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Cardiac MRI: Improved Assessment of Left Ventricular Function, Wall Motion and Viability

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Abstract

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Accurate imaging of the heart and its failure is important for a successful patient management and treatment. Multiple cardiac imaging modalities provide complementary information about LV function, wall motion, anatomy, myocardial viability and ischemia. It would be beneficial if a single imaging modality could yield reliable clinical information about the heart. This thesis proposes methods that would make cardiac MRI perform an improved assessment of LV function, wall motion and viability, helping it provide more comprehensive information about the heart.

Conventional cardiac MR imaging is performed at a temporal resolution in which the global left ventricular (LV) function can be reliably established. But functional metrics characterizing transient function like peak filling and ejection rates are not accurately assessed. Also, cardiac MR viability imaging faces image quality challenges in patients with severe arrhythmias. This thesis proposes 1) methods to acquire cine-images of the heart at a higher temporal resolution (~ 6 ms) and algorithms to acquire the LV volume across all cardiac phases that would yield functional metrics characterizing LV function and wall motion mechanics and 2) an arrhythmia insensitive inversion recovery (AIIR) algorithm that would significantly reduce artifacts that degrade image quality, thereby extending viability imaging to higher spatial resolution and in patients with severe arrhythmia.
Results from high temporal resolution imaging reveal that obtaining cine cardiac MR images at a temporal resolution of 6 ms is feasible, from which LV time-volume curve and functional metrics are reliably extracted. A dependence on temporal resolution is revealed, and a temporal resolution cut-off of 12 ms is proposed to reliably capture the temporal dynamics of the LV. Also, the AIIR algorithm performs significantly better than conventional MRI in both phantoms and human subjects, leading to a higher image quality scores in a blinded review.

In conclusion, this thesis proposes and implements methods that help cardiac MRI perform 1) a better function and wall motion assessment of the heart through high temporal resolution imaging and 2) a better assessment of myocardial viability through the AIIR algorithm.
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1 The Human Heart: Mechanics and Failure

1.1 The Human Heart

The contraction of the human heart is responsible for delivering nutrients to and removing waste from each organ of the body. The heart is also responsible for the transport of hormones, neurotransmitters and other messengers between various regions of the body (1). The structure and function of the heart muscle is more complex than the simpler skeletal muscle in the following ways: 1) the contractile property of the cardiac muscle is modulated with respect the pumping requirements of the heart. Also, 2) the initiation and conduction of the signal that activate the heart muscle is performed by specialized heart muscle cells and the nerves serve only in a regulatory role.

The muscular human heart pumps blood to all organs of the body through the blood vessels, by repeated rhythmic contractions. The human heart consists of four chambers, viz., right and left atria, and ventricles. Normal blood flow occurs in the following pattern: superior and inferior vena cava drain venous blood into the right atrium. The blood flows from right atrium to right ventricle through the tricuspid valve, from which blood is pumped to the lungs through the pulmonary artery. The arterialized blood from the lungs is collected at the left atrium through the pulmonary veins, flows to left ventricle through the mitral valve and is pumped to the body through the aorta. This pumping of the heart can be categorized into five different phases of the cardiac cycle (one heart beat) - 1) Isovolumic Contraction, 2) Systole (Ventricular Ejection), 3) Isovolumic Relaxation, 4) Early Diastole (Ventricular Filling) and 5) Late Diastole.
Section 1.2 discusses the changes that occur during various stages of the cardiac cycle in detail.

The cardiac muscle is called myocardium (comprised of cardiac myocytes, and is different from the other two types of muscle in the human body, viz., skeletal muscle and smooth muscle). This is enclosed in a fibrous sac of pericardium. The heart is connected to the peripheral nervous system through both the parasympathetic and sympathetic nervous systems, affecting both the electrical signal generation of sinus rhythm as well as the mechanical contractility. But neither the initiation, nor the conduction of the electrical signal that activates the heart involves nervous tissue. Instead, in a normal human heart, a specialized group of myocardial cells at the sinoatrial node (SA node) located at the lateral aspect of the junction between the superior vena cava and the right atrium, spontaneously generate an electric impulse (pacemaker) and establish the sinus rhythm. This electrical impulse is conducted via and this impulse is conducted in non-uniform anisotropic fashion through the atrial myocardium to the atrio-ventricular (AV) node (Figure 1-1: Image depicting the cardiac conduction system.). Having reached the AV node, the impulse is delayed to give atrial contraction the time to fill ventricles before it is transmitted rapidly through the AV conduction axis and the Purkinje network to trigger ventricular contraction from apex to base, thus expelling the blood into the arterial trunks (2). This electrical impulse throughout a cardiac cycle (heart beat) is measured as the Electrocardiograph (ECG) signal.

The mechanics of the heart during a cardiac cycle can be studied by measuring the LV motion during the cardiac cycle, especially that of the left ventricle (LV). The LV exhibits motion in the longitudinal (lengthening), circumferential and radial directions.
There is a thickening and shortening of myocardial wall during systole while the LV cavity also undergoes a twist during this process. The shortening can be measured in terms of longitudinal strain while the thickening can be expressed as circumferential strain. Figure 1-2 shows the radial twist expressed in degrees. The cardiac mechanics and ECG signal variation in the five different cardiac phases are explained in the following section.

Figure 1-1: Image depicting the cardiac conduction system.

The location of the SA node and the AV node marked. The electrical signal originates in the SA node and traverses the atria to the AV node. After a brief delay of 100 ms, it traverses to the right and left ventricle through the Bundle of His and the network of Purkinje fibers.

1.2 The Cardiac cycle

The cardiac cycle that refers to the various changes within the heart in one heart beat can be briefly classified into five phases – 1) Isovolumic Contraction, 2) Systole (Ventricular Ejection), 3) Isovolumic Relaxation, 4) Early Diastole (Ventricular Filling) and 5) Late Diastole. The following sections explain the changes that take place in the LV during each of these cardiac phases within the cardiac cycle. Each section explains the changes that occur in the LV pressure, associated valve opening and closing, changes
in LV volume, changes in the electrical impulse conduction (Electrocardiogram - ECG signal), and cardiac mechanics during each of the respective cardiac phase. The physiological events during the cardiac cycle are often represented in the so-called Wigger’s diagram, shown in Figure 1-3.

1.2.1 Isovolumic Contraction

Isovolumic contraction (IVC) is defined as the part of the cardiac cycle between the closing of the mitral valve and the opening of the aortic valve as the left ventricle gears for ejection of the blood (Figure 1-3). This period is characterized by an increase in LV pressure. As there is no net flow in or out of the left ventricle, the LV volume remains constant during this period. This period corresponds to the QRS wave in ECG signal, corresponding to the transverse of the signal from the AV node to the left and right ventricles (ventricular depolarization). The upslope of the R wave is when the electrical impulse transverses the right ventricle and the down slope is when the signal traverses the left ventricle. As both the valves are closed during this period, the right and left ventricular depolarization leads to the rapid increase in LV pressure, paving the way for ejection of blood through the aortic valve. The normal duration of IVC is around 80 ms.

In normal human heart, the LV motion during IVC includes longitudinal and radial components. With respect to the longitudinal motion, during IVC, the length of LV shortens during this period, corresponding to a negative strain (3). Simultaneously, there is an increase in the negative circumferential strain (radial thickening of LV). Here, a negative strain corresponds to a LV thickening radially. In short, an increase in negative strain leads to an increased LV pressure and to an outflow of blood from the LV (Figure 1-6). During IVC, all regions of the LV rotate counterclockwise when observed from the
apex (Figure 1-5). LV twist shown in Figure 1-5 and the longitudinal and circumferential strains in Figure 1-6 were obtained in human heart using 2D speckle tracking echocardiography (3) (briefly explained in chapter 2).

1.2.2 Systole

After the isovolumic contraction, the LV pressure increases beyond the aortic pressure, leading to the opening of the aortic valve. The opening of the aortic valve marks the onset of ventricular systole. During systole, LV pressure remains higher than the aortic pressure, and LV blood flows out of the left ventricle. When the LV pressure falls below the aortic pressure, aortic valve closes and this marks the end of systole. Electrically, systole comprises of the duration between the QRS complex to part of the T wave.

With respect to cardiac motion, during systole, the base rotates clockwise while the apex continues rotating counter-clockwise creating a wringing effect (Figure 1-5) (4). This is coupled with a longitudinal shortening of basal and apical portions of the ventricle, as well as radial thickening of the LV myocardium, as shown in Figure 1-6. This twisting and shortening occurs over a period of 100 ms after the S wave and constitutes the rapid ejection of blood from the left ventricle.
**Figure 1-3: The Wigger’s Diagram**

*The variation of left ventricular pressure and volume across various cardiac phases is shown. Variations of atrial and aortic pressures as well as ECG changes are depicted. Image Courtesy: http://en.wikipedia.org/wiki/File:Wiggers_Diagram.svg.*

### 1.2.3 Isovolumic Relaxation

Isovolumic Relaxation (IVR) is the time between the closure of the aortic valve and opening of the mitral valve opening following systolic ejection. During IVR, the LV myocardium starts untwisting and lengthening, possibly contributing to the drop in LV pressure. The untwisting of heart occurs predominantly during the IVR, before the mitral valve opening. The apex starts elongating during the IVR period while we see that the base does not start until after IVR.
The LV pressure significantly drops during this period to levels below the left atrial pressure, resulting in the opening of the mitral valve, and culmination of the IVR period. Electrophysiologically, this corresponds to the latter part of the T wave in the ECG. A healthy adult human heart has an IVRT value that’s falls around 80 ms. An impaired relaxation typically prolongs the IVR period. As in the case of IVC, the LV volume remains unchanged during IVR.

1.2.4 Early Diastole

The continued drop in LV pressure to levels below the atrial pressure results in the opening of mitral valve, and marks the onset of early diastole. In early diastole, there is rapid filling of the LV, and increase in LV blood volume. Nearly 70% of atrial blood volume in an adult normal human heart flows to the LV during this passive filling process. The ECG signal is nearly constant during this period, signaling relative electrical inactivity.

The left ventricle untwists back to its pre systolic position during early-diastole, with rapid lengthening. Rapid filling of the ventricle takes place early in diastole and the wall motion subsides during late diastole. The motion becomes negligible during the period leading to late diastole (3) (Figure 1-6).

1.2.5 Late Diastole

Late diastole starts with the end of early diastole, with the LV pressure still trailing the atrial pressure. The mitral valve remains open till the end of late-diastole, when it closes as the LV pressure increases more than the atrial pressure (leading onto IVC). Atrial depolarization (P-wave), and the ensuing left atrial contraction increases the
LV blood volume by about 30% in an adult normal human heart, during late diastole. In contrast to the passive filling of the LV during early diastole, the LV filling during late diastole is often characterized as ‘active filling’. Aging and impaired functioning of the heart increases the percentage of active filling the LV during late diastole (compared to early diastole).

The left ventricle twisting/untwisting is substantially diminished during this phase. The wall motion subsides during late diastole. Some longitudinal lengthening is seen along the left ventricle though the circumferential thickening is minimal. The motion becomes negligible during the period leading to late diastole (3). Figure 1-6 depicts the relevant strain plots with time, showing nearly no significant change in the LV motion.

**Figure 1-4: Illustration of a typical ECG recording.**

*The normal activation sequence of the electrical signal across the human heart after initiation by the SA node is explained here. After the pacemaker signal is generated (just prior to P wave), it traverses through the atrial myocardium to the AV node at a rate of 1-1.2 m/s, within around 150 ms (P wave and partial PR segment). From the AV node, the signal traverses across the ventricles through the His Bundle, Bundle branches and*
the Purkinje network for around 80 ms (just prior to QRS complex). Then the impulse traverses the left ventricle (QRS interval) for approximately 80 ms. Although there exists some correlation between the QRS amplitude and force of ventricular contraction, no significant relationship has been found between them (1).

Figure 1-5: Figure depicting the twist at basal and apical locations of the left ventricle.

**Figure 1-6: Plot of strain vs. time (cardiac phase)**

A plot of strain vs. time depicting the variation of longitudinal (top) and circumferential (bottom) strain of the LV at various locations. A negative strain in the longitudinal direction corresponds with the shortening of the LV and in the circumferential direction, a thickening of the LV. Phase 1, isovolumic contraction; 2, ejection; 3 isovolumic relaxation; 4, early diastole; 5, late diastole. Image Courtesy: Reference (3)

### 1.3 Heart Failure

Heart failure is one of the leading causes of mortality in the United States of America. As of 2007, around 82.6 million people (36.2 %) have some form of cardiovascular disease, 5.7 million people have heart failure and it accounts for more than 560,000 deaths every year (5).

Heart failure is the clinical syndrome accompanying the inability of the heart to maintain a cardiac output required to meet the metabolic requirements and accommodate venous return. It is caused by a loss of critical quantity of functional myocardial cells due
to a number of causes, the important of them being ischemia, hypertension, diabetes, disease of the myocardium and electrical conduction abnormalities (6). The clinical syndrome of heart failure can be initiated by a non-myocardial reason like hypertension or valvular disease or cardiomyopathies such as myocarditis.

1.3.1 Cardiac Imaging for Heart Failure

Primary imaging modalities used to assess the heart (and heart failure) are echocardiogram (echo), Magnetic Resonance Imaging (MRI), x-ray computed Tomography (CT), Single Photon Emission Computed Tomography (SPECT), and Positron Emission Tomography (PET). These imaging modalities are commonly used to assess (7):

1) Cardiac function/ anatomy – systolic and diastolic function

2) Cardiac wall motion mechanics

3) Ischemia of the heart

In general, physiological mechanisms leading to heart failure that can be detected by imaging are:

1) Global and Regional cardiac function: Cardiac LV function, as measured by ejection fraction (EF) and regional wall movement using cine images of the heart. Cine images are a set of images that capture the heart at various cardiac phases, which when played in succession show the motion of the heart beating across one R-R interval. The EF, a measure of global LV function, is calculated as the ratio of stroke volume (difference between end-diastolic volume and end systolic volume) of the heart to the end-diastolic
volume. Regional wall motion abnormalities (dyskinesia or akinesia) are often visually quantified by the physician, using qualitative or semi-quantitative scores. A reduced pumping efficiency of the heart due to various pathologies is reflected as a reduced EF, and an EF < 35 % is considered as an indication for potential pacemaker implantation. Multiple imaging modalities can give a wealth of information about LV function and wall motion mechanics.

2) Changed anatomy of the heart: This is also called ‘remodeling’, where the size and shape of the heart (mainly the left ventricle (LV)) adapts to compensate for its reduced pumping efficiency. This typically manifests as an increase in ventricular wall thickness and cavity size, a change in LV wall motion and a reduction in EF.

3) Coronary Artery Disease (CAD)/Ischemia: Accurate assessment of the reduction in blood flow to the heart muscle (myocardial ischemia) caused by obstruction of coronary arteries is an important clinical need that is met by multiple imaging modalities. Imaging techniques such as multi-detector computed tomography and x-ray angiography often help to visualize the narrowing of the coronary artery lumen due to atherosclerosis, and yield valuable information regarding the cardiac status of a patient. The other major approach is to assess the significance of coronary artery occlusion on the myocardium. In this context, two important physiologic states of the myocardium need to be identified. First, a clear idea about the presence and the extent of any reduction in micro vascular flow to the myocardium can significantly benefit patient management. Such an assessment is called myocardial perfusion measurement. Second, it is also important to understand the presence and extent of myocardial scarring that may be caused by myocardial infarction. This clinical assessment is often referred to as myocardial
viability assessment. In clinical practice, often both these measurements are done together.

An accurate assessment of the LV function (and its related wall motion mechanics) and ischemia is necessary for 1) proper diagnosis of causes of heart failure that can lead to effective treatment of the underlying condition and 2) deciding on the efficacy of treatment during follow-up studies. For example, in the case of non-ischemic cardiomyopathies such as dilated cardiomyopathy (DCM) (8,9), structural and functional changes of the heart yield objective, quantitative information about the underlying disease.

Similarly, in case of prolonged severe ischemia resulting in irreversible myocardial injury due to myocardial infarction, imaging modalities can help understand the exact location and size of the necrosis of the myocardium, which would lead to better treatment strategies. In cases of pacemaker interventions like cardiac resynchronization therapy (CRT), which is performed to treat dyssynchronous wall motion and is needed by around 30% of heart failure patients, an accurate assessment of 1) LV function, 2) LV wall motion mechanics, 3) cardiac scar size and location (if present) is important for performing a successful procedure (10-13), amongst other criteria. A reduced ejection fraction is necessary criterion for CRT while, response to CRT also depends on the site of placement of the pacemaker leads. Multiple studies have shown that the response to CRT depends significantly on the scar burden of the patients (10,11,13-15).
An abbreviated tour of various imaging modalities to assess the heart will be provided in chapter 2, with the aim of providing the reader about the role for MRI in evaluating heart disease.
2 Multimodality Imaging to Visualize LV Function, Wall Motion and Scar

Global and regional LV function (with its relevant wall motion mechanics), myocardial perfusion, and scar burden are often evaluated using imaging modalities such as echocardiography, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine (PET and SPECT). All of them offer relative advantages and disadvantages with respect to cardiac imaging and while some are more suitable for evaluating LV function and wall motion abnormalities; others may be more suitable for imaging scar burden. A brief introduction of all these imaging modalities is presented in this chapter.

2.1 LV Function and Wall Motion Analysis

Cardiac wall motion during the cardiac cycle has been described in detail in section 1.2. To adequately capture the cardiac wall motion, an imaging modality should meet the following requirements: First, the imaging modality should have the ability to resolve the myocardial anatomy with sufficient detail (spatial resolution), (ii) able to separate tissues of different types, e.g., normal and pathologic states of myocardium, with adequate contrast (contrast resolution), and (iii) the frame rate necessary to capture the dynamic motion of the heart with high fidelity (temporal resolution).

Imaging of the left ventricle is often the predominant focus of all imaging modalities because of its crucial role in supplying oxygenated blood to the body, and as a pump expends the most energy within the cardiac cycle (as compared to the right
ventricle and the atria). It is common practice to refer to the failure of the LV pump, as measured by an index such as LV ejection fraction, as heart failure.

An abbreviated list of commonly used imaging modalities to assess LV function and wall motion is listed below.

2.1.1 **Echocardiography**

In echocardiography, a piezoelectric transducer transmits ultrasound waves to tissue. Ultrasound is reflected at tissue interfaces and the intensity of these reflections gives information about the acoustic impedance difference between the layers. Reflected acoustic energy is captured by the piezoelectric transducer, and an image is formed from these measurements.

Various commonly used modes of measurement using echocardiography for assessing LV function and wall motion are.

- 2D echocardiography (Brightness-mode or B-mode)
- M-mode echocardiography
- Tissue-Doppler Imaging
- Speckle tracking
- 3D echocardiography

The various modes of echocardiography and their utility in measuring LV function and wall motion mechanics are described in the following sections. The advantages and disadvantages of the various measured parameters are described in Table 2-1.
2.1.1.1 **B-mode echocardiography**

B-mode echocardiography obtains a spatial sweep of 1D echo to generate a 2D image of the heart. The signal intensity or brightness (hence the name, B-mode) at each location indicates the strength of the reflected signal from that location. Of all the imaging modalities and methods, B-mode echocardiography is the most widely used method for estimation of ejection fraction due to its ease of use, widespread availability, its high temporal resolution (around 6 - 10 ms per cardiac phase) and lower cost (16). The main disadvantage of all ultrasound methods including B-mode ultrasound is the need for appropriate acoustic windows for ultrasound to propagate within the body. In large patients, the depth of penetration of ultrasound may not be sufficient to visualize the lateral wall of the myocardium. Furthermore, at present, B-mode echocardiography is not used for measuring other wall motion mechanics directly. B-mode echocardiography derived imaging methods like Speckle Tracking and 3D-echochocardiography are used for this purpose.

2.1.1.2 **M-mode echocardiography**

M-Mode echocardiography (Time-Motion mode) was one of the early tools in echocardiography. It gives an ice-pick view of the heart, where along the vertical axis a single line of reflected ultrasound signal (commonly referred to as the A-line or Amplitude line) captured by the transducer is plotted as a function of time along the horizontal axis. This motion mode or M-mode, display allows the interrogation of tissue motion at high temporal resolution. Due to the lack of two-dimensional spatial information, this technique is not used for measurement of global LV function metrics such as EF directly.
M-mode echocardiography is commonly used to evaluate the wall motion mechanics by measuring the Septal to Posterior Wall Motion Delay (SPWMD). This is a measure of LV intra-ventricular wall motion abnormality (dyssynchrony). SPWMD measures the time delay between the maximum displacement of the septum and the posterior wall in the left ventricle (from the short-axis view). In a single center study (n = 20), Pitzalis et al. (17) evaluated the clinical utility of measuring SPWMD to predict treatment response in patients undergoing CRT. As CRT is used to treat dyssynchronously beating heart, the authors studied the sensitivity and specificity of SPWMD as a predictor of response to CRT. Responders of the study were defined as those with significant reverse remodeling (an improvement in EF and an increased Quality of Life metrics). This study showed that the CRT responders had a baseline SPWMD = 246+/- 68 ms, while the non-responders had a baseline SPWMD = 110+/-55 ms. A SPWMD > 130 ms was considered as a differentiator between responders vs. non-responders to CRT. The single-center study had a specificity of 63% and sensitivity 80%.

An M-mode display of a subject with significantly long SPWMD is shown in Figure 2-1.
Figure 2-1: A B-Mode ultrasound image of the LV in the short axis orientation

An M-mode display of A-lines obtained across the dotted lines is shown in the bottom panel. Along the vertical axis, each line represents one A-line, capturing the reflected ultrasound. From top to bottom, the anatomical structures reflecting the ultrasound beam are the septal wall, blood pool within the LV, and the posterior wall. The undulations at the septal wall, and the posterior wall reflect the motion of these respective walls during and across the cardiac cycle. A simple measurement of time-delay between the peak contraction of the septum and the posterior wall yields the SPWMD. Image Courtesy: (17)

2.1.1.3 Tissue Doppler Imaging

Unlike B-mode and M-mode images which track the motion of the tissue along two or one spatial-temporal dimensions, Doppler methods measure the velocity of tissue motion using the Doppler principle. Tissue Doppler imaging (TDI) is a commonly used form of echocardiographic imaging and is often used to measure LV wall motion mechanics (17), but not to measure global LV function. It gives the longitudinal velocity along different segments of the left ventricle as a metric quantifying wall motion. The simplest evaluation measures the difference in time to peak velocity of septal and the posterior walls, while other studies compare 6-segments of the short axis or 12 segments
(6 segments in the basal and mid-cavity short axis views). They are represented as Ts-peak (Time to peak systole) or Ts-onset (time to onset of systole), Ts-LS (lateral-septal wall) or Ts-SD (SD of time to systole across 6 segments/ 12 segments). Previous studies have measured each of these metrics and their effectiveness in quantifying wall motion mechanics. These are enlisted in Table 2-1 along with the relative advantages and disadvantages of them. A representative image showing the measurement of peak velocity of the lateral and septal walls is shown in Figure 2-2

![Figure 2-2: Image depicting Tissue Doppler Imaging](image.png)

*The two images on the left show the left ventricle in the 4-chamber view. The top image is the color-coded tissue Doppler image. Regions of interest are drawn on the basal septal and posterior wall, and time to peak velocity is shown. Image Courtesy: (18)*

### 2.1.1.4 3D Echocardiography

Recent advances in echocardiographic hardware, and software methodologies, it is now possible to obtain 3D-echocardiographic images that capture the wall motion of
the entire LV. Using a 2D array of transducers, multiple B-mode images of the heart are simultaneously obtained and stitched together to obtain a 3D view of the heart. It has been shown to be effective in measuring normal LV function (16,19). Though 3DE provides more information about the heart when compared with 2D echocardiography, some reports have found that the 3D-echo technique systematically underestimates LV volumes (20). More studies are needed to establish the efficacy of 3D echocardiography.

For the measurement of wall motion mechanics, the following method is used. The heart (LV) is divided into multiple segments and volume of each segment is calculated across cardiac phases. The standard deviation of the time to minimum volume of each segment is used as a measurement index. If the time difference between various segments is huge, a significant wall motion defect is supposed to exist. But this method suffers from center detection problems (separating the LV into multiple segments) during post-processing of the images. Also, initial studies for measurement of wall motion mechanics were not promising (21-23). Specifically, the inability of 3DE to obtain full views of the heart in some cases, due to either poor image quality, or unavailable acoustic window makes it a difficult modality to obtain wall motion measurements. Its dependency on post processing to accurately quantify LV volume hinders its ability to be used clinically to faithfully reproduce LV volumes (24). Table 2-1 compares the parameter measured and enlists their advantages and disadvantages.

2.1.1.5 Speckle tracking/Strain rate imaging

Ultrasound speckles are artifacts caused by the interaction of a coherent ultrasound beam with scatterers that have a size below the spatial resolution of the imaging method. In echocardiography, as a coherent ultrasound beam scatters of the
heart, a characteristic speckle pattern emerges. The motion of these speckles provides information regarding the motion of the tissue. Therefore, tracking speckles in B-mode images can yield information regarding the regional wall motion, and parameters such as wall strain can be calculated. A time to peak strain across various segments of the heart yields information about any wall motion abnormality that might exist.

The method has been introduced relatively recently and studies are ongoing to compare the efficacy of speckle tracking for evaluation of LV wall motion mechanics. Table 2-1 compares the parameter measured and enlists their advantages and disadvantages. The following representative image shows the functioning of speckle tracking in normal volunteers and patients.

![Image A and B with text](Image)

**Figure 2-3 : Strain imaging using speckle tracking – echocardiography**

The image depicts speckle tracking echocardiography. The image A is for a normal person while the one on right is for a person suffering from heart failure. A significant difference is seen in the time to peak strain between 6 segments of the LV in the short axis. Image courtesy: (25)

<table>
<thead>
<tr>
<th>Echo Technique</th>
<th>Parameters measured</th>
<th>Wall motion mechanics –</th>
<th>Disadvantages</th>
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<table>
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<th>Method</th>
<th>Description</th>
<th>Dyssynchrony classification</th>
<th>Notes</th>
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<td>M-Mode</td>
<td>Septal to Posterior Wall motion Delay, SPWMD in short axis view (17)</td>
<td>SPWMD &gt; 130 ms</td>
<td>- Lower evaluable echocardiograms (71 %)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Lower sensitivity and specificity (~60 %)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Huge Inter and Intra-observer variability (~72%, 30 %)</td>
</tr>
<tr>
<td>Pulsed Doppler</td>
<td>Inter-ventricular mechanical delay (26)</td>
<td>IVMD &gt; 40 ms[3]</td>
<td>- Lower sensitivity and specificity</td>
</tr>
<tr>
<td>Tissue Doppler Imaging</td>
<td>Timing difference between septal and lateral wall (27,28).</td>
<td>Ts-LS &gt; 60 ms</td>
<td>- Prone to angle dependent errors</td>
</tr>
<tr>
<td></td>
<td>SD of time from QRS to peak systolic velocity in ejection phase for 12 left ventricular segments (6 basal and 6 middle) (29)</td>
<td>Ts-SD &gt; 33 ms</td>
<td>- Evaluable echocardiograms – 50%</td>
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<tr>
<td></td>
<td>Maximum difference of time to peak systolic velocity for 6 segments at basal level. (30)</td>
<td>Ts-peak (basal)&gt;83 ms</td>
<td>- Evaluable echocardiograms – 82%</td>
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<tr>
<td></td>
<td>Maximum difference of time to onset of systolic velocity for 6 segments at basal level (30)</td>
<td>Ts-onset (basal) &gt; 67 ms</td>
<td>- Lower sensitivity and specificity 50%</td>
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<td>Delayed longitudinal contraction measured in the 6 basal left ventricular segments with a systolic contraction component in early diastole by TDI and confirmed with strain rate imaging</td>
<td>DLC &gt;2 segments</td>
<td>- Evaluable echocardiograms – 82%</td>
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<td>Real time 3d echo calculation of systolic dyssynchrony index (SDI), which is the standard deviation of 12/16 segment model in the time to minimum systolic segmental volume (23)</td>
<td>SDI &gt; 8% (mean)</td>
<td>- Post-processing dependent/ speckles might be lost through cardiac phases</td>
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<td>Segmental Time Volume Curve quantification based on standard deviation of</td>
<td>STV &gt; 9.2 ml</td>
<td>- 23% improper myocardial delineation</td>
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<td></td>
<td></td>
<td></td>
<td>- Post-processing dependent</td>
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<td></td>
<td></td>
<td></td>
<td>- Need for good acoustic window</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No multi-center trials</td>
</tr>
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</table>
Table 2-1: Echocardiography based parameters for measuring wall motion mechanics.

2.1.2 Magnetic Resonance Imaging

Magnetic Resonance Imaging is a non-invasive method of whole body imaging and is a powerful imaging modality because of its flexibility to generate tissue contrast based on various physical properties. A brief description of the image generation process using MRI is given below. MRI is based on the absorption and emission of energy in the radio frequency range of the electromagnetic spectrum by atomic nuclei (such as $^1$H, $^{31}$P, $^{23}$Na, $^{13}$C) that have an odd number of protons or neutrons; hence possessing a net nuclear spin angular momentum ($I$) and a magnetic dipole moment ($\mathbf{m}$). The magnetic dipole moment and the angular momentum are related by the equation:

$$[1]$$

Where, $\gamma$ is the gyromagnetic ratio, characteristic of the nuclei.

When this nuclei is placed in an external magnetic field of strength $B_0$, a torque ($\mathbf{\tau}$) is exerted on the magnetic moment ($\mathbf{m}$) and is given as

$$[2]$$

From equations [1] and [2], we get

$$[3]$$
This is the so called Larmor equation that describes the motion of a magnetic dipole moment with a spin angular momentum in the external magnetic field. This motion is described as a precession (like a top), and the precessional frequency (Larmor frequency) is given as:

\[ f = \frac{1}{2\pi} \frac{1}{\gamma} \]  

The nucleus of interest in medical imaging is the hydrogen nuclei, due to its abundance in human body (water molecules). MR signal is generated and measured from these nuclei, and the processes of creating a measurable magnetization and creating images out of them (through a process called spatial encoding) is give in the following sections.

In a macroscopic sample, like a gram of water inside a static magnetic field (say 1.0 Tesla), all the protons will align with the external magnetic field in absolute zero temperature seeking the lower energy state. When the temperature increases, thermal motion of the atoms cause the dipoles to occupy two different energy states – one aligned with the magnetic field (lower energy state) and one aligned against the magnetic field (higher energy state). The relative population distribution between the two states is given by:

\[ n_\uparrow = \frac{1}{1 + e^{\frac{\Delta E}{kT}}} \]  

Where, \( k \) is the Boltzmann constant and \( T \) is the temperature of the sample, \( n \) is the number of spins in the given energy state (spin up is the lower energy state), \( \Delta E \) is the
energy difference between the two states ($\Delta E = \gamma B_o$). At room temperature in a 1.0 T field there is an excess of around 6 protons per million in the lower energy state than the higher energy state, leading to a small net magnetization ($M$). $M$ can be defined as the net average magnetic moment per unit volume that precesses at the Larmor frequency determined by the external magnetic field $B_o$. Though this magnetization is not directly measurable (as $M$ is relatively very small compared to $B_o$), it can be transferred to an axis perpendicular to the external magnetic field and be measured. The method for this is as follows: Let the component of $M$ that is present along the main magnetic field be called $M_z$, which is the longitudinal component of magnetization. If another magnetic field $B_1$ that is rotating at the Larmor frequency and is applied orthogonal to $B_0$, then the net magnetization vector is tilted away from the axis of the external magnetic field due to magnetic torque, resulting in a component of magnetization in a plane perpendicular to the main magnetic field. This measurable component of magnetization along this plane perpendicular to $B_0$ is often referred to as the transverse magnetization or $M_{xy}$. Once this $B_1$ field is removed, the resultant transverse magnetization (measured through the receiver coils) decays exponentially through different relaxation mechanisms. The signal measured immediately following an RF excitation is called the Free Induction Decay (FID) (Figure 2-4). The $B_1$ field required to tilt the magnetization is achieved through a radio-frequency (RF) field (a hydrogen proton spins at a frequency of ~43 MHz in 1.0 T magnetic field, corresponding to the radio frequency range). The measured signal is also a RF signal.
Figure 2-4: Free Induction Decay (FID)

*RF signal induced at the receiver coil following excitation from a single type of nuclei. The envelope of the decay (shown in green solid line) shows the exponential decay of the FID.*

The FID is what is measured in NMR spectroscopic measurements, where a spectral analysis of this signal gives information about the chemical composition of a hetero-nuclear sample. But for medical imaging, it is necessary that a 2D image is obtained from a homo-nuclear sample (hydrogen). For this, it is necessary to resolve the spatial location of the hydrogen sample giving the measurable magnetization. This is performed by a process called Spatial Encoding.

**Spatial Encoding:**
This process can be analytically derived from the Larmor equation. Let $\rho(r)$ be the spatial distribution of spins that need to be resolved. Let $G_r$ be a magnetic field gradient along the direction $r$, superimposed over the main magnetic field ($B_0$). From equation [4], the new Larmor frequency is expressed as:

$$\text{[7]}$$

This Larmor frequency is different for spins at different spatial locations. For a linear $G_r$, the time varying RF signal $s(t)$ induced in the receiver coil is the integral sum of all spins precessing at different frequencies. This is given by:

$$\text{[8]}$$

Where,

$$\text{[9]}$$

Equation [8] has the form of a Fourier transform, where $k$ and $r$ (spatial location) are conjugate variables. The temporal integral of the gradient waveform corresponds to the traversal of the conjugate space, often referred to as $k$-space. If data is acquired during such traversal of k-space, then the received temporal signal intensities correspond to measurements at those k-space locations. Therefore, the inverse Fourier transform of the received signal should yield the spatial distribution of spins weighted by their spin density,
Thus MR image formation process consists of 1) creation of a measurable magnetization, 2) spatially encoding the signal and 3) performing a Fourier Transform on the received signal. The above derivations assume that the relaxation effects are not present during acquisition. This is not true as there are two types of relaxation that occur.

**Spin-Lattice Relaxation (T_1 relaxation)**

The energy transfer between the spin system and the surrounding lattice is described by the spin-lattice relaxation (T_1). After a transverse magnetization is created by the B_1 field (RF) and the B_1 field terminated, it has been experimentally found that the net magnetization aligns with the main magnetic field over a period of time, returning back to the thermal equilibrium. The rate at which this happens is called the longitudinal relaxation rate (1/T_1). In other words, T_1 is a measure of time required to establish a thermal equilibrium between the spins and their surroundings.

**Spin-Spin relaxation (T_2 relaxation):**

Immediately after the cessation of the external RF field, all spins tipped to the transverse axis are coherent. But this phase coherence is lost rapidly over time, at a rate denoted by a time constant – T_2. This happens by changes in the static component of the magnetic field – caused either due to intrinsic molecular motion or external magnetic field inhomogeneities (ΔB). The envelope of the FID decays with a time constant given by:

```math
____ \quad ____
```
where $T_2$ is the true inter-molecular relaxation time, and the loss of spin coherence (and signal) due to $T_2$ is irrecoverable.

Contrast between protons within different tissue types can be created by exploiting the different relaxation mechanism of each ($T_1$ and $T_2$ relaxation) tissue type. This is performed by using various pulse sequences for this purpose. Broadly, the pulse sequences can be classified into two types: spin-echo and gradient-echo, based on the way an echo is generated after RF excitation. Cardiac MR imaging mostly uses gradient-echo sequences (that uses a gradient reversal to generate a measurable signal). Briefly, an echo is a measurable signal in the transverse magnetic field generated by an induced phase coherence of the spins with their magnetization tilted (either partially or completely) in the transverse plane.

Typical $T_1$ and $T_2$ values (at 1.5 T) for some tissue types are listed in the following table (Table 2-2). It should be noted that, in general, the $T_1$ relaxation times are on the order of several hundreds of milliseconds, whereas $T_2$ relaxation times are about an order of magnitude lower. Such relaxation rate differences impose some significant constraints in the data acquisition process. For example, the relatively long $T_1$ relaxation times, implies that once a portion or all of the equilibrium magnetization is transferred to the transverse plane, it takes several hundred milliseconds for this magnetization to regain its state of equilibrium before another RF excitation can occur. This period between successive RF excitations for the purpose of spatial encoding is often referred to as the repetition time or TR. Similarly, the relatively short $T_2$ relaxation time imposes an upper limit on the duration over which data acquisition can occur. Representative relaxation curves for myocardium and fat are show in Figure 2-5.
Furthermore, the image reconstruction process assumes a predefined source object magnetization distribution, \( \rho(r) \), that is time invariant. If \( \rho(r) \) varies during the acquisition process, then the reconstruction assumption is violated, and results in image artifacts. This is particularly important in the context of cardiovascular imaging, where the object of imaging - the heart - is in constant motion due to respiration, and cardiac pulsation.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Tissue</th>
<th>( T_1 ) (ms)</th>
<th>( T_2 ) (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Myocardium(31)</td>
<td>950</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>Blood(32)</td>
<td>1300</td>
<td>100 (Venous)/200 (Arterial)</td>
</tr>
<tr>
<td>3</td>
<td>Fat(32)</td>
<td>280</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Liver(32)</td>
<td>650</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Grey Matter (32)</td>
<td>950</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>White Matter (32)</td>
<td>650</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 2-2: Representative proton \( T_1 \) and \( T_2 \) relaxation values of various tissues at 1.5T.
Figure 2-5: T1 and T2 Relaxation of myocardium and fat.

Representative T1 and T2 relaxation curves for myocardium and fat are shown in figures (A) and (B) respectively. The regrowth of the longitudinal relaxation ($M_z$ normalized to the magnetization at thermal equilibrium - $M_o$) is shown as a function of the repetition time (TR), following a RF pulse ($90^\circ$) that has tilted all initial magnetization to the transverse plane. The corresponding decay in transverse magnetization ($M_{xy}$, normalized to $M_o$) is shown in figure (B), immediately following a 90° flip angle, as a function of the echo time (TE). Note that the transverse decay happens much faster than the longitudinal relaxation ($T_2<T_1$).

Specific Challenges of Cardiac MR:

Unlike the MR imaging of static structures such as the brain, spine, and the musculo-skeletal system, MR imaging of the organs of the thoraco-abdominal cavity, heart in particular, introduces some significant hurdles. As the T1 relaxation time of most soft tissues is on the order of several hundred seconds, conventional Fourier transform MR of the heart with sufficient spatial resolution using even fast imaging methods often lasts several seconds. In the case of cardiac imaging, there is substantial motion due to respiration and cardiac pulsation. As a result, special strategies need to be incorporated to combat the detrimental effects of motion cardiac MRI.
1) **Respiratory motion:** A commonly used strategy to minimize respiratory motion induced artifacts is the use of breath-holding in conjunction with rapid scanning methods. But this leads to a limited scan time of around 10 seconds per scan (a typical breath-hold capacity of patients) acquisition. If longer scans are required, then respiratory compensation techniques such as navigator guided acquisition can be used. In brief, a respiratory navigator is a one-dimensional MR acquisition method that tracks the movement of diaphragm during acquisition (free breathing). In these techniques, this real-time information about the respiratory phase is used to guide the acquisition. In one commonly used implementation, data is acquired during every heart beat, and this data is used for image formation, if this data was acquired during a pre-defined phase of the respiratory cycle, e.g., end-expiratory phase. If this data was acquired during any other part of the respiratory phase, the data is rejected and reacquired. Several such respiratory motion compensation strategies have been proposed in the literature.

2) **Cardiac pulsation:** Cardiac pulsation results in significant amount of motion during the cardiac cycle. The heart motion is quite significant during systole, and is substantially diminished during diastole. As a result, by using appropriate ECG gating, the data acquisition window can be synchronized to occur during diastole. This technique is quite useful for obtaining anatomic or morphologic views of the heart. For visualizing the dynamic motion of the heart using cardiac cine MRI, there are additional considerations. For example, given that the systolic motion of the heart is quite significant, a temporal resolution on the order of 50-60 ms is often necessary to adequately capture the motion of an adult heart. This limit translates to an imaging frame rate of 15-20 frames per second (fps). The development of rapid imaging methods has
greatly helped to meet the unique challenges associated with cardiac MRI. In particular, parallel imaging methods such as SENSE (Sensitivity Encoding) and \( k-t \) BLAST (spatial frequency (k)-temporal frequency (t) Broad-use Linear Acquisition Speed-up Technique), enable flexible exchange of imaging speed with signal-to-noise ratio without compromising spatial resolution. SENSE (33) uses advanced coil hardware (32 channel coils) to shorten imaging time by exploiting the spatial redundancy of data observed by multiple coils. \( k-t \) BLAST(34) exploits the redundancy of information along the spatio-temporal domain.

Table 2-3 details the MR based parameters measured for quantification of LV function and wall motion mechanics. Each parameter and the acquisition technique are explained in detail in the following sections.

2.1.2.1 Cine Wall Motion Analysis

Cardiac cine MRI is considered as the gold standard for the measurement of global LV function, i.e., EF measurement (16). Cardiac cine MRI captures the motion of the heart across various points during the cardiac cycle. The basic MR acquisition module consists of a fully refocused gradient echo method (steady state free precession, or SSFP) with a very short TR and TE. Using the cine SSFP technique, images of the heart can be captured at temporal resolutions on the order of 30-50 ms under suspended respiration(35). This sequence provides excellent contrast between myocardium and blood. Multiple, contiguous, two-dimensional images of the LV in the short axis orientation (of thickness ~ 8mm) are obtained. Breath-held scans (to reduce motion related artifacts) of around 8 seconds are acquired per scan are performed yielding a conventional temporal resolution of around 35 - 40 ms. For the estimation of LV
function, the cardiologist draws manual contours around the blood pool in the short axis view for every slice. This is done for both the end-systolic phase and end-diastolic phase to calculate the LV volume. From this the volume at end-diastole (EDV) and end-systole (ESV) are calculated, and ejection fraction is quantified.

For LV regional wall motion analysis, conventionally, the cardiologist draws the endocardial and epicardial boundaries manually. From this, radial cords are drawn, as shown in Figure 2-6. The cord length across the LV is tracked through time, with the length of the cord between the endocardial and epicardial boundary yielding the thickness of the myocardial wall. If this cord is displayed across the cardiac cycle, one can obtain an M-mode like image. The high soft-tissue contrast of the SSFP cine imaging method allows one to estimate the time to peak contraction of various segments of the LV. The standard deviation of the time to maximum contraction between various wall segments of the LV can be used as an index to quantify dyssynchrony. As an example, one method called Tissue Synchronicity Imaging (TSI) estimates a measure of dyssynchrony between the segments of the LV by estimating the cross-correlation of the radial motion of various segments of the LV wall with each other(12).

The advantages and disadvantages of the parameters based on this method are shown in Table 2-3. Figure 2-6 describes a wall motion analysis technique similar to M-mode in echocardiography that tracks the LV wall motion across cardiac phases. A dyssynchronously beating heart exhibits a lower peak strain with no clear pattern of contraction/relaxation.
Figure 2-6: LV wall motion analysis using cardiac MR cine imaging

The image describes cine wall motion imaging. The left images (A and B) shows the LV with (A) being a normal heart and (D) being a dyssynchronously beating heart. Cords (in green) drawn radially in myocardium gives radial motion along the cord. The graphs in the middle (B) and (E) describes the radial wall motion for (A) and (D). The plots on the right (C and F) show the variation of peak strain across all cardiac phases. A lower peak strain with a varying strain pattern across cardiac phases symbolizes dyssynchrony between wall motions of opposing LV segments. The data is from St. Luke’s Episcopal Hospital, Houston, Texas.

2.1.2.2 Phase Velocity mapping

Similar to the Doppler ultrasound method, phase velocity mapping method in MR measures the velocity of any tissue motion. It is based on the principle that MR signal emanating from spins that moving under the influence of a bi-polar gradient with zero net area can be manipulated to yield a net phase shift when compared to stationary spins. By varying the gradient strength, different types of motion (with varying velocity) can be calculated. This method is conventionally used to calculate the flow velocity and pattern of blood through the vascular system. By using sufficiently high gradient strength, this method can be extended to measure the velocity of tissue, like myocardium. During a
complete heart beat, the net phase of each pixel (at a given phase) gives a measure of the velocity of the individual proton spin.

Figure 2-7 shows a phase-contrast mapped velocity image. For a dyssynchronously beating heart, variations in the time to peak velocity exists between the lateral and septal wall that is significant. Also cross-correlation of the motion between various segments can be performed. Any variation in time of peak velocity between various segments that is greater than 31 ms yields a differentiation of normal volunteers from patients (36). Table 2-3 describes this in detail.

![Figure 2-7: Phase-contrast velocity mapping using MRI](image)

*The image on the left shows the phase-velocity mapping of a healthy volunteer in the 4 chamber view. The plot on right shows the longitudinal velocity obtained from the phase-mapped images, from two regions of interest (ROI) placed on the septal and lateral wall at the basal location. Note that there is not a significant dyssynchrony between the two walls. Image courtesy: (36)*
2.1.2.3 Tissue Tagging

Tissue tagging is a unique MR technique where the tissue of interest is first tagged magnetically and the tag deformation is studied with time. It is used to study the cardiac motion. Zerhouni et al. (37) first described the use of MR tagging to study regional myocardial motion. Tagging involves saturation of magnetization planes perpendicular to the imaging plane using preparation pulses that are applied prior to acquisition. This creates lines of hypo-intensity within the image. The cardiac tissue with this initial magnetization remains hypo-intense throughout the cardiac cycle. Thus, tracking this tag line deformation with time allows for quantification of the underlying myocardial displacement. The initial tagging methods suffered from fading tag lines which reduced the usability of the tags throughout the cardiac cycle (38,39). Improved acquisition methods have led to faster acquisition of MR tagging (40).

Enhanced tagged-MRI methods and sequences including spatial modulation of magnetization (SPAMM) have allowed for faster acquisition time and improved tagged quality (40). However, two-dimensional (2D) myocardial tagging is limited in that it does not account for the 3D motion of the heart and spatial resolution is constrained by tag line density. Furthermore data processing of the tags is complicated even after recent developments (41). Table 2-3 further discusses the advantages and disadvantages of the parameters based on this method. Figure 2-8 depicts a tagged cardiac LV short axis image obtained from a normal human heart.
Figure 2-8: Tagged LV short axis image

Images showing cine tagged short axis slice of the LV and RV across cardiac phases (Increasing cardiac phase, every 40 ms, from right to left, top to bottom) from an asymptomatic person. The tags undergo deformation with the motion of tissue, from which strain can be calculated after post-processing the tag data. Also, note that the tags fade with the cardiac phase, as the tagging pulse is applied at the start of every heart beat.

<table>
<thead>
<tr>
<th>MR Technique</th>
<th>Parameters measured</th>
<th>Wall Motion Mechanics/ Dyssynchrony classification</th>
<th>Disadvantages</th>
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<tbody>
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<td>Cine Wall motion</td>
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<td>CMR-TSI &gt; 40 ms</td>
<td>• Manual contour drawing;</td>
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<tr>
<td></td>
<td>• a =mean segmental radial motion;</td>
<td></td>
<td>• Ignoring through plane and circumferential movement. (But heart twist &lt;5° at base and &lt; 10° at apex. Also circumferential strain dominates longitudinal strain (studied in canine heart model)</td>
</tr>
<tr>
<td></td>
<td>• b = sinusoidal segmental wall motion;</td>
<td></td>
<td>• Assumption of radial sine motion.</td>
</tr>
<tr>
<td></td>
<td>• c = phase shift between various segments of the</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2-3: Summary of MR based wall motion mechanics quantification

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Phase velocity mapping</td>
<td>Cross-correlation delay (XCD). Correlation of the velocity of basal myocardial opposing segments (36)</td>
<td>XCD &gt;31 ms</td>
<td>• 10 normal/ 10 heart failure patients – small study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Long scans/respiratory motion.</td>
</tr>
<tr>
<td>Tagging</td>
<td>Time to onset of contraction, Time to peak contraction (Calculated with respect to circumferential strain using 2D CSPAMM technique) (42)</td>
<td>No significant study done differentiating normal and Dyssynchronous patients</td>
<td>• Complex post-processing.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Not proper validation done.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Effectiveness of dyssynchrony based measurements (Time based)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>questioned (40).</td>
</tr>
<tr>
<td></td>
<td>Coefficient of Variation (CV), Difference in Septal to Lateral Circumferential Strain</td>
<td>Better than Time to onset and peak. Correlation done with dP/dt study.</td>
<td>• Small study. Low correlation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CURE (Circumferential Uniformity ratio index)/TUS (Time Uniformity Index)(43)</td>
<td>0-1; 0- dyssynchrony; 1- synchrony. (&lt;0.75 for dyssynchrony)</td>
<td>• Canine model studied</td>
</tr>
</tbody>
</table>

2.1.3 Computed Tomography (CT)

X-ray computed tomography (CT) is widely used for cardiac imaging, especially for the visualization of coronary arteries, aided by the superior spatial resolution of CT when compared to MRI or echocardiography. Though estimation of LV function using CT can be accurate, retrospectively gated acquisitions are necessary for obtaining a higher temporal resolution. Such an acquisition can impose significant ionizing radiation burden (around 16 mSv per patient) (16).
Also, for the estimation of LV wall motion mechanics, the main disadvantage of CT is the exposure to ionizing radiation. Even with the advent of multi detector technology, which significantly reduces the radiation exposure (sub mSv per scan using a 128 element detector) (44), the risk of ionizing radiation increases with an increased temporal resolution. As per our knowledge (from extensive search using pubmed – on September 15, 2012), there have been only two studies till date which analyzed the ventricular wall motion abnormality using CT (45,46). The acquired temporal resolutions for these studies are 150 and 60 ms, which are at the lower end of temporal resolution compared to MRI and echocardiography, thereby affecting the detection of any wall motion abnormality. Previous studies show that CT also exhibits a lower sensitivity in visualizing mild hypokinesis of the myocardial wall when compared to echocardiography or MRI (47). For these reasons, CT is currently not used for the study of cardiac wall motion analysis.

2.1.4 Nuclear Medicine

Nuclear medicine broadly comprises of single photon emission computed tomography (SPECT) and positron emission tomography (PET). In cardiovascular imaging, nuclear medicine is mostly performed for the estimation of myocardial perfusion (MPI). Both SPECT and PET use photon (gamma radiation)-imaging techniques with gamma cameras, from which 3D images are produced. SPECT imaging uses a photon emitting radioisotope injected intravenously into the blood stream using radioligands that bind to specific tissue. For example, when the radioisotope technetium-99m is attached with the ligand methoxyisobutylynitrile (called Technetium ($^{99m}$Tc) Sestamibi), it targets the myocardium. The myocardial uptake of Technetium ($^{99m}$Tc)
Sestamibi is proportional to the myocardial blood flow, and hence this technique is widely used for myocardial perfusion imaging (MPI) (48).

PET imaging is similar to SPECT, except that it uses a positron emitting source instead of a gamma source. It also has a radioisotope and a radioligand. For example, $^{18}\text{F}$ is used to label de-oxy glucose to produce FDG (fluoro-deoxy glucose) which is taken up by any cell that has a heavy glucose usage (for example - brain, cancer, and myocardium).

PET imaging has the following advantages over SPECT imaging. SPECT imaging has a lower spatial resolution of around 6-10 mm, and is also affected by attenuation artifacts. PET systems are more sensitive than SPECT systems due to a higher count rate of photons, and offer the possibility of attenuation correction using the coincidence of detection of the gamma rays travelling in opposite direction by the cameras. But PET imaging suffers from a higher cost, compounded by the fact that some of the clinically used radioisotopes have short half-life from the time of production from the cyclotron (49).

Though nuclear imaging is very relevant for the detection of myocardial perfusion defects, its spatial resolution (6 – 8 mm) and temporal resolution (typically 8 or 16 images per cardiac cycle) makes the identification of LV function and wall motion abnormality challenging when compared to the other modalities (echocardiography, MRI or CT). The current methodology involves measuring the photon count per frame at any specified area of the heart, and linearly correlating it with wall thickness, to obtain the wall thickness (50).
Also, the higher dosage of radiation per SPECT or PET scan (3-6 mSv per scan) adds to the risk of radiation (48,50). For these reasons of lower spatial resolution, lower temporal resolution and ionizing radiation, nuclear medicine is also generally not widely used clinically for LV function and wall motion mechanics assessment.

2.1.5 Summary of Current Metrics of Measuring LV Function and Wall Motion

This section compares the metrics obtained by using echocardiography and MRI, as the other imaging modalities do not currently provide comparable metrics to qualify and quantify LV function and wall motion mechanics for varying reasons already described. Though their physics are different, MRI and echocardiography measure the same parameters for quantification of wall motion mechanics. They measure either the time to peak contraction or the absolute values of the metric, and a criterion is established for distinguishing people with dyssynchrony from others. Figure 2-9 describes this pictorially.
Some of the disadvantages of the current metrics used are:

- Metrics based on displacement measurement are faster, while they do not track the tissue and might lose critical data regarding wall motion. Reports have suggested that M-mode echocardiography suffers from poor SNR and huge inter-observer variability (see Table 2-1).
- Metrics quantifying wall motion based on velocity measure only the longitudinal component of LV motion (in the case of echocardiography), ignoring the circumferential twist and contraction. A previous study has shown that the circumferential motion is higher (strain) when compared to longitudinal motion (41). Unlike ultrasound, MRI permits the evaluation of all components of the
velocity vector, it is time consuming, and is not often performed in routine clinical practice.

- The *strain* based measures in echocardiography are based on TDI or Speckle tracking. Measurements from TDI are prone to angle-dependent errors, while speckle tracking suffers from the poor SNR of m-mode imaging. MRI based measures necessitate a somewhat more involved post-processing tools. Furthermore, the temporal resolution of MR based methods is somewhat inferior to echocardiographic methods.

- The current method based on *volume* measurement is Segmental Time Volume (STV). Volume measurement serves as a surrogate to all the above said metrics as a change in the filling pattern of the left ventricle corresponds to a change in either or all of the above said metrics. Currently 3D Echocardiography is used for this purpose. The high temporal resolution of acquisition is an important advantage while the poorer SNR (with respect to other imaging modalities), dependence on operator and the post-processing software are significant disadvantages of this method.

This section described the key imaging methods for the evaluation of global and regional LV function. Another key aspect of cardiac imaging is the evaluation of myocardial scar, which will be described in the next section.

### 2.2 Viability (Scar Burden) Assessment

Non-invasive assessment of myocardial scar is an essential part of comprehensive cardiovascular evaluation in patients. Until recently, radio-pharmaceutical based methods have been predominantly used for evaluating myocardial viability in clinical
practice. However, recent advances in MRI have made it a method of choice. Some recent studies have highlighted promising approaches using echo and x-ray computed tomography. In this section, there will be a brief overview of the relative merits of these competing imaging approaches.

2.2.1 Echocardiography

There are two approaches for evaluating myocardial scar using echo. The widely used method is stress echocardiography, in which the contractility of the myocardium to progressively increasing levels of stress (physiologic or pharmacologic) is assessed using echocardiography. In simple terms, the information from the stress echo is interpreted as follows. If a dysfunctional segment at rest continues to remain dysfunctional at progressively increasing stress levels, then the segment is evaluated as non-viable. On the other hand, if the dysfunctional segment at rest demonstrates some functional recovery at low dose levels, but has worse function at high dose levels, then the segment is classified as viable. In clinical practice, this test is often augmented with the addition of echo contrast agents, e.g., bubbles, to visualize LV blood pool, and with tissue harmonic imaging to better visualize the myocardium. For an extensive description of the current guidelines for performing stress echocardiography, please refer to Douglas et al (51) (2011 ASE echo guidelines). The usage of 2DSE for identification of myocardial viability suffers from the same disadvantages of 2D echocardiography – namely poorer SNR and poorer acoustic window. As 2DSE depends on detection of wall motion abnormalities, the poorer SNR of 2D echocardiography hampers its widespread usage. Contrast enhanced (micro-bubbles) echocardiography might help visualize the wall
motion better, but the higher number of contra-indications for the contrast agent makes its widespread usage improbable currently (52,53).

Another approach to visualize myocardial scar using echo has been recently described, which attempts to visualize the scar as regions of hyperechoic signal in 3D echocardiography in conjunction with echo-contrast administration. As of September 2012, few studies have been performed to evaluate myocardial scar using echocardiography. A recent study involving 3D echocardiography compared hyper echoic signals from LV scar with Delayed-Enhanced cardiac Magnetic Resonance Imaging (54) and found a generally good correlation of scar sites and transmurality between echocardiography and MRI images. But, the presence of septal stripes and probe angle resulted in false positives, and a substantially lower sensitivity (48 %) of detection of scars in posterior, lateral and septal regions of the LV. Also, the hyper intense echo signals from the scar region are generated only for a chronic myocardial infarction which has a higher deposition of collagen fibers as well, making the visualization of scars less than a few months old significantly difficult. Alternatively low dose stress testing using 2D echocardiography (2DSE) is used as a surrogate to assess regions of viability, though it is pre-dominantly used for the estimation of ischemic regions of myocardium (55).

2.2.2 Magnetic Resonance Imaging

Areas of scaring and fibrosis have an increased extracellular space when compared to normal myocardium in both acute and chronic myocardial infarction. In the acute setting, the myocellular membrane integrity is lost and there is a transient increase in the extra-cellular space. In the chronic setting, the regions of scar or irreversible injury
have increased deposition of collagen fibers, and a resulting increase in extra-cellular space. The contrast agent kinetics of extra-vascular contrast agents such as Gadolinium chelates is different in these irreversibly-injured scar regions compared to regions of normal myocardium. The differences in the extra-cellular space between normal myocardium and irreversibly injured myocardium, as well as the difference in the contrast-agent kinetics are exploited in the so-called delayed-enhancement MRI (DE-MRI) method to visualize regions of scar. The mechanism of contrast generation between normal and irreversibly injured myocardium in the delay-contrast enhanced cardiac MRI (DE-MRI) technique is as follows. In regions of irreversible injury, both the wash-in and wash-out rates for commercially approved extra-vascular contrast agents such as gadolinium-chelates are slower compared to normal myocardium. In addition, the distribution volume available for gadolinium-chelates is larger in scar tissue than in normal myocardium (56). As a result, there is greater accumulation of gadolinium-chelates in regions of irreversible injury following contrast administration. DE-MRI technique exploits this differential accumulation of gadolinium chelates to generate contrast between normal myocardium and scar. It uses a gradient echo sequence.

DE-MRI method provides valuable prognostic information that can aid the clinical management of patients, and is very reproducible (57-61) As a result, DE-MRI has found widespread acceptance and is routinely used in clinical practice (59). Delayed Enhanced cardiac Magnetic Resonance Imaging is currently considered the gold standard for the visualization and estimation of scar burden in the LV (62,63). This is one of the more useful clinical applications of cardiac magnetic resonance (CMR).
2.2.3 X-ray Computed Tomography

X-ray Computed Tomography is extensively used for the imaging coronary artery stenosis and for the assessment of coronary artery disease. But for myocardial viability assessment, the utility of cardiac CT is yet to be proven. There have been few reports studying the assessment of myocardial scar using CT, especially due to its poor CNR between myocardium and non-viable tissue, and radiation dose exposure. Earlier reports had a high radiation dosage and were academic in nature. But recent advancements in CT have made sub-mSv radiation dose per scan possible for viability study. A recent study by Goetti et al (44) that used such a scanning methodology used contrast-enhanced (iodine) CT scans to detect the hyper-intense myocardial scar and compared the results with MRI. Though it had a much higher specificity, the per segment scar identification sensitivity of CT was poorer in comparison to MRI, and CNR between myocardium and scar is significantly higher for MRI. Other studies have showed good correlation between CT and DE-MRI for identification of transmural scar. Further technical advancements and large scale studies would give CT the potential to assess myocardial scar.

2.2.4 Nuclear Medicine

Nuclear medicine – SPECT and PET are predominantly used for perfusion imaging, as explained in the earlier section. However, their ability to differentiate viable tissue from non-viable tissue suffers from their poorer spatial resolution. Studies have shown that when compared to MRI, SPECT underestimates the detection of sub-endocardial scars (64-68), and is also affected by imaging artifacts in cases of severe LV dysfunction. MRI has started gaining acceptance as the method of choice for the assessment of chronic myocardial scars, given its high sensitivity in identifying the
smaller sub-endocardial scars. This has already been shown to be necessary for the placement of the excitation leads in the LV for CRT.

2.2.5 Summary of Current Modalities Imaging LV Scar

It can be seen that all the imaging modalities have an ability to assess and quantify LV scar. In the past, nuclear imaging has been extensively used for the assessment of non-viable myocardial tissue. Large outcome trials had earlier shown that nuclear medicine had a considerably good sensitivity and specificity for the identification of viable myocardium, and the prognosis of patients with a high percentage of viable myocardium, as assessed by nuclear medicine was very good, with a annual mortality rate of <1 % for those with greater than 50 % viable myocardium.

One of the primary reasons for DE-MRI not being widely used currently is the lack of large clinical outcome studies. But the recently published CE-MARC and MR-IMPACT (64,67) studies that compared the performance of MRI and nuclear imaging point towards a significant advantage of MRI in identifying viable and non-viable myocardium with respect to its sensitivity and specificity. This has given an additional impetus for the usage of DE-MRI for the assessment of LV scar.

2.3 Comparison of Multiple Imaging Modalities

This chapter has discussed the importance of imaging LV function, wall motion and scar burden. This section briefly summarizes them and also discusses the desired features necessary for assessing LV function, wall motion and scar, and where each imaging modality stands with respect to attaining the desired features.
2.3.1 LV Function and Wall Motion Mechanics

As stated previously, the key requirements for a CMR imaging modality are adequate SNR in a reasonable scan time, CNR between the myocardium and neighboring tissues (blood and fat), and sufficient temporal resolution to monitor dynamic phenomena associated with cardiac pulsation, blood flow, and respiration.

Table 2–4 lists how each modality performs in each category. The qualification of how well an imaging modality performs is listed as one of the following three categories: poor, acceptable, or good. It can be seen that every imaging modality has its own strength when compared to others. It can be seen that all the imaging modalities have something to be desired with respect to estimation of LV function and wall motion mechanics. For example, echocardiography lags from poor SNR and its dependence on operator efficiency and post-processing software, while MRI lacks from its poorer temporal resolution (w.r.t. Echo) and relaxation and cardiac motion related artifacts. If MRI can be extended to provide a higher temporal resolution image with less complex post-processing involvement, it can successfully alleviate some of the challenges it faces in performing an efficient LV function and wall motion analysis.

<table>
<thead>
<tr>
<th>Desired imaging Feature – wall motion</th>
<th>Echo</th>
<th>MRI</th>
<th>CT</th>
<th>Nuclear Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR</td>
<td>Acceptable</td>
<td>Good</td>
<td>Good</td>
<td>Acceptable</td>
</tr>
<tr>
<td>CNR (with or w/o contrast)</td>
<td>Acceptable /Good</td>
<td>Good</td>
<td>Good</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Temporal Resolution</td>
<td>Good</td>
<td>Acceptable</td>
<td>Poor</td>
<td>Poor</td>
</tr>
</tbody>
</table>
2.3.2 Scar Burden Assessment

As with the function and wall motion assessment, this section lists out the relative merits of each imaging modality in its ability to assess scar burden. As discussed in detail before, DE-MRI performs better than other imaging modalities in imaging scar burden and is currently considered the gold standard for reliable estimation of scar burden. Table 2-5 lists the comparison between different modalities with respect to scar/viability assessment.

<table>
<thead>
<tr>
<th>Desired imaging Feature – Scar Burden</th>
<th>Echo</th>
<th>MRI</th>
<th>CT</th>
<th>Nuclear Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR</td>
<td>Poor</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>CNR (with or w/o contrast)</td>
<td>Acceptable/Good</td>
<td>Good</td>
<td>Acceptable</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Spatial Resolution</td>
<td>Acceptable</td>
<td>Acceptable</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Poor</td>
<td>Good</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Specificity</td>
<td>Acceptable</td>
<td>Good</td>
<td>Acceptable</td>
<td>Good</td>
</tr>
</tbody>
</table>

Table 2-5: Performance of various imaging modalities for estimation of LV Viability
2.4 Other advantages offered by MRI

Table 2-4 and Table 2-5 make a convincing argument for using MRI as the modality of choice for estimating scar burden. In addition to the above listed reasons, MRI offers the following intrinsic advantages for cardiac imaging.

- **Superior Soft-tissue contrast:** Among all imaging modalities, soft tissue contrast is greatest with MRI and is most versatile. For example, in bright blood cine imaging the blood to myocardial contrast is very high, with blood being much brighter than myocardium. With simple addition of magnetization preparation pulses, the blood signal intensity can be nulled (made dark), and one can make the myocardial signal intensity brighter than the blood. Such flexibility of contrast manipulation is an essential advantage of MR that is not available to other imaging modalities. Such a high soft-tissue contrast and the flexibility of contrast manipulation may lead to more robust tools for semi-automated and automated image processing methods. This yields itself to the faster automated estimation of LV function, better specificity for identification of scar tissue, among other applications.

- **Unrestricted Field-of-View (FOV):** An accurate visualization of the anatomy of the patient to be imaged with no restrictions of acoustic windows, as with echocardiography.

- **Visualization of Coronary Sinus:** In the event of CRT, the coronal sinus can be imaged properly, that would help with the placement of CRT leads transvenously. Currently, CT provides a better visualization inherent to its superior spatial resolution.
• **Visualization of ischemic regions:** MRI is gradually being accepted in the clinical community for its ability to visualize ischemic regions of myocardium (other than scar) by studying perfusion changes in myocardium during a pharmacologically induced stress test.

The primary limitations of MR as a CMR imaging modality are as follows. First, compared to echo, MRI is relatively expensive, requires significantly higher technical expertise, contra-indicated in patients with non-MR compatible implants, and for claustrophobic patients. A study conducted by Bruder et. al (69) (for the European Cardiovascular Magnetic Resonance Registry) with more than 11000 patients concluded that 86% of patients who had MRI did not require any further imaging. The same study stated the images were of diagnostic quality in 98% of the cases. This represents a significant value proposition when considering the expense of the procedure. Another main disadvantage of MRI is its absolute contra-indication for patients with pacemaker, making it difficult to follow-up on patients with pacemakers. But recent pacemakers are designed to be MR safe (70), and is in the process of clinical acceptance.

In summary, while MR offers the possibility of comprehensive evaluation of cardiovascular disease, there are some significant handicaps, if addressed could lead to wider clinical acceptance of CMR is a clinical tool. In specific, at present the temporal resolution of CMR is too low to permit routine evaluation of both systolic and diastolic function. Furthermore, in clinical practice, many MR imaging methods are sensitive to arrhythmias. Making these MR imaging techniques less sensitive to arrhythmias would
permit the development of high resolution MR imaging techniques. The purpose of this thesis is to address some of these current limitations of MR.

3 Specific Aims

The objectives of this thesis are to develop suitable MRI imaging and post processing methods to improve cardiac MR imaging. It should be able to:
1) Characterize systolic and diastolic LV function accurately (at higher temporal resolution),

2) Yield a comprehensive set of parameters quantifying regional LV wall motion mechanics, and

3) Accurately delineate the presence of scar tissue in people with myocardial infarction in the presence of arrhythmias

Based on these objectives, the thesis statement is listed below.

3.1 Thesis Statement

It is possible to perform an improved assessment of the heart using MR imaging of the LV that can provide more and better information about 1) the LV function and wall motion mechanics and 2) the scar burden and location in the myocardium.

Based on the thesis statement, the specific aims and their motivations are enlisted in the following sections. The thesis is explained using two specific aims, with the first specific aim dealing with the methodology developed in acquiring better LV function and second aim dealing with better information about scar burden and location of the myocardium.
3.2 Specific Aim 1 – Assessment of LV function using high temporal resolution

This specific aim deals with obtaining high temporal resolution cardiac MR cine images and processing the data to generate LV volume across all the cardiac phases. This objective has been further described in five parts.

3.2.1 Specific Aim 1.a – High temporal image acquisition

The first part of the first specific aim is to design suitable MR imaging protocols and utilize state of the art MR hardware, to obtain high temporal resolution cine images of the heart.

3.2.2 Specific Aim 1.b – Image processing – Slice volume extraction

The second part of the first specific aim is to adapt and develop an image processing algorithm that would automate the process of endocardial boundary segmentation, yielding time-volume curve (variation of volume across all cardiac phases of the slice of interest), with minimal user interference.

3.2.3 Specific Aim 1.c – LV volume modeling

The third part of the first specific aim of this project is to obtain time-volume curve across the entire LV with minimal number of projections such that the human subject experiences negligible discomfort during the imaging procedure.

3.2.4 Specific Aim 1.d – LV function metric acquisition

The fourth part of the first specific aim involves numerically processing the time-volume curve of the LV (volume of the LV across all cardiac phases) and obtaining suitable LV
functional metrics that might identify and quantify LV function and wall motion mechanics.

3.2.5 Specific Aim 1.e – Temporal Analysis to analyze the effect of temporal resolution

The fifth part of the first specific aim involves studying the effect of temporal resolution on the obtained metrics quantifying LV function and wall motion.

3.3 Specific Aim 2 – Improved Scar Burden Assessment

The second specific aim of this project is to develop the theoretical basis, implement and validate a DE-MRI technique that is insensitive to arrhythmias so as to permit clear delineation of scarred regions. This aim involves changing the pulse-sequence of MR imaging acquisition to perform a real-time correction of arrhythmia induced imperfections.

3.4 Motivation for specific aim -I

3.4.1 MR Cine imaging for LV function/ Wall Motion Mechanics

MR cine imaging, as explained in chapter 2, has become the gold standard for estimation of LV global systolic function (explained in Chapter 1) because of its superior SNR and contrast between LV myocardium and blood. The global ejection fraction is a reflection of the systolic functioning of the LV, while information on diastolic functioning as well as wall motion mechanics remains missing. Cine cardiac imaging
provides information of the volume filling pattern of nearly the entire cardiac cycle while only two time points (end-diastole and end-systole) are used for global ejection fraction estimation. Knowledge of diastolic function (that reveals the relaxation of the LV) is important as it is one of the common causes of heart failure (around 40-50 % of all heart failure) (71). Also, a detailed analysis of LV systolic and diastolic function also conveys more about the LV wall motion mechanics - previous studies using SPECT and radionuclide ventriculography have clearly established that sub-optimal LV wall motion mechanics (leading to a dyssynchronously beating wall) causes suboptimal filling of the LV – decreases the LV filling time, increases the isovolumic contraction time, increases the LV end-systolic volume and end-diastolic volume. It is necessary to study the LV filling (diastolic) and ejection (systolic) patterns for acquiring an understanding of the LV contraction and relaxation (72-77). These studies have revealed a significant difference between normal asymptomatic subjects and heart failure patients. But these imaging methods by themselves suffer from poorer temporal resolution and are typically obtained at a temporal resolution of 60-120 ms. These challenges can be alleviated by performing cardiac cine MRI with a higher temporal resolution.

Conventional MR cardiac cine imaging provides the following advantages that can be exploited to provide a better analysis of LV function and wall motion.

1) A scalable temporal resolution (further explained in section3.4.2).and

2) Non-complicated post-processing of data (further explained in sections3.4.3 and 3.4.4).
3.4.2 Motivation for obtaining high temporal resolution cardiac cine images

To characterize the LV systolic function and diastolic function, it is essential to capture the filling (relaxation) and ejection patterns (contraction) of the LV accurately. Temporal resolution for conventional cine imaging using MRI is 40 – 50 ms, with which accurate quantification of end systolic and diastolic volumes and ejection fraction can be reliably made. However, it is unclear if this temporal resolution is sufficient to quantify transient physiologic events such as peak filling rate (PFR), peak ejection rate (PER), etc. For example, the IVRT of a normal LV is around 80 ms, while an impaired relaxation leads to an increased value of IVRT (~ 100 - 120 ms). A cardiac MR cine acquisition with a temporal resolution of 50 ms is clearly insufficient to capture and accurately estimate IVRT. Also, the peak ejection rate reduces by around 10-15 % for an ischemic heart when compared to a normal heart (1,78,79). These mechanics of the LV cannot be effectively captured using the conventional temporal resolution of 40 ms. To study the LV function and wall motion mechanics of the LV, the differences between the normal and abnormal values have to effectively captured, meaning that the effective temporal resolution should be able to visualize this. A LV volume curve that has been sufficiently sampled over the duration of the cardiac cycle (time-volume curve) can provide valuable insight into the performance of the cardiovascular pump. Echocardiographic B-mode cine images are obtained at a rate of around 50-150 frames (cardiac phases) per second. This corresponds to a temporal resolution as high as 6 ms per cardiac phase. Therefore, a key constraint of the current cardiac cine MR imaging methods is the relatively poor temporal resolution compared to echocardiography. However, increasing the temporal resolution of cine MR comes at the cost of proportional increase in acquisition time. A
six fold increase in temporal resolution would require a six fold increase in breath-holding time, rendering such an acquisition beyond the breath holding ability of most clinical patients.

In this regard, recent advances in parallel imaging techniques and manipulation of spatio-temporal relationships can provide the means to attain such high temporal resolution without compromising spatial or contrast resolution. Recent advances in MR-imaging methodologies that exploit spatial coil sensitivity variations (sensitivity encoding [SENSE]) and spatiotemporal correlations (the k-t broad-use linear-acquisition speedup technique [k-t BLAST]), acquisition of partial k-space, and improvements in MR-imaging hardware (multichannel radiofrequency coil systems) (33,34,80-82), have made it possible to acquire cardiac cine MR images very rapidly. This ability has been exploited to reduce the image-acquisition time, increase the spatial resolution, or increase coverage within the limits of a single patient breath-holder.

3.4.3 Motivation for development of efficient Image segmentation algorithm

Increasing the temporal resolution or frame rate of cardiac cine MR images by a factor of five or six, also increases the number of images that are produced by the same amount. Such an increase places significant burden on post-processing needs.

In conventional cardiac cine images, a cardiologist typically draws the endocardial boundary manually to delineate the blood from the myocardium, thereby obtaining the volume of blood present in the cavity. This is done over a stack of short axis slices covering the entire LV to yield the entire volume, from which LV functional parameters such as ejection fraction, end-diastolic volume and end-systolic volume can
be obtained. This necessitates the cardiologist to delineate two boundaries per cardiac slice (one at diastole and one at systole). Typically there are 8-12 slices covering the entire LV, and the cardiologist manually identifies around 16 endocardial boundaries per patient. However, for obtaining the time-varying characteristics of the entire LV volume, the myocardial boundary has to be delineated for every cardiac phase in all slices.

Assuming an attainable temporal resolution of 10 ms, a 60 beats per minute heart rate is going to yield 80-90 images corresponding to 80-90 cardiac phases per slice. Assuming that 8-12 slices are acquired to completely cover the LV, this gives rise to around 640-1080 images on which LV contours have to be drawn. This is a clinically unrealistic task for the reporting physician. Also, theoretically an even higher temporal resolution is possible, yielding higher number of images. This necessitates the use of an automated or semi-automated computer algorithm that can process the short axis images so that the endocardial boundary is automatically detected.

Such a segmentation algorithm should be able to accurately identify the endocardial boundary within acceptable limits, with the manual tracing of an experienced cardiologist serving as a gold standard. The segmentation algorithm is required to be validated against the same.

3.4.4 Motivation for development of appropriate model for LV volume estimation

The need for a LV volume model arises from the fact that increasing the temporal resolution increases the scan time per slice acquisition. The following example lists various scenarios and time required for acquisition. For imaging a field of view of 320*320*8 mm, with a pixel size of 2*2 requires an acquisition matrix of 160 * 160. If the patient has a heart rate of 60 bpm (1000 ms per heart beat or RR interval) and each
line in k-space is acquired every 3 ms, for a desired temporal resolution of 40 ms, the acquisition time is around 13 seconds (without any type of image acceleration involved). Conventional acquisitions use some sort of acceleration (parallel imaging or filling half the k-space with compromises to SNR) to reduce the scan time to around 7 seconds per 2D slice. For acquiring a higher temporal resolution (say every 12 ms), there would be more than a 3 fold increase of breath-hold time, leading to a breath-held time for around 22 seconds. Such a high breath-hold time is beyond the realm of breath-holding capacity of most patients, especially those with chronic pulmonary disease (83). Also, repetitive breath-holding leads to a decreased breath-holding capacity (84).

For these reasons, obtaining more than 10 slices in the short axis (needed for estimation of complete LV volume) is prohibitively time consuming, and there is a need to obtain LV volume from a minimum number of projections using appropriate models. Obtaining the LV volume from a lower number of slices (projections) would alleviate this problem. Also, it would lead to a lower total scan time per patient. Another important motivation for desiring a model to estimate LV volume is that the volume calculated using the short-axis stack faces the challenge of the basal descent (during systole), that leads the most basal slice of the LV to share a part of the outflow tract, thereby making it difficult to calculate LV volume across all cardiac phases. Measuring the basal descent from a long axis view of the LV could alleviate this problem.

3.4.5 Motivation for development of new functional metrics to measure LV function and wall motion mechanics

Conventional cine MRI quantifies only systolic function, while diastolic function is not quantified. For example, variations in the filling rate (reduction) and iso-volumic
relaxation time (increase) are indicative of diastolic dysfunction. Heart failure with preserved ejection fraction (also called diastolic dysfunction) is a major reason of morbidity and mortality (85), and quantification of diastolic filling function of the heart is necessary. Also, the variations in systolic and diastolic functional metrics are representative of the wall motion (72-76). Radionuclide ventriculography and nuclear medicine have functional metrics like the peak filling and ejection rates that quantify LV function using this method. Such metrics are not conventionally obtained from MRI, and it is desired that an algorithm be developed that can yield these metrics. As seen earlier, they are indicative of both LV function and wall motion mechanics. Also, cine imaging is currently the MRI method of convention used to semi-quantify wall motion. The physician looks at the wall motion in various segments of the heart (like the 17 segment AHA model) to quantify this LV wall motion as akinetic and dyskinetic. By extending this to a higher temporal resolution, cine MRI could provide a higher sensitivity in detecting any wall motion abnormality.

3.4.6 **Motivation for performing temporal analysis for estimating optimal temporal resolution**

The motivation for a higher temporal cine acquisition has already been established. But the effect of temporal resolution has not been studied currently from MRI derived LV functional metrics. Nuclear medicine studies have a temporal resolution of 8 or 16 frames per second (~50 to 100 ms per frame), while 2D - echocardiographic analysis has a temporal resolution as high as 10 ms per frame. M-mode (or 1D) echocardiography has a sub-ms temporal resolution. Each of these imaging method (and methodology) measures
different metrics. For example, the peak filling rate can be measured using nuclear studies, while iso-volumic relaxation time can be measured using M-mode echocardiography. The filling process is a continuous process while iso-volumic relaxation time is a discrete time event (marked by valve opening and closing). This means that the temporal resolution affects the filling rate (and by extension, the peak filling rate) differently than the iso-volumic relaxation time. Both these metrics characterize LV function, and it is important to study how the temporal resolution affects these (and other derived) LV functional metrics.

3.5 Motivation for Specific Aim -II

As established in chapters 1 and 2, estimation of cardiac viability using contrast-Delayed hyper Enhanced Magnetic Resonance Imaging (DE-MRI) has fast become the gold standard. The combination of high spatial resolution, myocardial to scar contrast, as well as reproducibility of the DE-MRI technique has made it a routinely used clinical tool (59,60). A significant issue with DE-MRI technique is the sensitivity of the MR sequence to arrhythmias.

In the absence of arrhythmias, DE-MRI sequence is robust as every RR-interval matches the entered heart-rate, and the steady-state longitudinal magnetization ($M_z$) reached before the first shot remains the same throughout the acquisition. However, in patients suffering from premature ventricular contractions (PVC) and premature atrial contractions (PAC) (86,87), this assumption of regular RR intervals is violated. The severity of the artifacts depends on the irregularity of the sinus rhythm. The problem of arrhythmia (PVC) is more pronounced in patients with myocardial infarction (88). The
occurrence of PVCs increases with the presence of scars. This leads to more arrhythmias and hence more artifacts in images.

Current MR imaging acquisitions skip data acquired during such irregular RR intervals, at the cost of prolonging the acquisition time. Such prolongation of acquisition time might make the DE-MRI sequence beyond the realm of a reasonable breath holding time of about 12-16 heart beats for most clinical patients. Also, for a higher spatial resolution image (that is clinically required for patients with small LV sub-endocardial scar, RV scar or wall ablation) the scan time increases beyond the breath-hold capacity of the patients. In these instances, respiratory motion compensated methods like navigator are used (as seen for cardiac cine images). This prolongs the scan time to around 2 minutes for the entire scan, meaning that for a patient having a 60 bpm heart rate, the acquisition duration would be around 120 heart beats. Longer acquisition leads to stronger artifacts due to arrhythmia (even in mild instances of arrhythmias). These artifacts manifest as an overestimation of scar region, improper nulling of the myocardium (leading to a decrease in ratio of the myocardium to scar signal intensity), lessened sensitivity to smaller (sub-endocardial) scars etc.

Figure 3-1 shows representative 2D DE-MRI images with and without varying heart rhythms that demonstrates artifacts introduced due to arrhythmias. The effect of arrhythmias was simulated (mimicked) in this patient to demonstrate artifacts due to arrhythmia in a breath-held acquisition. In such situations, there is a need to compensate for the fluctuations of longitudinal magnetization during acquisition process, caused by the varying heart rate. This provides the motivation for developing an algorithm that could significantly reduce the artifacts caused by an arrhythmic heart.
Figure 3-1: Artifacts caused due to heart rate variation (arrhythmia)

(A) shows a short-axis image with scar in the infero-lateral wall (bright region in the sub-endocardium), after gadolinium contrast has been administered. This is acquired for a patient with a normal sinus rhythm. For a patient with a varying breathing scenario is shown in (B). Significant artifacts that might impair the diagnostic quality of the images can be introduced due to arrhythmias.
4 Assessment of LV Function using High Temporal Resolution

From the Specific Aim I described in chapter 3, the need to image the LV at a high temporal resolution is established. The need (motivation) for developing image processing algorithms and volume that can accurately quantify the amount of LV blood every cardiac phase obtained is also established. In this chapter, we discuss the methods used, results obtained and discussion of results while fulfilling the Specific Aim 1. This includes 1) the data-acquisition methodology for obtaining the high temporal resolution (~6 ms) cardiac cine MR images, 2) image processing algorithm needed behind the processing of the slice volume and 3) extraction of the complete LV volume from limited projections, 4) processing of LV volume to extract LV functional metrics, and 5) temporal analysis of this data to decide on a proper temporal resolution of acquisition.

Briefly, the primary purpose of MRI cine image acquisition is the estimation of LV function and wall motion. Quantification of LV function is performed by the acquisition of a series of short axis images covering the entire left ventricle. Contours delineating the endocardial boundary for all the slices are obtained manually at two phases – end-diastolic and end-systolic phase. From this the LV volume at the two cardiac phases are obtained (LV_{EDV}, LV_{ESV}). Ejection fraction is calculated as EF = (LV_{EDV} – LV_{ESV})/LV_{EDV}. Ejection fraction is a quantification of systolic function. By measuring the LV volume at all the cardiac phases (from the data already acquired), information about LV diastolic function as well as more information about systolic function can be obtained. Such information also leads to more information about the wall motion. This also leads to a better visual assessment of the wall motion.
The methods used for each part of the specific aim 1, and the results obtained are discussed, followed by a discussion of the results obtained. The methods and results for each part of the specific aim are discussed before proceeding to the next part of the specific aim as the succeeding methods depend on the preceding results.

Prior to a description of methods in each part of the specific aim, the subject population used for fulfilling this entire specific aim, the hardware used and the conventional imaging protocol for obtaining the initial scout images as well as conventional temporal resolution cine images are explained in the following sections.

**Subjects:**

There were two sets of asymptomatic subjects used in this study (covering the entire Specific Aim1). In the first group of 13 subjects (12 m, mean age = 28 ± 6 years) the high resolution cardiac MR imaging was performed. In the conventional temporal resolution images obtained from the second group of 20 subjects (6 f; average age: 38±9 years; mean ejection fraction: 58.1±5.2 %), validation of the semi-automatic LV segmentation algorithm and the modified Simpson’s algorithm were performed. The study was approved by the Institutional Ethics Committee and complied with the Health Insurance Portability and Accountability Act of 1996. All subjects gave written informed consent before being enrolled in the study.

**Image Acquisition: Hardware**

All imaging was done with a 1.5T commercial scanner (Achieva, Philips Medical Systems, Best, The Netherlands). A 32-element phased array cardiac coil was used for image acquisition purposes. The coil has two sets of 16 coil elements (4 rows * 4
columns) distributed in the anterior and posterior sections of the coil. The outside coil dimensions were 30 cm (LR direction), and 25 cm in the FH direction. The signal picked up from each coil element was independently processed by a receiver chain before image reconstruction. Vector-cardiographic gating (VCG) was used cardiac image acquisition. The VCG keeps track of the R wave of the subject’s ECG signal. This is used to synchronize the imaging protocol with the ECG signal such that the desired cardiac phases are obtained.

Image Acquisition: Conventional Imaging Protocol

The following image acquisition protocol was performed on all subjects. Scout images of the thoracic cavity were obtained along three orthogonal planes with a non-VCG–gated SSFP technique. With these single-phase scout scans, a series of VCG-gated cine- balanced Steady State Free Precession (bSSFP) images were acquired during suspended respiration in the following order: a two-chamber view, a four-chamber view, and a series of contiguous short-axis slices (8 – 12 slices) covering the entire left ventricle from the apex to the base (the level of the mitral valve annulus). The imaging parameters used for the conventional temporal resolution of 40 to 50 ms were as follows: Repetition time (TR)/Echo time (TE)/flip angle = 3.0-3.2 ms/1.5-1.6 ms/ 55°; acquired voxel size = 2×2×8 mm³; reconstructed voxel size = 1.76×1.76×8 mm³; SENSE acceleration factor = 2; typical field of view (FOV) acquired for the short axis slices = 350 * 350 mm; breath-hold duration = 6 to 8 heartbeats per slice.

Image Post-Processing:
All the images were stored in the Digital Imaging and Communications in Medicine standard format (DICOM; NEMA, Rosslyn, VA) and PAR/REC format (Philips Health Care, Best, The Netherlands). The post processing was performed in both the formats.

4.1 Specific Aim 1a: High Temporal Resolution Cardiac Cine Images

‘Design suitable MR imaging protocols and utilize state of the art MR hardware, to obtain high temporal resolution cine images of the heart’

4.1.1 Methods

As explained in Chapter 3 (Specific Aim 1a), obtaining high temporal resolution images is necessary for an accurate evaluation of the filling characteristics of the left ventricle. Recent advances in MRI methodologies that exploit spatial coil sensitivity variations (sensitivity encoding [SENSE]) and spatiotemporal correlations (the k-t broad-use linear-acquisition speedup technique [k-t BLAST]), as well as improvements in MRI hardware (multichannel radiofrequency [RF] coil systems), have made it possible to acquire cardiac cine MR images very rapidly (80-82). Studies using these methodologies have already successfully been used to either reduce image acquisition time or increases the spatial resolution of acquisition within the realm of a normal breath-hold time in patients (33,34). In this section, image acquisition protocol using SENSE and k-t BLAST acquisition with a temporal resolution of around 6 ms per cardiac phase is presented.
Subjects

The first group of 13 asymptomatic subjects (12 m, mean age = 38 ± 9; mean ejection fraction = 58.1 ± 5.2) are imaged here using the high temporal resolution acquisition protocol.

Image Acquisition

Scout images of the thoracic cavity were obtained using the protocol prescribed above.

High Temporal Images: After the acquisition of the scout images, high temporal cardiac cine bSSFP images of the LV were obtained in a) four chamber view, b) LV outflow tract (LVOT) view, and c) three locations in the short-axis view – basal, mid-cavity and apical locations. Acquired temporal resolution was 5.8 to 6.2 ms per cardiac phase. The mid-cavity slice was positioned as equi-distant between the apex and mitral valve annulus (in diastole). The basal and apical slices were positioned equi-distant from the mid-cavity slice such that both were well within the LV during systole. The image acquisition parameters were: Repetition time (TR)/Echo time (TE)/flip angle (α) = 3 ms/1.5 ms/55°; Voxel (Volume element) size = 2.5×2.5×8 mm³; half-scan factor = 0.625; number of phase-encoding steps acquired per heartbeat = 2. Rapid image acquisition techniques - SENSE and k-t BLAST, were used to keep the breath-hold time within an acceptable limit. 1) The SENSE acceleration technique had an acceleration factor of 3 in the phase-encoding direction and 2) k-t BLAST (without SENSE) had an effective acceleration factor of 3.8 (k-t factor = 5). The number of phase encoding steps required to achieve the prescribed spatial resolution was about 175 (350*350 mm FOV). The combination of
half-scan, parallel imaging acceleration (3 for SENSE), or 3.8 (for k-t BLAST), and segmented k-space acquisition (turbo factor = 2), reduced the number of heart beats required to collect all the necessary phase encoding steps to around 18-22. The SENSE-accelerated acquisition was retrospectively gated, and the k-t BLAST–accelerated scan was prospectively triggered. A retrospectively gate sequence is one in which the acquisition is continuously made without any interruption to steady state. The occurring R waves are kept in memory, and any occurring RR interval mismatches are corrected in the end. A prospectively triggered scan waits for the R wave to occur at the end of the previous heart beat, and the acquisition is made. A retrospective scan offers the advantage of uninterrupted steady state across the acquisition as well as capturing all details of the heart motion at end-diastole.

4.1.2 Results

The MR acquisition was performed successfully in the 13 subjects. Depending on the heart rate of the subject at the time of acquisition, around 120 to 176 cardiac phases were acquired in these volunteers.

4.2 Specific Aim 1b: Semi-Automatic Estimation of Slice Volume and Validation

‘Adapt and develop an image processing algorithm that would automate the process of endocardial boundary segmentation, yielding time-volume curve (variation of volume across all cardiac phases of the slice of interest), with minimal user interference’

This section explains the post processing tools developed a) to obtain the slice volume semi-automatically (with minimal user input) from the short axis views.
4.2.1 Methods

The LV slice volume was segmented by using a custom-written algorithm/program in MATLAB (Release 14; version 7.0.4; The MathWorks, Inc., Natick, MA, USA). In this method, after acquisition of the cardiac cine images in the short axis view, the heart region was selected and other regions cropped out as seen in Figure 4-1.

- Manually locate the left ventricle within the image; the user drew a rectangular region of interest (ROI) on ED image, encompassing the heart.
- After anisotropic diffusion filtering (20) of the excised ROI, the intensity histogram revealed a bimodal pattern that depicted pixels as belonging either to the blood pool (right or left ventricular) or to the myocardium. Otsu’s algorithm (21) was used to obtain an imaging threshold for segmenting the blood from the myocardium.
- After segmentation of the blood, the LV-ROI was identified by manually drawing a rectangle in the ED phase. All subsequent analyses described below were performed in this sub region extracted across all the phases.
- The Otsu’s thresholding was performed within the specified LV-ROI followed by the regional labeling. The LV was identified as the single largest labeled region.
- A “two-dimensional (2D) ray reflection(89)” was generated, in which rays were projected in radial manner (a ray per 20 degrees from every “non-blood” pixel of the subimage). Any ray hitting a “blood” pixel was considered to be reflected. Any non-blood pixel with more than 7 reflected rays was considered to be part of the blood or papillary muscle and included in the LV cavity.
Thus the entire LV blood volume present in the slice of interest was calculated for each cardiac phase. After the volume was obtained for an entire heart beat, the blood volume was smoothed spatio-temporally to obtain the LV blood volume curve for the slice of interest.

**Subjects and Validation:** The LV volume per slice was computed and validated in the second group of 20 volunteers and were used to validate the semi-automatic LV segmentation algorithm. The validation was performed on stack of short axis cine images covering the entire LV obtained at conventional temporal resolution (40-50 ms). These images were transferred to a commercial post processing workstation (ViewForum; Philips Healthcare, Andover, MA). An experienced cardiac MR expert (with 5 years of clinical cardiovascular MR experience) reviewed the stack of short-axis images and manually drew contours to obtain the end-diastolic volume and end-systolic volume. This data was also used to validate the LV volume estimation model (modified Simpson’s algorithm) explained in the next section.
Figure 4-1: Steps involved in the segmentation of the LV blood volume from a short axis

1) The location of the heart is cropped from the acquired image, and 2) filtered using an anisotropic diffusion filter. This filtered image is then 3) segmented using a bimodal Otsu’s thresholding algorithm and the LV region identified. 4) Ray closing is performed to identify the papillary muscle region and the 5) entire LV blood volume is calculated. The segmented blood is overlaid on the actual image (6).

4.2.2 Results

Conventional temporal resolution cine-SSFP MR images of the heart were successfully obtained in all the subjects. The LV cavity was represented by a total of 240 (20x12) short-axis slices in subgroup of 20 volunteers, which were segmented by using the semi-automated algorithm to yield the EDV and ESV values. The presence of the LV outflow tract in the basal region, papillary muscles in the mid-ventricular region, and near obliteration of the LV cavity during systole in the apex all posed different challenges to successful segmentation of the LV cavity across these regions. The performance of the segmentation algorithm across the LV cavity was compared against the results of the manual contours drawn by an expert observer using Bland-Altman analyses(90). Bland-
Altman analyses, as seen in Figure 4-2, showed that the semi-automated method underestimated the LV volumes with percent mean bias less than 2.6% (limits of agreement 2.5%) and 7.8% (limits of agreement 8.9%) of the total volume in ED and ES, respectively; these findings were consistent with those cited in previously published reports (91).

**Figure 4-2: Validation of LV segmentation algorithm**

Validation of results obtained in 20 volunteers by using a semi-automated left ventricular (LV) segmentation algorithm across the left ventricle, as compared to manual contours drawn by an expert observer. The graph of the bias (dark line) and standard deviation (shaded bars) were computed with Bland-Altman analyses in terms of percentage differences in LV volume corresponding to the basal, mid-cavity (mid), and apical sections of the left ventricle, as well as the total left ventricle. SD = standard deviations. Compared to manual contours, the semi-automated method slightly underestimates the resulting values.

4.3 **Specific Aim 1c: LV Volume Calculation and Validation: Modified Simpson’s Algorithm**
To obtain time-volume curve across the entire LV with minimal number of projections such that the human subject experiences negligible discomfort during the imaging procedure.

Chapter 3 has laid the foundation for the need to obtain the entire LV volume across all imaged cardiac phases (time-volume curve) from minimal number of slices to reduce scan time and account for the basal descent and the apical ascent. Previous studies (92,93) have compared various models for generating entire LV volume. Thiele et al. (92) compared the full 3D reconstruction of the LV volume (Figure 4-3) (where short-axis slices covering the entire stack were obtained) with various models (modified Simpson’s algorithm, biplane ellipsoid method, Techoltz model, hemisphere cylinder model etc.), in 25 patients with and without regional LV wall motion abnormality. The LV volume was reconstructed at the end-diastolic and end-systolic phase from the full 3D reconstruction and the various models. It was seen that the results from modified Simpson’s algorithm best correlated with the full 3D reconstruction in patients. The modified Simpson’s method assumes a two model theory, in which the basal and mid-cavity regions of the LV are modeled as a cylinder (with the area of the mid-cavity slice serving as a constant volume across this entire region) and the apical region as a cone.

For capturing the dynamics of wall motion of the LV, it would be beneficial to extend this method such that more information about the LV is captured. The modified Simpson’s method used in this prior study suffers from the disadvantage that the assumptions of the model do not conform to the 17 segment AHA model (94) recommended by the American Heart Association. The 17 segment model involves acquisition of three short-axis slices as shown in Figure 4-4, one in the basal location,
one in mid-cavity and one in apical location, along with the apex location. The 17 segment model was suggested for both cine imaging (to look at wall motion) as well as angiographic imaging, so that the wall motion can be associated with regions of ischemia. For example, if there is a stenosis of the coronary artery (say Left Anterior Descending (LAD) artery) in the mid-cavity region, then all motion at the basal slice might not be as impaired as the mid-cavity region. Thus characterizing the entire LV basal and mid-cavity region using just the information from the mid-cavity region might not truly reflect the dynamics of LV wall motion, and there is a need to incorporate the wall motion information from the basal slice also in the LV volume model.

\[
\text{Full 3D reconstruction} \\
\text{LV volume} = (A_1 + A_2 + A_3 + \ldots A_n) \times \text{Slice Thickness}
\]

\[
\text{Modified Simpson's Algorithm} \\
\text{LV volume} = (A_m + (A_m + A_p)/2 + A_p/3) \times L/3
\]

\[
\text{Hemisphere Cylinder Model} \\
\text{LV volume} = (A_m + 2A_m/3) \times L/2
\]

\[
\text{Combined Triplane Model} \\
\text{LV volume} = (A_1 \times A_2 \times A_p)^{1/2} \times (4/3)/\sqrt{\pi} \times 0.752
\]

Figure 4-3: Existing models for LV volume reconstruction from minimum projections.

Some of the existing models of image reconstruction using minimum number of projections of LV are shown in this picture. Image A is the complete reconstruction with minimal assumptions of shape of the LV and is the gold standard of reference. This model is currently used for LV volume reconstruction using conventional cine MRI. The
modified Simpson’s model (B) performs close to (A) for both patients with and without regional dysfunction in LV wall motion. Image adapted from (92).

**Figure 4-4: The 17 segment American Heart Association model for LV function**

The 17-segment model has been recommended by the American Heart Association for effectively capturing the LV wall motion. Short axis information at the basal, mid-cavity and apical location, along with information about the apical movement using a long-axis view is needed to effectively capture the LV function. Also, the reduced number of projections helps reduce acquisition duration.

In this section, the method involved in developing this extended modified Simpson’s algorithm is discussed.
4.3.1 Methods

The total left ventricular (LV) volume was calculated by means of this extended modified Simpson’s algorithm using the areas of the three short-axis slices of the left ventricle instead of the two-slice model described originally (92,93). Also, two long axis views of the LV were acquired, and the short axis planes were projected onto them (Figure 4-5, Figure 4-6). The total length of the left ventricle at each phase was measured from either of the long-axis view as

\[ L = L_1 + L_2 + L_3 + L_4 \]

where \( L_2 \) and \( L_3 \) are the inter-slice gaps from the basal slice and the apical slice to the mid-cavity slice, respectively. \( L_1 \) is the distance from the basal slice to the mitral valve annulus, and \( L_4 \) is the distance from the apical slice to the apex. The total volume \( (V) \) of the left ventricle was calculated from the area (obtained from Specific Aim 1b) of the LV cavity in the basal \( (A_b) \), mid \( (A_m) \), and apical \( (A_a) \) slices by using the following formula (using custom written code in MATLAB™):

\[
V = \left \{ L_1 \times A_b + L_2 \times \left \{ \frac{A_b + A_m}{2} \right \} + L_3 \times \left \{ \frac{A_m + A_a}{2} \right \} + L_4 \times \frac{A_a}{3} \right \}
\]

Subjects and Validation: A group of 20 volunteers (same group used for the validation of the LV segmentation algorithm) were used to validate the modified Simpson’s method to obtain the entire LV volume. The ejection fraction obtained from the modified Simpson’s algorithm was compared with the values obtained from a cardiac MR expert for validation.
Figure 4-5: Schematic description of using Modified Simpson’s model to obtain the entire LV volume

This figure describes the slice geometry for calculating the modified Simpson volume. The LV geometry is assumed to be the sum of the volumes of a cylinder of height $L_1$, two cut cones of heights $L_2$ and $L_3$, and a cone of height $L_4$. $L_2$ and $L_3$ remain constant throughout all cardiac phases. $L_1$ and $L_4$ that represent the basal descent and the apical ascent vary along the phases. The distance between the mitral valve annulus and the LV apex ($L_1 + L_2 + L_3 + L_4$) was measured manually for each cardiac phase from the long-axis view, and entire LV volume calculated from this information and the segmented volume from the three short-axis views located at the basal, mid-cavity and apical locations.

Figure 4-6: Pictorial description of planning of the three short axis slices on a 4-Chamber view in Systole and Diastole
The three short axis projections as shown in Figure 4-5 are depicted here on a four-chamber view. Diastole (A) and Systole (B) are shown in the four-chamber view. \( L_1 \) is the distance from the mitral valve annulus to the basal slice while \( L_4 \) is the distance between the most apical slice to the apex. \( L_2 \) and \( L_3 \) are inter-slice gaps that remain constant throughout all cardiac phases.

4.3.2 Results

The total LV volume computed by using the modified Simpson’s algorithm on three short-axis slices acquired from the basal, mid, and apical regions was in good agreement with the total LV volume computed from endocardial contours manually drawn by an expert on a stack of contiguous short-axis slices by means of the disk-summation method in 20 subjects. The results show a) that the EDV, ESV and EF values obtained from modified Simpson’s algorithm agree strongly with the values obtained from the short axis stack (Figure 4-7) and b) that the percent mean bias and limits of agreement determined by Bland-Altman analyses for estimation of the EDV, ESV, and EF (-7.3±6.8%, 2.4±15.3%, and -1.7±6.1%, respectively) are in close agreement with the inter-observer and intra-observer variability of the experienced observers (95).
Figure 4-7: Comparison of results between modified Simpson’s algorithm and the conventional stack.

The EDV (A), ESV (B) and EF (C) values obtained between modified Simpson’s algorithm and the short axis stack corresponded very well. EDV – End-Diastolic Volume; ESV – End-Systolic Volume; EF – Ejection Fraction.
4.4 Specific Aim 1d: Estimation of Parameters Characterizing LV Systolic and Diastolic Function

4.4.1 Methods

Parameters characterizing LV function derived from the total LV-volume curves, as well as the individual slices (in the basal, mid-cavity and apical locations) obtained from the high-temporal-resolution cine images are described in this part of specific aim 1 (in the first set of 13 asymptomatic subjects). The LV cavity in each of the three short-axis slices acquired at a high temporal resolution was segmented by using the semi-automated image-analysis algorithm. From the segmented LV volumes, the time-volume curve was generated for each of the three slices. In addition, a total LV-volume curve was generated by using the modified Simpson method. The following steps were involved in analyzing the time-volume curves: 1) the raw segmented time-volume curves were smoothed by using a moving average filter with a kernel size of 3 (< 3% of the actual length of data); 2) the derivative of the smoothed time-volume curve was obtained by using a three-point kernel to perform a linear fit calculation. The slope of the three-point linear fit was taken as the value of the mid-point in the dV/dt curve. The following parameters were derived from the total LV time-volume curve obtained from SENSE and k-t BLAST imaging techniques (Figure 4-8 depicts the parameters involved pictorially):

1) Time to end-systole (TES): The time (cardiac phase) when the LV blood volume measured is at its minimum. This time corresponds to a zero crossing (from a negative to a positive value) of the rate of change in the LV volume (dV/dt) curve (96-99). TES is measured as the time interval from the start of acquisition (occurrence of R-wave,
corresponding to time \( t = 0 \) to the time corresponding to zero-crossing in the \( dV/dt \) curve.

2) \textit{Peak filling rate (PFR) and time to PFR (TPFR)}: The PFR is defined as the peak value in the \( dV/dt \) curve after the occurrence of the TES, i.e., when the passive (early) filling rate is maximal. The TPFR is the duration between the TES and the PFR.

3) \textit{Peak active filling rate (PAFR)}: The PAFR is the peak LV filling rate during the active (late) filling phase.

4) \textit{Peak ejection rate (PER) and time to PER (TPER)}: The PER is defined as the negative peak in the \( dV/dt \) curve before the occurrence of TES, which indicates the maximal LV ejection rate. TPER is the time of occurrence of PER.

5) \textit{Iso-volumic Relaxation Time (MR) (IVRT\textsubscript{MR}) Time}: The onset of the iso-volumic relaxation (IVR) phase begins shortly after the TES, when there is minimal LV filling or a near-constant LV volume. The end of the IVR phase is characterized by a rapid increase in filling, represented as the local minimum of the \( dV/dt \) curve between the TES and the TPFR. The time between the onset and end of the IVR phase is characterized as IVRT\textsubscript{MR}. This IVRT\textsubscript{MR} coincided with the occurrence of conventional iso-volumic relaxation time (IVRT), that is defined as the time between the closure of aortic valve and the opening of mitral valve after TES has occurred, which can be visualized using transmitral Doppler echocardiography.

6) \textit{E/A\textsubscript{MR} ratio}: The E/A\textsubscript{MR} ratio was calculated as the ratio of PFR to PAFR. This was performed only for the data obtained from SENSE imaging, as k-t BLAST acquisition relies on prospective VCG gating and does not fully capture the atrial-contraction phase
during the cardiac cycle. This metric is similar to the E/A ratio reported using echocardiography.

**Echocardiographic measurement:** In the 13 subjects who underwent high-temporal-resolution cine imaging of the heart, echocardiographic images (GE Vivid 3; GE Medical Systems, Milwaukee, WI) were also acquired within an hour after the MR examination. Subjects were placed in the left lateral decubitus position, and standard echocardiographic views were recorded.

The IVRT and the transmitral E- and A-wave velocities were measured as previously described (100). The IVRT was measured by using a continuous-wave Doppler technique with the Doppler cursor aligned in a position between the mitral and the aortic valve in the apical five-chamber view. The E and A velocities were obtained by using a pulsed-wave Doppler technique with the sample volume placed at the level of the mitral annulus. The transmitral velocities and IVRT were obtained by averaging the results over six to eight cardiac cycles.
Figure 4-8: Estimation of parameters characterizing LV systolic and diastolic function.

LV time-volume curve and its rate of change (dV/dt) are shown in this figure. The Peak ejection rate, filling rate and the time of occurrence of important systolic and diastolic functional landmarks are obtained from the dV/dt curve. The following diastolic parameters were measured: TPER, time to peak ejection rate; TES, time to end-systole; TPFR, time to peak filling rate; TPAFR, time to peak active filling rate; IVRT\textsubscript{MR} \textsubscript{MR}, MR derived iso-volumic relaxation time; PER, peak ejection rate; PFR, peak filling rate; and PAFR, peak active filling rate.

4.4.2 Results

The total LV volume measured with the modified Simpson approach was used to generate the LV time-volume curves in 13 subjects with high-temporal-resolution cine-SSFP data. The previously described derivative-based method was used to analyze these curves successfully. Bland-Altman analyses revealed good agreement between the TES, PER, TPER, TPFR, and PFR values derived from the SENSE-accelerated and k-t BLAST–accelerated acquisitions. Table 4-1 summarizes the actual values and presents the filling and ejection rates normalized to the end-diastolic volume (expressed as EDV/s). Parameters of atrial function (i.e., PAFR and TPAFR) were derived only on the
SENSE scans, as the k-t BLAST–accelerated scans missed the distal portion of end-diastole.

<table>
<thead>
<tr>
<th></th>
<th>TES</th>
<th>TPER</th>
<th>TPFR</th>
<th>PER</th>
<th>PFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(ms)</td>
<td>(ms)</td>
<td>(ms)</td>
<td>(ml/s)</td>
<td>× EDV/s</td>
</tr>
<tr>
<td>SENSE</td>
<td>301±29.1</td>
<td>139±49.8</td>
<td>156±36</td>
<td>722.4±136.5</td>
<td>4.9±0.9</td>
</tr>
<tr>
<td>k-t BLAST</td>
<td>318.5±49.8</td>
<td>128.3±43.9</td>
<td>163±43</td>
<td>750.6±155.4</td>
<td>5.5±1.0</td>
</tr>
<tr>
<td>Bland-Altman</td>
<td>-17.5±30</td>
<td>8.4±40.5</td>
<td>-11.5±20.9</td>
<td>-26±80</td>
<td>-0.6±0.7</td>
</tr>
</tbody>
</table>

Table 4-1: Absolute values of various diastolic functional indices derived from the Time-Volume curves generated from the SENSE-accelerated and k-t BLAST-accelerated acquisitions (mean ± SD).

SENSE, sensitivity encoding; k-t BLAST, spatial frequency-temporal frequency broad-use linear acceleration technique; SD, standard deviation; TES, time to end-systole; TPER, time to peak ejection rate; TPFR, time to peak filling rate; PER, peak ejection rate; PFR, peak filling rate. PER and PFR are also expressed as normalized with respect to the corresponding end-diastolic volumes and expressed as EDV/s.

The analysis of time-volume curves obtained at each of the three short-axis slice locations revealed a substantial difference in the filling patterns between the curves; this difference reflected regional variations in contraction-relaxation across the left ventricle during the cardiac cycle (Figure 4-9). Furthermore, for ~45% of the slices from the apical and basal locations, there was no discernible IVRT_{MR}.
Figure 4-9: Normalized regional left ventricular (LV) volumes of individual basal, mid-cavity, and apical slices, and total LV volume

*The asterisks indicate the time to end-systole (TES), as computed by the data-analysis algorithm. Note the substantial regional variation in LV contraction-relaxation across the slice locations.*

**Comparison of the IVRT/IVRT\text{MR} and the E/A Ratio with Echocardiography versus MR**

The IVRT\text{MR} values derived from the MR-based LV time-volume curves were in broad agreement with estimates of the IVRT derived from echocardiography, having a mean bias of -0.4±13 ms and -6±16 ms with SENSE and k-t BLAST, respectively (Figure 4-10). The comparison was performed for 12 volunteers, as the IVRT values could not be obtained for 1 volunteer by means of echocardiography, although the E/A ratio was obtained for all 13 volunteers.

The mean E/A ratio calculated from the time-volume curves obtained with MR imaging was 2.2±1.0, and that obtained with Doppler echocardiography was 1.89 ± 0.9.
Although the E/A$_{\text{MR}}$ was in the same range as the E/A obtained echocardiographically, the two values were significantly different from each other ($p = 0.43$, paired Student’s t-test).

![Figure 4-10: Bland-Altman analysis of iso-volumic relaxation time obtained with magnetic resonance (IVRT$_{\text{MR}}$) versus echocardiography (IVRT)](image)

Views A and B compare the IVRT$_{\text{MR}}$s obtained with the SENSE and k-t BLAST imaging techniques for the total volume with echocardiography. The values were in the similar range.

4.5 Specific Aim 1e: Effects of the Temporal Sampling Rate on LV functional Parameters
4.5.1 Methods

To study the effects of the temporal sampling rate, the time-volume curve obtained at the highest temporal resolution (~6 ms) was under sampled by factors of 2, 3, 4, 5, and 6 to yield a temporal resolution of 12, 18, 24, 30, and 36 ms. Because the acquired temporal resolution among patients varied from 5.5 to 6.2 ms depending on the heart rate, the volume curve was resampled at a 1 ms temporal resolution using piecewise linear interpolation. From this resampled data, the volume curve was down sampled to temporal resolutions of 12, 18, 24, 30 and 36 ms for subsequent analysis. The derivative of the time-volume curve was re-calculated for the new under sampled data. The data analysis was performed to calculate the new values of the diastolic parameters, which were then compared with the “6-ms”-resolution values.

4.5.2 Results

Figure 4-11 depicts the effect of temporal under sampling of the time-volume curves. With increasing under-sampling factors, the local minima used to identify the onset of the rapid-filling phase disappeared, making it difficult to estimate the end of the IVRT<sub>MR</sub> (Figure 4-11). Calculation of the cardiac phase where the end of IVRT<sub>MR</sub> occurred failed for temporal resolutions ≥18 ms. Also, as the temporal resolution worsened, there was a progressive decline in the ability to estimate all the filling rates (ie, PER, PFR, and PAFR) (Figure 4-12), and this decline was significant (p<0.01, paired Student’s t-test) between the filling rates at all temporal resolutions.
Figure 4-11: Effect of sub-sampling on the estimation of the isovolumic relaxation time (IVRT\(_{MR}\))

The algorithm fails to determine the isovolumic relaxation period at lower temporal resolutions (>12 ms). Top panel: a representative time-volume curve at a resolution of 6 ms. Center panel: the corresponding rate of change in the LV volume (dV/dt) values at different sampling rates. Bottom panel: Enlarged version of the dV/dt values during the isovolumic phase. Note the complete disappearance of the local minima after the TES, indicating the end of the IVRT\(_{MR}\) at temporal resolutions of >18 ms (solid arrow). Also note the progressive decline in the peak filling rate from 6 to 24 ms (double arrows).
A statistically significant decline in PER, PFR and PAFR is observed as the temporal resolution of imaging declines. SD, standard deviation; PER, peak ejection rate; PFR, peak filling rate; PAFR, peak active filling rate.

<table>
<thead>
<tr>
<th></th>
<th>6 ms</th>
<th>12 ms</th>
<th>18 ms</th>
<th>24 ms</th>
<th>30 ms</th>
<th>36 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>PER</td>
<td>(ml/s)</td>
<td>724±131</td>
<td>592±96</td>
<td>564±96</td>
<td>547±92</td>
<td>533±83</td>
</tr>
<tr>
<td>× EDV/s</td>
<td></td>
<td>4.9±0.9</td>
<td>4.1±0.8</td>
<td>3.9±0.8</td>
<td>3.8±0.8</td>
<td>3.7±0.7</td>
</tr>
<tr>
<td>PFR</td>
<td>(ml/s)</td>
<td>734±144</td>
<td>635±96</td>
<td>614±93</td>
<td>588±87</td>
<td>566±84</td>
</tr>
<tr>
<td>× EDV/s</td>
<td></td>
<td>5.0±0.9</td>
<td>4.3±0.6</td>
<td>4.2±0.6</td>
<td>4.1±0.6</td>
<td>3.9±0.5</td>
</tr>
<tr>
<td>PAFR</td>
<td>(ml/s)</td>
<td>420±123</td>
<td>331±92</td>
<td>304±90</td>
<td>283±74</td>
<td>268±74</td>
</tr>
<tr>
<td>× EDV/s</td>
<td></td>
<td>2.8±0.9</td>
<td>2.2±0.6</td>
<td>2.1±0.6</td>
<td>1.9±0.5</td>
<td>1.9±0.5</td>
</tr>
</tbody>
</table>

Table 4-2: Variation of Filling and Ejection Rates with Temporal Resolution (Mean ± SD)

Figure 4-12: Variation of PER, PFR and PAFR with temporal resolution
Progressive decline in filling rates with worsening temporal resolution is seen. The filling rates shown are absolute values. PER, peak ejection rate; PFR, Peak Filling rate; PAFR, peak active filling rate.

4.6 Discussion of Results

The results from specific Aim I show that with modern multi-channel MR hardware and acceleration techniques such as SENSE or k-t BLAST, it is feasible to obtain cardiac cine MR images at a temporal resolution on the order of a few milliseconds (approaching the limits of the repetition time) without compromising the spatial or contrast resolution. By utilizing proper post-processing algorithms, functional metrics describing the LV function and wall motion mechanics at higher temporal resolution can be successfully attained. A number of issues are worth discussing regarding the estimation of clinically relevant quantitative parameters from these high-temporal-resolution data. The discussion of these results is listed in the order of specific aims fulfilled.

One of the challenges in processing high-temporal-resolution cine-SSFP images is the need to delineate the LV cavity for volumetric analysis. Manual contouring of more than 100 phases per slice would be prohibitively time-consuming and, thus, not usable in routine clinical practice. Therefore, the clinical adoption of high-temporal-resolution cine-SSFP imaging necessitates that some degree of automation be used for LV segmentation. The discussed LV-segmentation algorithm utilizes a bimodal histogram of the cine-SSFP images along with the convexity of the LV cavity; the margin of error in segmenting various sections of the left ventricle was within reasonable limits (80). The current semi-automated processing approach, including the previously described manual
ROI-selection process, takes about 90 seconds per slice on a modern desktop personal computer (i.e., a 2.80-GHz Intel Xeon processor with 3 GB of RAM). With optimization, this time could be further reduced.

Acquiring high-temporal-resolution cine-SSFP images that cover the entire left ventricle with contiguous short-axis slices necessitating one breath-hold per slice may not be clinically practical, especially in this case where the breath-hold times range anywhere between 18-24 seconds per slice. Therefore, models are needed that would accurately predict the LV volume on the basis of minimum data acquisition. Thiele and coworkers (92) have experimented with various mathematical models for estimating LV volumes by using as few as two slices. In this study, we extended the modified Simpson model from two slices to three. These results showed that the total LV volume computed from the modified three-slice approach was very close to that obtained by an expert observer with the stack of contiguous slices covering the entire left ventricle. The three-slice approach relied on fewer assumptions regarding the LV shape and allowed us to assess the regional differences in the LV filling and relaxation parameters. It also complies with the 17-segment AHA model, resulting in better qualification of wall motion analysis visually. The three-slice approach may prove to be more robust than the two-slice method for evaluating LV volumes in a clinical setting, where one would encounter a wide variety of LV shapes. The results from this study suggests that EF, EDV and ESV values from the three-slice Modified Simpson’s model correlates better with the reference standards than the values from the two-slice modified Simpson’s model obtained in earlier studies (92).

The k-t BLAST approach, unlike the SENSE approach, exploits redundancies in information in both the spatial and temporal domains. Nevertheless, the results of this
study confirmed that key metrics derived from the time-volume curves obtained with SENSE or k-t BLAST techniques were in good agreement. However, two points are worth noting in regard to the k-t BLAST technique. 1) For the acceleration factor used in this study (3.8), the spatiotemporal under sampling intrinsic to k-t BLAST acquisition did not appear to degrade the temporal fidelity of the time-volume curves. The under sampling might become a major source of temporal blurring at higher acceleration factors, and it needs to be carefully considered. 2) Although this is not an intrinsic limitation of the technique itself, current implementation of k-t BLAST requires prospective cardiac gating, which misses about 5% to 10% of end-diastole (as explained in the methods section of specific aim 1a). This makes it difficult to estimate parameters that characterize atrial filling such as the PAFR. On the other hand, the SENSE technique uses retrospective gating and acquires data throughout the cardiac cycle. In addition, SENSE relies on the redundancy of coil-sensitivity information in the spatial domain, so it does not have any potential limitation with respect to temporal blurring. Therefore, the SENSE-accelerated technique may be more suitable for assessing LV functional indices derived from LV-volume filling patterns. It should be noted, however, that SENSE acquisition, in particular, greatly benefited from the 32-channel radiofrequency coil array that we used for imaging. The 32 channel configuration allows potential for SENSE acceleration along the Right-Left, Anterior-Posterior, and Foot-Head directions because of its coil geometry. Therefore, independent of the orientation of the heart within the thoracic cavity, this coil geometry permits higher SENSE acceleration factors. It has been previously shown that cardiac cine SSFP images acquired using a 5 channel coil with a SENSE acceleration factor of 2 yielded LV volumes with sufficient SNR that are
comparable to conventional cardiac cine acquisitions without SENSE (101). However using a five-channel coil array at acceleration factors greater than 2 (for obtaining similar 2D images) significantly limits the available signal-to-noise ratio (SNR). This study used a 32 channel coil that allows for a higher SNR at the same acceleration factor. This gain has been traded here for a higher acceleration factor and maintaining a similar SNR as a conventional acquisition (82).

The metrics that characterize the filling patterns derived from the mid-ventricular slices corresponded closely with those derived from the total LV-volume curves. On the other hand, the filling patterns of the LV basal slice varied qualitatively from those of the mid-cavity and apical slices. The basal slice typically had a longer TES than did the mid-cavity and apical slices (Figure 4-9). Determination of the IVRT$_{	ext{MR}}$ from the data-analysis algorithm failed in nearly half (45%) of the basal and apical slices, as the isovolumic phase was entirely indiscernible from the time-volume curves. Instead, at the basal and apical locations, the regional volume curves simply had a sustained gradual reduction in LV volume throughout the isovolumic phase, resulting in a prolonged TES compared to that of the mid-ventricular volume curve or the total volume curve. This finding suggests that, whereas there was very little change in the total LV volume during the isovolumic phase, there were shape changes along the LV length at different LV locations. We speculate that these changes were perhaps due to the differences in the regional contraction patterns across the length of the left ventricle throughout the cardiac cycle. Such a regional variation in contraction patterns has also been reported with regard to strain-encoded MR imaging and other methods (4,102,103). For example, Zwanenburg and coworkers (103), as well as other investigators (102), have shown that in comparison
with the basal and apical slices, the mid-cavity slice undergoes the least longitudinal strain and that its maximal radial strain rate occurs more closely with the time of mitral valve closure. The results from this study results also suggest a similar phenomenon, in which the TES obtained from the mid-cavity slice is closest to the TES calculated for the entire LV volume. Hamdan and coauthors (102) have reported that the onset of peak circumferential and radial strain, as well as maximal strain, varies across the basal, mid, and apical portions of the left ventricle.

After sampling a signal at a high frame rate, it is possible to subsample the acquired data to study the effect of temporal resolution on the derivation of quantitative metrics. This study showed that determination of the IVRT\(_{MR}\) by using the above-described analysis algorithm fails for all temporal resolutions \(\geq 18\) ms. The normal IVRT is approximately 80 ms, and conventional cine MR acquisition with a temporal resolution of 30 to 50 ms is insufficient to accurately capture such a transient phenomenon. IVRT\(_{MR}\) serves as a surrogate marker of the ability of the imaging method to capture such rapidly occurring transient phenomena.

The results also showed that IVRT and E/A values measured from echocardiograms versus the IVRT\(_{MR}\) and E/A\(_{MR}\) obtained from the total LV-volume curves (MR images) were in close agreement (Figure 4-10). The derivation of the IVRT relies on two distinct approaches with these methods. Echocardiography measures the IVRT as the time between aortic valve closure and the onset of transmitral flow, whereas MR imaging measures it as the duration of the slowly varying volume period obtained from the time-volume curve after occurrence of the TES. In the long-axis view, valve closure and opening may conceivably be used to directly estimate an echo-analogue for
the IVRT, but the initial efforts to identify the exact onset of valve opening or closure were unsuccessful due to poor contrast between the valve leaflets and the surrounding blood. Also, the computation of the $E/A_{\text{MR}}$ ratio in MR imaging is fundamentally distinct from computation of $E/A$ in echocardiography. The MR-imaging estimates rely on the total LV filling rates, whereas echocardiographic estimates rely on the peak velocity measurement in the early and late filling phases across the mitral valve. Numerous investigators have attempted to compute $E/A_{\text{MR}}$ ratios from phase-contrast measurements performed across the mitral valve. To the best of our knowledge, however, this is the first study to describe an LV-volume–based method for estimating the $E/A_{\text{MR}}$ ratio at high temporal resolutions.

The peak filling rates and ejection rates have a direct dependence on LV function and wall motion. There was a progressive decline in all the filling rates as the temporal resolution worsened. For example, the PFR declined from $724\pm131$ ml/s ($5.0\pm0.9$ EDV/s) at a temporal resolution of 6 ms to $544\pm93$ ml/s ($3.8\pm0.5$ EDV/s) at a temporal resolution of 36 ms. These results suggest that the temporal resolution is a key parameter that needs to be taken into account when estimating the filling or ejection rates. For example, previous investigators (104, 105) who used lower-temporal-resolution MR imaging and other researchers (73, 74, 106-108) reported filling and ejection rates that were substantially less ($PFR \sim 3.3\pm0.6$ EDV/s) than those observed in our study. Our results suggest that such reductions in the filling and ejection rates arise from a lower temporal resolution. A similar decline was evident for the PER and PAFR. These previous studies have already reported a decrease in the PFR (of about 10-15% at a lower temporal resolution) and an increase in TPFR in case of a diastolic dysfunction (impaired
relaxation). A higher sensitivity to the filling rates is necessary to confidently distinguish an impaired relaxation from a normal relaxation. A high temporal resolution acquisition provides this. Further age matched studies with a larger patient database would lead to better resolution of these values.

Cardiovascular magnetic resonance imaging is regarded as the gold standard in the assessment of left ventricular systolic function. As described in chapter 2, investigators have also used other MR imaging sequences (e.g., tissue tagging) to evaluate LV function and wall motion mechanics. Nevertheless, these methods are often too time-consuming and labor-intensive for use in data acquisition and analysis. Echocardiography, CT and nuclear medicine have their own short-comings, as seen in chapter 2. It is shown here that it is possible to obtain cine-SSFP images with a temporal resolution comparable to echocardiography (B-mode, approximately 6 ms) by using modern multi-channel MR hardware and appropriate acceleration techniques such as SENSE and k-t BLAST. The effect of a higher temporal resolution on the filling rates is shown, and a quantitative metric to determine the optimal temporal resolution (≤ 12 ms) is also provided in this chapter.

In Conclusion, this chapter shows that MRI can be extended to capture LV function and wall motion mechanics at a higher temporal resolution. A temporal resolution of 12 ms or better is proposed to capture the dynamics of LV systolic and diastolic processes in a cardiac-cine MR imaging sequence.
5 Arrhythmia Independent Delayed Enhancement MRI

In this chapter, the theory, methods to fulfill Specific Aim II (section 3.3), and the results obtained are listed, with a discussion of results in the end.

Delayed hyper-enhancement MRI (DE-MRI) has been shown to be a reliable method to identify irreversible myocardial injury (60). In regions of scar, both the wash-in and wash-out rates for commercially approved extra-vascular contrast agents such as Gd-chelates are slow compared to normal myocardium. In addition, the distribution volume available for Gd-chelates is larger in scar tissue than in normal myocardium (56). DE-MRI technique exploits these differences to generate contrast between normal
myocardium and scar such that a viability imaging of the myocardium is performed. The combination of high spatial resolution, myocardial to scar contrast, as well as reproducibility of the DE-MRI technique has made it a routinely used clinical tool (59).

Currently, to maximize the $T_1$ contrast between normal myocardium and scar following contrast administration, the DE-MRI technique uses an inversion recovery prepared turbo-field echo sequence (IR-TFE) for data acquisition (109). The basic principle behind this technique and its typical clinical implementation is as follows. As discussed previously, the longitudinal magnetization in regions of scar and normal remote myocardium recovers at different rates, following contrast administration. In a typical clinical implementation, an inversion recovery preparation pulse is applied as a preparation pulse to maximize contrast between irreversibly injured and normal myocardium. Following the inversion pulse, the magnetization of the two tissues (irreversibly-injured, and normal myocardium) recover toward their equilibrium magnetization at different rates. If data acquisition is timed to occur at the time point at which the contrast difference between the two issues is greatest, then irreversibly injured myocardium can be clearly identified.

In a routine clinical implementation, the acquisition is cardiac gated, and the data acquisition is timed to occur during the quiescent part of the cardiac cycle (diastole). The data acquisition window is typically restricted to be less than 200 ms (for normal heart rates), and the acquisition lasts multiple RR intervals. This type of gradient echo acquisition is also commonly referred to as the segmented k-space acquisition. Scar regions, which have accumulated contrast, have a significantly lower $T_1$ value, ensuring that they have a higher regrowth of magnetization, thereby contributing to a higher
contrast between myocardium and scar. The inversion time (TI) is chosen to null the signal from normal myocardium after 10-15 minutes following administration of a 0.1 mmol/kg or 0.2 mmol/kg of Gd-chelate using a T₁ scout sequence. IR-TFE based DE-MRI sequence is robust if every RR-interval matches the entered heart-rate, and if steady-state longitudinal magnetization (Mₐ) reached before the first shot remains the same throughout the acquisition. However, IR-TFE sequence is sensitive to arrhythmias and this is particularly true in patients suffering from premature ventricular contractions (PVC) and premature atrial contractions (PAC) (86). This is because the TI time remains constant irrespective of the heart beat duration. If there are variations in heart beats, the nulling of myocardium does not happen at the desired time, creating artifacts. The severity of the artifacts depends on irregularity of the sinus rhythm.

Current MR imaging acquisitions skip data acquired during such irregular RR intervals, at the cost of prolonging the acquisition time. Such prolongation of acquisition time might make the IR-TFE sequence beyond the realm of a reasonable breath holding time of about 16 heart beats for most clinical patients. Also, in clinical cases where a higher spatial resolution is desired, the acquisition time increases (even for patients with mild or no case of arrhythmias). In these instances, a non-breath hold sequence is desired using respiratory compensation (to account for any respiratory motion that might occur during breathing). This is typically performed using a navigator echo based respiratory motion compensation method (as explained in section 2.1.2). This typically prolongs the acquisition time in patients by a factor of two to three from the actual acquisition time, depending on the navigator efficiency of acquisition. As a result of the lengthening of acquisition time, there is increased likelihood of an arrhythmic episode to corrupt the data.
acquisition, and this is frequently the source of significant image artifacts in clinical practice.

It is hypothesized that these artifacts can be significantly reduced by designing a real-time feedback algorithm to prospectively correct the ill-effects of arrhythmias on an inversion recovery TFE sequence. The hypothesis of this work is that by keeping track of the magnetization across the entire acquisition duration, it is possible to adaptively modify the acquisition parameters to combat the detrimental effect of arrhythmias during acquisition.

The theory behind this algorithm is given in the next section followed by methods and results.

5.1 Theory

After administration of contrast, an IR-TFE sequence is performed for determination of the scar and viable tissue in the myocardium (called scar image/viability image henceforth). In this sequence, following an inversion pulse, the time (TI) it takes for the signal from a given tissue with a longitudinal relaxation time ($T_1$) is given by the expression below (110):

$$TI = \frac{1}{TR_{inv}} \log_2 \left( \frac{1}{2} \right), \quad [1]$$

where, $TR_{inv}$ is the time between the inversion pulses and varies with varying heart rate. When $TR_{inv} \gg T_1$, this equation simplifies to the more familiar form $TI = \ln(2) * T_1$. 

While equation [1] is valid for a constant TR, it needs to be updated in the context of DE-MRI sequence where the recovering magnetization is perturbed by the TFE readout, as well as potential variation in TR_{inv} between TFE shots due to irregular heart rate. The method for adapting equation [1] for a varying heart rate, in the context of DE-MRI sequence is given below.

The data acquisition in the IR-TFE sequence used in myocardial viability assessment should simultaneously meet the following two requirements: (a) the TI should be chosen such that it nulls the signal from normal myocardium, and (b) the data acquisition should occur at a prescribed portion of the RR interval, e.g., at diastole to minimize the effect of cardiac motion. A linear profile order is assumed during the TFE readout throughout this analysis (111).
Figure 5-1: Variation of longitudinal magnetization of myocardium across 2 RR intervals

The growth of longitudinal magnetization $M_z$ every cardiac cycle is shown with the time points of magnetization evolution specified for the first RR interval. The longitudinal magnetization is labeled at various stages of regrowth are suffixed with the time point of magnetization evolution and the RR interval number. For example, the magnetization at time point ‘c’ in the 2nd RR interval is named as $M_z(2)$.

The recovery of the longitudinal magnetization ($M_z$) during the first two TFE shots is depicted in Figure 5-1. $M_z$ at different points during the sequence are labeled as:

$M_a(n) = M_z$ at the time of occurrence of R wave,

$M_b(n) = M_z$ just prior to application of inversion pulse,

$M_c(n) = M_z$ at the start of TFE acquisition,

$M_d(n) = M_z$ at the end of TFE acquisition. ‘n’ refers to the specific RR interval for which the magnetization is calculated.
Let the IR-TFE acquisition have the following acquisition parameters:

- $\alpha = \text{flip angle}$,
- $\text{tf} = \text{TFE factor}$,
- $k = (\text{tf}/2) = \text{the number of flip angle applications before the center of TFE acquisition}$,
- $\text{TI} = \text{Inversion time for tissue of interest - defined as the time from the application of the inversion pulse to the start of the acquisition. For a low-high phase encoding order of the k-space, this is the actual inversion time while for a linear phase encoding order, the actual inversion time is } \text{TI} + (k \times \text{TR})$,
- $T_1 = T_1 \text{ value of tissue of interest (calculated from the entered TI and heart rate or from T}_1 \text{ map)}$,
- $T_d = \text{time delay from R wave to start of acquisition}$,
- $\text{RR}_{\text{end}}(n) = \text{time from end of acquisition to the occurrence of (n+1)th R wave}$,

For the first RR interval (occurring between the first and second ‘R’ wave), it can be assumed that the longitudinal magnetization just prior to the application of the first inversion pulse is:

\[2\]
The longitudinal magnetization of a tissue after an application of ‘k - 1’ α pulses (just before the application of k\textsuperscript{th} α pulse) from its thermal equilibrium (M\textsubscript{0}) is given by (32):

Similarly, the longitudinal magnetization at the center of acquisition during the n\textsuperscript{th} RR interval from a starting value of M\textsubscript{c}(n) (the magnetization at the start of the acquisition for the n\textsuperscript{th} RR wave) can be easily derived as:

And the magnetization at the end of acquisition can be shown as:

From the second RR interval (from the occurrence of the 2\textsuperscript{nd} R wave to the 3\textsuperscript{rd} R wave) onwards the longitudinal magnetization at the different time points can be calculated as:
From the duration of the n-1\textsuperscript{th} RR interval, the magnetization at different $M_a(n)$ can be calculated from equations [2] – [6]:

\[\text{[7]}\]

\[\text{[8]}\]

\[\text{[9]}\]

\[\text{[10]}\]

\[\text{[11]}\]

It should be noted that during the first heart beat, $M_z$ recovers from $M_0$, and as a result, $M_{\text{center}}(1)$ is very different from $M_{\text{center}}(n)$ where $n>1$. To avoid this, most clinical scanners do not use the data acquired during the first shot (dummy shot), acquisition proceeds from the second RR interval onwards. From equation [5], one can derive the expression for $M_c(n)$ for all $n > 1$:

\[\text{[12]}\]
This value of $M_c$ is constant for every acquired RR interval, irrespective of the previous RR duration. For achieving this value of $M_c$, the TI value has to be adjusted to take into account the magnetization growth during the previous RR interval. Another criterion to account for is that the phase of acquisition should be maintained constant, e.g., diastole, for all TFE shots. In other words, this condition implies that ‘$T_d$’ remains constant between TFE shots. So, any change in TI value will have a change in the time of application of the inversion pulse from the R wave ($T_d – TI$).

From the knowledge of the duration of ($n-1)^{th}$ RR wave we can calculate $M_a(n)$ from equation [7]. From this value, the desired value of $M_b$ at which the inversion pulse has to be applied, and its corresponding TI can be calculated as follows:

From equations [8] and [9]

\[ \text{[13]} \]

\[ \text{[14]} \]

Summing up equations [13] and [14], we get
Let $M_a(n)$ can be calculated from the length of the $(n-1)^{th}$ RR interval. From this, the value of $X$ can be calculated as the other terms in equation [16] are known. From equations [15] and [16] we get

\[ \text{[17]} \]

The value of TI desired can be prospectively obtained from equations [17] and [13].

\[ \text{[17]} \]

Just after the $n^{th}$ R wave occurrence, if the desired TI value is updated with $\text{TI}_{\text{desired}}$, it is expected that the artifacts would decrease significantly.

This hypothesis is simulated, tested on phantoms and human subjects. The methods and results involved in this testing are given in the following sections.

### 5.2 Methods
5.2.1 Simulation

The impact of an irregular pattern heart beat between TFE shots on image quality was simulated for two different clinically relevant scenarios: 1) bigeminy (where every other RR interval is shorter than the other due to PVCs), and 2) missed beat (an ectopic beat, that occurs prematurely. As the scanner is not expecting this, it misses this beat and waits for the next one, thereby creating a long time between the first R wave detected and the next one). Simulations were performed using MATLAB®. The signal modulation resulting from variable RR intervals was Fourier transformed to obtain the point-spread-function (PSF) (112) of the resulting simulated acquisition. For purposes of numerical simulation, a mathematically generated circular object (mimicking a vial) was subjected to IR-TFE data acquisition during arrhythmic as well as regular heart beats.

The modulation of signal intensity during the TFE readout across multiple heart beats was captured. Without phase encoding, the Fourier transform of the measured signal is the projection of the object along the frequency encoding direction, and gives a direct indication of the signal modulation across k-space. A Fourier transformation of the measured signal intensity modulation yields the Point-Spread-Function (PSF) of the pulse-sequence.

The PSF obtained from the arrhythmia insensitive inversion recovery (AIIR) prepared update of TI value was compared with the PSF without real-time update of RR interval (called the conventional method). Acquisition parameters for the simulation mimicked routine clinical IR-TFE sequence parameters: TR/TE/flip = 8 ms/ 3 ms/ 15°. Trigger delay = 600 ms; user entered heart rate: 60 beats per minute (bpm); user entered TI = 300 ms (Corresponding to a T₁ of 555 ms); TFE factor = 20; start up echoes = 4;
start up shot = 1. The simulations were performed for three tissue types – the tissue of interest (to be nulled, $T_1 = 555$ ms), a tissue with shorter $T_1$ ($T_1 = 300$ ms) and a tissue type with a longer $T_1$ ($T_1 = 1000$ ms).

The variation of the artifacts with varying $T_1$ values was also studied by measuring the artifact power at various $T_1$ values. The artifact power was calculated as the square root of the sum of squares of difference between the intensities of every pixel of the numerically generated ‘ideal’ image and the image acquired with simulated arrhythmia.

### 5.2.2 Validation – Phantom Imaging

The AIIR preparation algorithm was implemented using the Philips pulse programming environment (PPE) and patched on to the 1.5 T MRI clinical scanner (Achieva, Philips Health Care, Best, The Netherlands). This scanner was used for both validation and patient imaging.

Numerical and theoretical predictions were validated in a phantom model. Three vials containing agarose doped with Magnevist™ (Bayer HealthCare Pharmaceuticals, Wayne, New Jersey, USA) to yield $T_1$ values of 555 ms, 1215 ms and 305 ms were made, and were imaged under the conditions of arrhythmia and normal sinus rhythm, with and without the use of AIIR preparation. The acquisition parameters of the IR-TFE sequence were: $\text{TR/TE} = 8/3$ ms; $\text{flip} = 15^\circ$; TFE factor = 22; field of view = 400 mm * 400 mm * 8 mm; voxel size = 2 mm * 2 mm * 8 mm; $\text{TI} = 300$ ms; start-up echoes = 4; k-space filling profile = linear (sequential). IR pulses were applied every heart beat. The images were obtained for the two different heart scenarios: missed beat (9 RR intervals – 4
*1000 ms; 1600 ms; 4*1000 ms) and bigeminy (9 RR intervals – alternating 1000 and 800 ms intervals), each simulated using the heart rate simulator feature in the scanner.

Two sets of data were acquired, one with conventional frequency and phase encoding to generate the 2D images, and the other with in-plane phase encoding gradients turned off. Turning off the phase-encoding gradients results in 1-dimensional projection images of the vials (1DFT), and enable the user to capture the signal evolution during the read-out.

The quality of phantom images obtained (both 2D and 1DFT) with and without AIIR preparation is compared against each other.

5.2.3 Validation – Patient Imaging

22 patients undergoing clinical cardiac MR imaging were recruited for patient imaging purposes. The study was approved by the local ethics committee, and all subjects provided written informed consent.

After running the initial scout sequences, images of the heart were obtained in the long axis, the 4-chamber, and the short axis views. The contrast agent, Magnevist (Bayer HealthCare Pharmaceuticals, Wayne, New Jersey, USA), was administered and a Look-Locker (113) sequence was performed ~ 10 minutes after the administration of the contrast agent to identify the presence of the scar in the myocardium, and an appropriate inversion time. After identification of the scar region, a myocardial viability sequence (IR-TFE) of the short axis view of the left ventricle at the scar region is obtained using the following typical imaging parameters: TR/TE = 8/3.5 ms; flip = 15°; TFE factor = 22; field of view = 350 mm * 350 mm * 8 mm; voxel size = 2 mm* 2 mm * 8 mm; TI = 300
ms; start-up echoes = 4; k-space filling profile = linear (sequential); start-up shot(s) = 1. Acquisition was made in around 7 RR intervals, depending on the FOV and the actual heart rhythm of the patient.

Then, 3D images were obtained (with and without the AIIR preparation), covering the entire left ventricle. Typically 12-14 slices are obtained in the short axis orientation with a slice thickness of 8 mm. The imaging parameters for the 3D imaging are: startup shot = 1; number of RR intervals = 11-14 shots; field of view = 360 mm; TR/TE/flip = 4.8/2.3/15; TFE factor = 20; voxel size = 2.0 *2.0* 8 mm. Typical acquisition duration ~ 25-30 seconds. Navigator compensation for respiratory motion is used. Total scan duration is anywhere between 60 – 246 seconds.

The 3D image quality obtained with and without AIIR preparation were compared with each other by an expert cardiac observer (> 7years experience in cardiac MRI). Each image was scored blindly for the a) overall image quality; b) overall scar quality and c) nulling quality of myocardium. The scores were between 1 through 5, with 1 being non-diagnostic and 5 being excellent image quality. In both the cases, the number of RR intervals and their length during acquisition for all the patients were recorded during the acquisition.

5.3 Results

5.3.1 Simulation

The signal evolution across k-space during the TFE readout in the case of bigeminy is shown in Figure 5-2 A. Note the oscillating signal intensity as a result of the
periodically varying RR intervals in the case of bigeminy. The corresponding PSF demonstrates a sharp variation in the central lobe (resulting in insufficient nulling) as well as significant increase in signal intensity at side lobes (resulting in ghosts). With AIIR preparation, this extent of variation in signal intensity across the readout is substantially diminished (solid line). The corresponding improvement in PSF with diminished signal intensity in the side-lobes can also be seen (Figure 5-2 B).

In the case of a missed beat, notice the prominent increase in signal during one shot (Figure 5-2 C, dotted line), and the elimination of this signal modulation with AIIR preparation (Figure 5-2 C, solid line). With AIIR preparation, the side-lobes of the PSF have diminished signal intensity (Figure 5-2 D) resulting in lower amplitude ghosts.

The artifact power calculated for the two different heart rhythms (bigeminy and missed beat) as a function of the $T_1$ of various tissues normalized to the tissue $T_1$ (defined as $\beta$) of interest is shown in Figure 5-3. It can be seen that the artifact power of the AIIR preparation is significantly lower when compared with the conventional method for a wide range of $T_1$ values around the tissue of interest for both arrhythmia conditions considered above.
Figure 5-2: Signal Intensity evolution and Point-Spread Function in arrhythmia

Numerical simulations of the signal intensity evolution during image acquisition (left panels) and the corresponding point spread function (PSF) of data acquisition are shown (right panels). In the case of bigeminy (top row), note that reduction in the amplitude of the oscillatory signal with AIIR preparation (solid lines), compared to conventional IR preparation (A). There is a corresponding reduction in the amplitude of the side-lobes in the PSF (B). In the case of missed beat (bottom row), the extent of signal variation caused by the missed beat is substantially reduced with AIIR preparation (solid lines), and a corresponding improvement in the PSF with AIIR preparation can be seen (D).
Figure 5-3: Variation in artifact power with varying $T_1$ values

The artifact power for a range of $T_1$ values is shown in this figure. The x-axis corresponds to the ratio of the $T_1$ values of the tissue with respect to the $T_1$ value of the tissue to be nulled ($\beta$). Figures A and B each show the comparison in artifact power between the AIIR preparation and without AIIR preparation for a bigeminy and missed beat scenario respectively. The artifact power is significantly reduced with AIIR preparation for a wide range of $T_1$ values.

Figure 5-3 depicts the artifact power calculated for the two different heart rhythms (bigeminy and missed beat). It can be seen that the artifact power of the AIIR preparation is significantly lower when compared with the conventional method for a wide range of
T₁ values. It is also observed that the artifact power increases at T₁ values much shorter that the T₁ value of the tissue desired to be nulled.

5.3.2 Validation – Phantom Imaging

The phantom imaging results from the experimental verification of theoretical predictions for the arrhythmic conditions of bigeminy and missed beat are shown in Figure 5-4 and Figure 5-5 respectively.

In the case of bigeminy, as predicted by theory, the signal intensity across the shots fluctuates as demonstrated by the 1D line profile drawn across the non-phase coded acquisition (Figure 5-4 A-C). This variation is substantially minimized with AIIR preparation. The corresponding improvement in image quality with and without AIIR preparation is shown in Figure 5-4 D, and E. A similar trend can be observed in the 1DFT and the 2DFT images acquired with and without AIIR preparation in the context of missed beat, as shown in figure 5 (see legend for more details). Results from various other arrhythmic scenarios (not shown) also showed that AIIR preparation was robust in reducing artifacts.
Figure 5-4: Experimental results: 1DFT and 2DFT images of a phantom for bigeminy

Figures A and B correspond to the 1DFT phantom validation images for the tissue $T_1$ of interest. Figure A corresponds to conventional acquisition while B corresponds to AIIR preparation. Figures C corresponds to the line profile across the 1DFT image (shown as a white line across the 1DFT phantoms in A and B) for both with and without AIIR preparation. Images (D) and (E) correspond to 2D images acquired without and with AIIR preparation respectively. It can be seen that the AIIR preparation significantly nulls the tissue of interest as well as significantly reduces the artifacts induced in the image as compared to the conventional algorithm (white arrows).

Figure 5-5: Experimental results: 1DFT and 2DFT images of a phantom for ectopic beat
**1DFT and 2DFT image of a phantom with a T\textsubscript{1} value mimicking the tissue of interest is shown in case of a missed beat.** Figures A and B correspond to the 1DFT phantom validation images for the tissue T\textsubscript{1} of interest. Figure A corresponds to conventional acquisition while B corresponds to AIIR preparation. Figures C corresponds to the line profile across the 1DFT image (shown as a white line across the 1DFT phantoms in A and B) for both with and without AIIR preparation. Images (D) and (E) correspond to 2D images acquired without and with AIIR preparation respectively. It can be seen that the AIIR preparation significantly reduces the artifacts induced in the image as compared to the conventional algorithm (white arrows).

### 5.3.3 Validation – Patient Imaging

Of the 22 recruited patients, 17 of them completed the comparison study. The study could not be completed in the remaining 5 patients, either due to contrast wash-out (these were clinical patients, and the research part had to be performed at the end), or the patients opted-out of the research part when they were inside the scanner (reasons: claustrophobia, longer stay inside the scanner). Of all the completed 17 patients, blinded Image Quality assessment of an experienced CVMR imager found that the overall image quality was improved (4.3±0.7 vs. 3.3±0.8) and nulling of myocardium (4.2±0.7 vs. 3.3±0.8) was consistently better (or equal) with AIIR than without. In 7/16 patients that had scar present, the scar quality with AIIR was consistently better (4.6±0.5 vs. 3.3±0.8). All comparisons were statistically significant (p<0.02, paired Student’s t-test). Figure 5-6 and Figure 5-7 show representative patient images obtained with and without AIIR preparation. Figure 5-6 also has the histogram of RR intervals acquired for that particular patient, demonstrating the variation in heart beat through the acquisition.
Figure 5-6: 3D acquisition of IR-TFE viability images with and without AIIR algorithm

The histogram of heart beats during the course of a volumetric IR-TFE acquisition with and without AIIR preparation are shown in panels A and B respectively. Note that although the histogram of the RR intervals reveals a broader spread and longer acquisition time with AIIR preparation compared to without, the visualization of irreversible injury in images acquired with AIIR prepared IR-TFE sequence (C) is better than the image quality of the sequence without AIIR preparation (D).
Figure 5-7: Viability images obtained from patients with and without AIIR preparation

MR viability (Scar) images obtained from three different patients are shown. The sequences were acquired for about 80-120 seconds each, using a navigator guided IR-TFE sequence. The scar appears on all three patients as the bright region in the dark (nullled) myocardium. The scar appears sharper with AIIR algorithm, while without AIIR an overestimation of scar region occurs, as well as a poorer nulling of myocardium. An expert observed rated that the AIIR preparation produces superior a) overall image quality; b) scar quality and c) nulling of myocardium when compared to images obtained without AIIR preparation.

5.4 Discussion of Results
The results from phantom imaging and patients demonstrate that the AIIR preparation yields superior scar images when compared to conventional images with no AIIR preparation. A detailed discussion of the results from this chapter is presented below.

It is well known that even in subjects with normal sinus rhythm, heart rate can vary substantially during the course of the imaging session, and even within a single breath hold. There are many clinical conditions in which cardiac patients suffer from periodic and aperiodic arrhythmias such as bigeminy or ectopic beats. Several strategies have been proposed to minimize the impact of such heart rate variations, e.g., prospective arrhythmia rejection, or motion correction. Such arrhythmias have a detrimental effect on image quality, particularly for inversion recovery prepared acquisitions.

The results from fulfilling specific Aim II demonstrate the following. First, the theoretical and experimental simulations show that the presence of arrhythmias such as bigeminy and missed beat during acquisition can significantly degrade image quality. The creation of side-lobes with significant power results in image ghosts, and can mask the pathology of interest. In addition to the presence of ghosts, in the case of bigeminy, there is a significant loss of contrast in the object of interest, which is substantially restored with AIIR preparation.

Secondly, the algorithm proposed in this chapter attempts to optimize the nulling of a specific tissue with a pre-determined $T_1$. However, numerical simulations in Figure 5-3 show that the algorithm effectively reduces the artifact arising due to arrhythmias for a broad range of $T_1$ values. The artifact power is increased with the AIIR preparation for
tissue $T_1$ values that are less than 60% of the $T_1$ of the tissue of interest selected for signal nulling. However, in the context of DE-MRI imaging, this is not an issue for the following reason. In clinical practice, the typical TI chosen in DE-MRI to null the myocardium is in the range of 210-420 ms (corresponding to an effective $T_1$ in the range of 300-600 ms). There are very few biological tissues of interest at $T_1$ values that are less than 300 ms. In particular, in the context of myocardial viability imaging, all relevant tissues, blood, myocardium, and fat have $T_1$ values that are in excess of 200 ms. This can be seen in all the clinical images obtained as well, where there were no significant induced artifacts present, as seen in Figure 5-7.

Thirdly, the patient results demonstrated that the algorithm performed significantly better on overall image quality, scar quality and nulling of myocardium. This result was seen consistently on all the 17 patients imaged, in whom the AIIR prepared scar images scored equal or better than the scar images acquired using conventional sequence (without AIIR preparation). This helps the physician determine the exact location and burden of the scar. A blurred scar might over-estimate the burden of scar as well its location. Clinically it is important that the imaging methodology yields these results with the best accuracy possible for better treatment planning and response.

Fourthly, AIIR preparation offers other advantages as well. For example, in conventional IR-prepared sequences, data from the first shot is discarded to allow the longitudinal magnetization to reach a steady state. AIIR preparation allows for the possibility of including the data from the first shot if the duration of the TI and readout fit within the confines of an RR interval. Although not demonstrated now, an effective alternative would be to reduce the flip angle of the inversion pulse to fit the TI within the
boundaries of available RR interval. While this particular chapter deals with the implementation of an AIIR preparation in the context of DE-MRI sequence (for better viability images), it can easily be adapted to other cardiac gated or respiratory gated IR prepared sequences as well.

Lastly, the result from the acquisition mimicking arrhythmias dramatically demonstrates the degradation in image quality even with one or two episodes of arrhythmias during acquisition Figure 3-1). This is particularly important in the context of high resolution imaging. There is an increasing clinical need for obtaining high resolution DE-MRI sequences for the accurate visualization of small sub-endocardial scar, fibrosis, e.g., visualization of atrial or pulmonary venous scar in patients following ablation, or in the evaluation of fibrous replacement of RV free wall in subjects suspected to have RV dysplasia, or other non-ischemic cardiomyopathy. Such high resolution acquisitions need data collection to occur over several tens of heartbeats, and the probability of encountering arrhythmias during the prolonged scan time is much higher.

Overall, although the conventional breath-held IR-TFE acquisition is robust against small variations in the heart rate, it becomes problematic for the patients with heavily varying heart rate. Also, for scans involving higher spatial resolution and/or limited breath-holding capacity of the patient, free breathing respirator guided scans (with increased scan time), even smaller variations in RR intervals add up to cumulatively higher artifacts. Recent advances in IR-TFE sequence such as phase sensitive inversion recovery (PSIR) sequences require two RR intervals for each shot (114), and such long RR intervals make the DE-MRI sequence more robust against variations in RR intervals. The penalty of PSIR sequences is the near doubling of scan time, which in the context of
3D imaging could be particularly costly. Given the growing importance of obtaining a high spatial-resolution 3D viability/scar image for better sensitivity towards thin sub-endocardial scars, AIIR preparation assumes more significance in providing a better scar image. Scar burden directly relates to mortality and morbidity. This is particularly helpful when performing CRT-pacemaker implantation where the scar burden and location decides the treatment planning and response.

Some challenges in the current implementation of the AIIR prepared DE-MRI sequence is the need for the knowledge of the apparent $T_1$ of the tissue of interest. This typically requires an additional acquisition, e.g., a Look-Locker, or a MOLLI type of sequence that entails an additional breath hold (115,116). But such sequences are already performed as part of the conventional scanning protocol to determine the exact tissue inversion time.

In conclusion, in this chapter, the theoretical basis and experimental verification of an implementation of an arrhythmia insensitive inversion recovery prepared sequence has been presented. The results from the study show that arrhythmias can introduce significant artifacts in conventional IR-prepared DE-MRI sequence. Results from numerical simulations, and phantom validation studies show that AIIR preparation can effectively address these artifacts. Human clinical studies reveal the clinical utility of this approach. AIIR preparation might be particularly beneficial for obtaining high resolution DE-MRI images.
6 Conclusions, Limitations and Future Work

6.1 Thesis Statement:

'It is possible to perform an improved assessment of the heart using MR imaging of the LV that can provide more and better information about 1) the LV function and wall motion mechanics and 2) the scar burden and location in the myocardium.'

Results from Specific Aims I and II show the methods proposed in this thesis and the algorithms developed have extended the applications of MRI to perform an improved assessment of A) LV function and wall motion mechanics and b) the scar burden and location assessment.

Chapter 2 has established that the existing multiple imaging modalities provide information about specific pathologies of the heart. The ideal modality should successfully image the: 1) LV function and wall motion mechanics; 2) Morphology of the heart and surrounding vascular structures; and 3) Perfusion and viability of the myocardium.
There is ongoing research to obtain maximum amount of information from a single imaging session. For example, the recently introduced 3D echocardiography has increased the SNR of echocardiography (compared to 2D), thereby estimating the LV volume and function more reliably; better hardware (like the 320 slice CT scanners) has significantly decreased the radiation burden associated per scan. Similarly, this thesis concentrates on extending the benefits offered by MRI for heart imaging, by mitigating some of the challenges it faces, such that MRI could potentially become a one-stop choice for heart imaging. Based on the discussion in Chapters 2, and 3, while MRI has a number of favorable attributes such as soft-tissue contrast, freely angulated field-of-view without the constraints of acoustic windows, lack of radiation burden, and the ability to measure tissue velocity, it has some significant limitations to make it the imaging modality of choice for assessing cardiovascular disease.

Two of the major limitations of MRI are the poor temporal resolution (compared to echocardiography) in assessing diastolic functional indices such as IVRT, and the sensitivity of many imaging methods to motion artifacts caused by arrhythmias during data acquisition. This leads to the two challenges identified through this thesis: 1) The relative inability of MRI to provide comprehensive information regarding LV function and wall motion and 2) its challenges in reducing arrhythmia related artifacts in viability imaging.

The specific contributions of this thesis are as follows.

First, the current clinical CMR assessment of LV function is restricted to systole, primarily due to the low frame rate on the order of 20-30 fps. This work demonstrated
the feasibility of improving the temporal resolution of cardiac cine imaging to the tune of 120-150 fps that is roughly in the same line with echocardiographic methods. Increasing the frame rate of cardiac cine imaging scales the post-processing requirements, and could hamper the extraction of LV functional metrics. Furthermore, to facilitate the clinical adoption of this high frame rate acquisition, the clinical feasibility of improving the temporal resolution of cardiac cine MR to a rate of about 120-150 fps.

The lack of a high temporal resolution and complex post-processing were proposed as the primary challenges facing MR imaging to provide comprehensive information regarding LV function and wall motion. Cine imaging was decided as an ideal methodology primarily due to its relatively simpler post-processing. A combination of newer hardware, post-processing algorithms to extract the time-volume information, and data-processing algorithm to extract functional metrics (that were already proven to distinguish a diseased LV function from normal function in other imaging modalities) were proposed and implemented. A final temporal resolution of 6 ms was achieved, and an extensive search in ‘pubmed’ reveals that this is the highest temporal-resolution achieved so far in cine cardiac MR imaging. The in-house developed and validated post-processing algorithms were able to yield the LV time-volume curve from which LV functional metrics were obtained successfully. The temporal dependence of the functional metrics and a temporal cut–off of 12 ms were also established. This high-temporal resolution cine MR imaging provides a temporal resolution comparable to 2D echocardiography while also providing significantly improved SNR and volume characterization.
MR imaging of myocardial viability (and scar) is the current industry gold-standard. Though MR is superior to other modalities in identifying irreversible injury, it still faces challenges that restrict it from providing high spatial-resolution images or from imaging patients with severe arrhythmia. These challenges are primarily due to the respiratory physiology and cardiac arrhythmias. This thesis has proposed an algorithm that would alleviate the artifacts induced due to arrhythmias, thereby extending this method to a higher spatial resolution, respiratory motion compensated lengthier imaging session. The algorithm was simulated, and experimentally verified on phantoms. The efficacy of this algorithm was proved in a group of 17 patients, by a blinded scoring of images, in which the algorithm significantly improved the image quality of the viability images.

This thesis has proposed novel algorithms to extend MR imaging to high temporal resolution functional imaging and high spatial resolution viability imaging. Certain limitations exist in this thesis. Few of them can be addressed through further work, while others are inherent to the methodology used. These limitations are listed below, with some of the future work needed that could address these limitations.

6.2 Limitations and future work

1) Reference value for LV functional metrics: This thesis establishes the need for high temporal cine imaging, and the needed temporal resolution for imaging. Previous literature has established normal reference values of functional metrics like PFR and PAFR in nuclear medicine. The values they have reported are significantly lower than the values seen in this study, probably due to the poorer temporal resolution. For clinical
utilization of these metrics, reference values in normal volunteers and in patients with impaired function (impaired relaxation and impaired ejection) have to be established. Such a study needs to have a significantly higher number of subjects. This study should entail age-and gender matched groups (age group of 20-80 divided into 6 groups, with 20 patients (10 male) in each group and an equal number of normal subjects). A similar population is required in the patient group with impaired LV function. This would need a patient/volunteer size of n = 240, and a correspondingly longer study.

2) The Modified Simpson’s Model: The modified Simpson’s model helps avoid acquisition of multiple short-axis slices. But it significantly increases the work load as the length between the mitral-valve annulus and the apex are determined manually. This also introduces error in measurement that can be partially mitigated by averaging. A simpler (automated or semi-automated) method to determine the length needs to be devised to make this method more practical. For example, the mitral valve annulus can be tagged and tracked by image-processing algorithms such that the lengths can be calculated automatically.

3) Temporal Resolution cut-off value: The 12 ms cut-off temporal resolution would be suspect in patients with significantly high heart rate (>100 bpm) as the transient events occur faster. This has to be studied further on these patients.

4) Contrast wash-out in viability imaging: One of the limitations of the proposed AIIR algorithm for viability imaging is that there is a wash-out of the contrast during acquisition, leading to a change in the T₁ value of the myocardium. But the entire acquisition duration is around 2 minutes with normal navigator efficiency, and the
contrast wash-out during this acquisition is negligible. In cases of patients with poor respiratory compensation, this might prove to be a burden.

5) High heart rate issue in viability imaging: In people with high heart rate (>100 bpm), the AIIR algorithm might not have enough room to adjust the inversion time during runtime and maintain the same cardiac phase of acquisition. In these cases, acquisition can be made every other heartbeat, where the algorithm would still be useful, although increasing the acquisition duration.

*In conclusion, this thesis extends MR imaging to perform an improved assessment of the heart (LV) that can provide more and better information about 1) the LV function and wall motion mechanics and 2) the scar burden and location in the myocardium.*
REFERENCES


