” values of SQUEEZ

We can compute the fractional change in linear distance on the triangle mesh in the circumferential and longitudinal directions. This may give us insight into any asymmetric sensitivity to deformation direction. Using a study design similar to Chapter 4, we could compute circumferential and longitudinal SQUEEZ from the mesh displacement used to create the SQUEEZ map and compare the results to strain measurements from tagged MRI. This will help us understand the relationship of the underlying myocardial shortening to the directional sensitivity of SQUEEZ.
Chapter 6. Conclusion

Cardiac CT has rapidly become a widely adopted method for imaging cardiac morphology, performing non-invasive coronary angiography, and myocardial perfusion. Modern wide detector CT systems coupled with new iterative reconstruction techniques allow imaging in a few heartbeats with low dose. The accuracy of CT for CHD diagnosis can be improved by adding functional information with the addition of the measurement of local ventricular function. **We hypothesize that 4D cardiac CT data can be obtained that will permit the computation of measures of regional myocardial function that have sensitivity and specificity to the detection of ischemia comparable to tagged MRI.** In order to validate this hypothesis we proposed SQUEEZ: a method for tracking local endocardial features in 4D CT data that uses the tracked features to compute indexes of regional myocardial function similar to circumferential shortening.

In chapter 2 we introduced SQUEEZ as a method to track the endocardial wall motion. The method requires minimum user interaction and can be acquired in 1-2 heartbeats during a routine coronary CT angiography scan. One of the major advantages of SQUEEZ is the removal of segmentation and user interaction from the analysis of LV function.

We also compared the performance of SQUEEZ to the CT manufacturer supplied image analysis software package; the 3D tracking algorithm used in SQUEEZ does not suffer from through plane motion artifacts, and does not require segmenting the endo and epicardium.

Next we showed that SQUEEZ could be used to assess myocardial dyssynchrony. This is especially important in cardiac resynchronization therapy (CRT), where venous coronary CT scan is already used to plan pacing lead implantation13.
With the growing number of cardiac CT scans, the long-term effects of ionizing radiation have become the center of software and hardware improvements to push the radiation dose as low as reasonably achievable\textsuperscript{103}. Chapter 3 helped us answer the question: How much radiation dose is required to achieve acceptable precision in wall motion tracking?

We refined the acquisition parameters and tested the performance of SQUEEZ in noisy acquisitions in ways that are not possible in human volunteers. We plan to look at the fall off in performance as dose goes down over a range of doses for humans. However, due to radiation dose limitations we will not be able to acquire relatively ‘noise-free’ images in humans. This analysis gave us an understanding of the minimum possible dose to produce SQUEEZ values with a specified precision. The results showed that dose reductions of \(~10\) fold are achievable using the current technology. The clinical translation of this method requires testing in a relevant patient population that can benefit from the development of this technology.

Lastly, in Chapter 4, we investigated the agreement of CT-SQUEEZ to tagged MRI in estimating metrics of regional cardiac function in acute myocardial infarction. The results indicate very good correlation between SQUEEZ and circumferential strain from tagged MRI in regional myocardial mechanics.
References


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Publications

Journal Papers


In preparation

A. Pourmorteza, J. Van der Pals, A. E. Arai, M. Y. Chen, E. McVeigh. Quantitative Assessment of Regional Cardiac Function By SQUEEZ From 4D CT In Acute Infarction: Validation Against Circumferential Strain From Tagged MRI. (to be submitted to Journal of Cardiac CT)

A. Pourmorteza, A. Lardo, M. Y. Chen, E. McVeigh. Quantitative 4D assessment of regional wall motion abnormality from very low dose cardiac CT images. (to be submitted to Journal of Cardiac CT)

Conference Papers


Abstracts

A. Pourmorteza, N. Keller, R. Chen, J. Van der Pals, A. E. Arai, M. Y. Chen, E. McVeigh. Quantitative Assessment of Regional Cardiac Function By SQUEEZ From 4D CT In Acute Infarction: Validation Against Circumferential Strain From Tagged MRI. Annual Scientific meeting of Society of Cardiovascular...
Computational Tomography (SCCT 2014), San Diego, CA

A. Pourmorteza, F. Dawoud, A. Lardo, M. Y. Chen, E. McVeigh. Quantitative 4D assessment of regional wall motion abnormality from very low dose cardiac CT images. Annual Scientific meeting of Society of Cardiovascular Computed Tomography (SCCT 2014), San Diego, CA


F. Dawoud, K.H. Schuleri, A. Pourmorteza, R.T. George, A.C. Lardo. Computed tomography electromechanical activation imaging to guide lead placement for cardiac resynchronization therapy. Annual Scientific meeting of Society of Cardiovascular Computed Tomography (SCCT 2012), Baltimore, MD


Intellectual Property


Honors and Awards

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• Siemens pre-doctoral research fellowship (2008)
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