CARDIAC TISSUE CHARACTERIZATION FOLLOWING MYOCARDIAL INfarCTION USING MAGNETIC RESONANCE IMAGING

by

Jay S. Detsky

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

Graduate Department of Medical Biophysics

University of Toronto

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Abstract

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This thesis describes the development of new magnetic resonance imaging (MRI) methods to characterize cardiac tissue with myocardial infarction (MI). Wall motion imaging (for visualizing myocardial contraction) and viability imaging (to identify MI) are two components of cardiac tissue characterization used for prognosis and treatment planning. MRI-based wall motion and viability methods are considered the gold standard in imaging, and characterization of MRI viability images has been correlated with inducibility for ventricular tachycardia (VT). However, viability imaging with MRI has limitations such as difficulty visualizing the blood-infarct border. Wall motion and viability images are acquired separately, each requiring cardiac gating and breath holds, leading to long scan times. A novel multi-contrast delayed enhancement (MCDE) sequence was developed that simultaneously acquires wall motion and viability images. In a patient study, the MCDE sequence was demonstrated to provide improved visualization of MI compared to the conventional inversion-recovery gradient echo (IR-GRE) sequence, particularly for small infarcts adjacent to the blood pool. MCDE images
also provided accurate wall motion images that could be used to calculate the left ventricular ejection fraction. An image processing algorithm was developed to analyze MCDE images to segment and classify the infarct gray zone, which is hypothesized to represent heterogeneous infarct responsible for causing VT. In a study of 15 patients with MI, the MCDE-derived gray zone was shown to be less sensitive to image noise than the IR-GRE-derived gray zone, and did not require manual contours of the blood pool which contributes to additional variability in the IR-GRE gray zone analysis. Finally, a real-time delayed enhancement (RT-DE) method was developed to provide black-blood viability images without requiring cardiac gating or breath holds. RT-DE imaging was shown to have a high sensitivity for detecting MI in a study of 23 patients. The methods described in this thesis help expand the patient population that can undergo a cardiac viability exam and help improve the visualization of myocardial infarct. Further modifications in the pulse sequences to improve the temporal and spatial resolutions are proposed with the goal of predicting and guiding treatment of ventricular tachycardia resulting from myocardial infarct.
Acknowledgements

I need to first thank my supervisor, Graham Wright, who guided me through every step of my graduate degree, whose insight helped shape the contents of this thesis, and who always challenged me to see the big picture. I also need to thank my committee, Anne Martel, Alex Vitkin, and Sandy Dick in particular, for helping to make the process of obtaining my degree as smooth as possible. Sandy always had time to discuss the clinical aspects of my research, and he showed me the impact cardiac MRI can have on patients’ lives.

It is difficult to express how grateful I am to Sandy’s fellows, John Graham, Ram Vijayaraghavan, Kim Connolly, and Gideon Paul. All four worked tirelessly to recruit patients for my studies and spent countless hours analyzing data for my papers and discussing interesting cases. The unique friendships I have with each of them made my time at Sunnybrook that much more enjoyable.

None of this work would have been completed without the efforts of a large number of additional people at Sunnybrook and beyond. I would like to recognize Chris Macgowan for giving me my start in cardiac imaging research. I am grateful to Warren Foltz and Rohan Dharmakumar, who showed me the ropes when I first arrived in the Wright lab. Special thanks go out to other Wright group members Garry Liu, General Leung, and Kevan Anderson for insightful feedback on my research. I owe a huge debt of gratitude to Mihaela Pop for our collaboration on the animal arrhythmia model, and for always keeping me on my toes (and for doing the same to Graham).

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and continues to be an incredible resource for the entire Wright group. I would like to acknowledge the extremely hard work of the animal technicians Carrie Purcell, Denise Pantlin, Krista Holdsworth, and Jen Graham, who worked extremely long nights to make sure our animal imaging experiments went smoothly. I would also like to thank the MRI technologists Caron Murray, Ruby Endre, and especially Rhonda Walcarius, for their expertise in scanning hundreds of cardiac patients as part of research studies I have been involved with.

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## List of symbols and abbreviations

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<th>Full Form</th>
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<tbody>
<tr>
<td>BW</td>
<td>Bandwidth</td>
</tr>
<tr>
<td>CNR</td>
<td>Contrast-to-noise ratio</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>DE-MRI</td>
<td>Delayed enhancement magnetic resonance imaging</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection fraction</td>
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<tr>
<td>EP</td>
<td>Electrophysiology</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full width half maximum</td>
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<tr>
<td>Gd-DTPA</td>
<td>Gadolinium diethylene triamine pentaacetic acid</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>Hematoxylin and eosin</td>
</tr>
<tr>
<td>ICD</td>
<td>Implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>IR</td>
<td>Inversion recovery</td>
</tr>
<tr>
<td>IR-GRE</td>
<td>Inversion-recovery gradient echo</td>
</tr>
<tr>
<td>IR-SSFP</td>
<td>Inversion-recovery steady-state free-precession</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle or left ventricular</td>
</tr>
<tr>
<td>MCDE</td>
<td>Multi-contrast delayed enhancement</td>
</tr>
<tr>
<td>MCE</td>
<td>Myocardial contrast echocardiography</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic resonance angiography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NEX</td>
<td>Number of excitations</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PM-MI</td>
<td>Papillary muscle infarction</td>
</tr>
<tr>
<td>PSIR</td>
<td>Phase sensitive inversion recovery</td>
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</table>
RF  Radiofrequency
RT-DE  Real-time delayed enhancement
RV  Right ventricle or right ventricular
SD  Standard deviation
SI  Signal intensity
SNR  Signal-to-noise ratio
SPECT  Single photon emission computed tomography
SS  Steady-state
SSFP  Steady-state free-precession
T₁  Longitudinal relaxation rate
T₂  Transverse relaxation rate
TD  Delay time
TE  Echo time
TI  Inversion time
TR  Repetition time
TTC  Triphenyl tetrazolium chloride
VPS  Views per segment
VT  Ventricular tachycardia
**Statement of Contribution**

This thesis presents work done by myself in conjunction with other members of the Wright group lab and with cardiology fellows at Sunnybrook Health Science Centre. The ideas for the research presented were developed by me, but with a great deal of feedback and guidance from my supervisor, Dr. Graham Wright. All simulations were performed via computer modelling, which was done solely by me. The two new pulse sequences, described in Chapters 2 and 4, were written by me with help from Jeff Stainsby and Venkat Ramanan. The image processing described in Chapter 3 was developed and the software was written exclusively by me.

The MRI data was acquired by an experience MRI technologist under the supervision of Dr. Graham, Dr. Vijayaraghavan or Dr. Paul. However, the real-time data described in Chapter 4 was acquired by me. All data analysis was performed by me other than the manual contours of wall motion images and the visual scores of images (Chapter 3) that required a cardiologist with experience reading MRI scans. All studies described in Chapter 5 are being organized by me with the exception of the two studies in Section 5.4.5, which are being led by Dr. Yuesong Yang using the multi-contrast delayed enhancement pulse sequence that I developed.
Chapter 1

1 Introduction

Ischemic heart disease (IHD) is characterized by reduced blood flow to myocardial tissue, normally due to the progression of atherosclerosis in the coronary arteries. An atherosclerotic plaque can build up gradually, creating a stenosis (narrowing) in a coronary artery. A stenosis may lead to an insufficient supply of blood to an area of cardiac tissue when there is an increased demand for oxygen, for example during exercise. Alternatively, an atherosclerotic plaque can rupture which can lead to a thrombosis at the site of rupture or an embolus in the coronary artery downstream from the plaque. This may lead to the complete obstruction of blood flow to downstream tissue. Ischemia refers to the situation where the oxygen demand of the tissue is not met by the supply of oxygen due to reduced blood flow. Ischemic myocardium exhibits reduced contractile activity, limiting the pumping ability of the heart. Severe and prolonged ischemia may lead to permanent damage in the form of cell death, called myocardial infarction (MI). MI can lead to heart failure, a situation where the heart cannot pump a sufficient amount of blood to oxygenate other organs in the body.

This thesis deals with the assessment of myocardial tissue in patients with known or suspected MI due to IHD. Magnetic resonance imaging (MRI) is considered the gold standard for the assessment of myocardial contractility and for the detection of MI; therefore, this thesis presents new MRI-based methods for improved characterization of cardiac tissue following MI. Chapter 1 discusses the context in which an imaging assessment of myocardial tissue is performed; the current state of the art in myocardial imaging with MRI and other imaging modalities is also described. The limitations of the current MRI-based methods for cardiac tissue assessment are examined and provide the motivation for the bodies of work described in Chapters 2, 3, and 4. This thesis concludes with future directions for myocardial imaging with MRI in Chapter 5.
1.1 Myocardial infarction

1.1.1 Importance and impact

Cardiovascular diseases are the underlying cause of death for 1 in 3 Canadians [1]. Ischemic heart disease (IHD) accounts for the greatest percentage of deaths attributed to cardiovascular disease (56%). Cell death, or myocardial infarction, may occur in regions of ischemic tissue. Myocardial infarction begins with cellular necrosis characterized by the rapid loss of cellular homeostasis and plasma membrane rupture [2]. Collagen deposition begins at the site of the MI approximately seven days after necrosis begins, and ends three to four weeks later [3]. Infarcted myocardial tissue has limited or no contractile activity and leads to impairment in the heart’s pumping ability; the heart may then progress towards heart failure.

Patients with MI may present in the acute or chronic setting. The acute setting occurs immediately after an atherosclerotic plaque rupture or during stress-induced ischemia (angina) in the presence of a coronary artery stenosis. During an acute episode, the goal of treatment is the rapid restoration of blood flow (called reperfusion) to eliminate ischemia and limit the amount of MI. Percutaneous coronary intervention (PCI) is the reperfusion method of choice during an acute MI, and the benefit is maximized if the time from the onset of symptoms to the PCI procedure is kept to less than 90 minutes [4]. Medical therapy, an alternative to PCI, uses thrombolytic agents and anticoagulants to try to break down any blood clots in the coronary arteries. Coronary bypass surgery is another alternative therapy for reperfusion; bypass surgery involves the implantation of an artery or vein to bypass an occlusion or stenosis. In the acute setting, an electrocardiogram (ECG) and biomarkers are used to determine whether or not a patient’s symptoms are in fact caused by ischemia (see Sec 1.2). If the ECG is positive, the patient is normally sent for an emergency PCI procedure.
However, ECG and biomarkers are frequently inconclusive for chronic infarcts (see Sec 1.2 for details). In these cases, an imaging assessment of the myocardium can be used to determine the best course of treatment. An infarct is normally considered chronic four weeks or later after the ischemic episode. Chronic infarcts are found in a number of different scenarios. Chronic MI may be downstream of a stenotic artery that has not been successfully treated, or one that has never been treated at all. Restenosis, an atherosclerotic build up at the site where a metal stent was placed during PCI, can cause ischemia and potentially increase the amount of scarring at a pre-existing MI. Chronic MI may also be asymptomatic; unrecognized myocardial infarction has been found in 23% of patients with suspected coronary artery disease but no history of prior MI [5]. In contrast to the acute setting, an emergency procedure is not typically required for a chronic MI; therefore, an in-depth imaging assessment can be used for prognosis and to help determine the best course of treatment. For this reason, the scope of this thesis is limited to myocardial tissue imaging of chronic MI.

The first question that needs to be answered with regards to a chronic MI is whether reperfusion would provide any benefit. The goal of reperfusion is to eliminate ischemia to limit the amount of MI and to allow the tissue to recover some contractility. However, the recovery of wall motion is dependant on the transmurality of the infarct [6]. Transmurality refers to the percentage of tissue across the myocardial wall thickness that is infarcted (Figure 1.1). A fully transmural infarct has almost no chance of wall motion recovery because there is no residual viable tissue with contractile potential. On the other hand, MI with less than 25% transmurality has an 80% chance of functional recovery [6]. Results also show that patients who undergo interventional revascularization procedures without any residual viability (i.e. a fully transmural infarct) in the tissue downstream from the affected coronary artery have a poorer long-term prognosis than patients who have some residual viability [7]-[9]. Therefore, infarct transmurality may be used to determine whether PCI or bypass surgery can provide any benefit in terms of functional myocardial improvement. Quantification of infarct size is also important for any patient with chronic MI because patients with a large infarct are six times more likely to die in
Figure 1.1: Magnetic resonance short-axis viability images from a patient with a left ventricular (LV) myocardial infarct. The LV myocardial wall is located between the two red circular contours, while the right ventricular (RV) blood pool can sometimes be seen in these short-axis images. (a) A non-transmural infarct (area with a bright signal intensity, circumscribed in green) that spans 50% of thickness across the myocardial wall. (b) A fully transmural infarct (circumscribed) that extends through the entire thickness of the myocardial wall.

the two years following their heart attack than patients with a small infarct [10]. For asymptomatic patients with suspected coronary artery disease, the presence or absence of MI is useful for prognosis because there is a strong association between the presence of MI and increased cardiac mortality [5],[11].

Visualization of cardiac wall motion can be used to assess the size of any ischemic and/or infarcted tissue with reduced contractility. Cardiac wall motion information can be used to determine the ejection fraction (EF) of the heart, the percentage of blood in the left ventricle that is ejected during each heart beat. The EF in a normal individual is between 55 and 70 percent. EF is the most important clinical descriptor of global left ventricular function, and an EF of less than 40% is indicative of systolic heart failure [12]. Clinicians are also interested in whether an MI may lead to other cardiac abnormalities, such as arrhythmias, in order to plan secondary preventative measures (see Sec 1.1.2). Image assessment of myocardial tissue can provide answers to the clinical questions posed above, and is therefore a valuable tool for diagnosis and treatment planning for patients with chronic MI.
1.1.2 Relationship to cardiac arrhythmias

Surrounding infarcted tissue is a peri-infarct rim that exhibits reduced contractile activity. Areas of the peri-infarct rim may be comprised of a mixture of scar tissue and surviving myocytes [13],[14]. This mixture of electrically conducting (viable) and non-conducting (infarcted) tissue can lead to the formation of a reentry circuit [15]. A reentry circuit is an area of tissue around which the action potential (an electrical wave that stimulates the contraction of myocytes) is altered; this causes the myocardium to be re-excited (electrically) before the next sinus (normal) wave arrives, causing additional high frequency heart beats. Reentry circuits can potentially lead to ventricular tachycardia (VT), a rapid heart rate (>100 beats per minute) originating in the ventricle. VT can degenerate into ventricular fibrillation and cardiac arrest, potentially leading to sudden cardiac death.

VT is increasingly being treated with an implantable cardioverter-defibrillator (ICD) [16]. An ICD continuously monitors the electrical activity of the heart and administers a shock to reset the heart into normal sinus rhythm if it detects VT or fibrillation. The use of ICDs for primary prevention (implantation prior to any episodes of VT) has been increasing because recent studies have shown that ICDs decrease mortality in patients with chronic myocardial infarct [17],[18]. However, there are no known non-invasive tests that accurately predict which patients with myocardial infarction will go on to develop ventricular arrhythmias.

While ICD therapy is a palliative approach to patients with VT, radiofrequency (RF) ablation offers a potential curative therapy. RF ablation kills the remaining viable myocytes in an area of heterogeneous scar in order to eliminate the reentry circuits that cause VT. Currently, the identification of the reentry circuits is achieved with electrophysiology (EP) mapping, a technique that constructs voltage maps of the endocardium via an intracardiac catheter-based procedure. However, this EP procedure is an invasive and extremely long procedure (on the order of two hours) [19], maps are recorded at a low spatial resolution (4 – 5 mm) and may fail to identify reentry circuits deep in the myocardium [20]. These limitations contribute to the 30 – 40% failure rate of
RF ablation procedures, where the presence of VT is not eliminated [21]. A high resolution and non-invasive imaging method to identify these reentry circuits may help to guide the RF ablation procedure and improve the success rate.

1.2 **Myocardial assessment in ischemic heart disease**

1.2.1 **Biomarkers and the electrocardiogram**

When a patient presents with a suspected acute MI, the first two tests that are performed are an electrocardiogram (ECG) and blood tests to look for specific biomarkers. On an ECG, an abnormal Q-wave (defined as a Q-wave with a duration of 30 ms or more) is used to identify MI [22]. However, 25% of MIs are clinically unrecognizable on the ECG [23], and the ECG cannot always determine the site of infarction. An elevation of the ST segment of the ECG is indicative of ongoing ischemia; the ST segment occurs during the time between the S wave (the end of ventricular depolarization) and the beginning of the T wave (ventricular repolarization). Blood biomarkers, such as the enzyme creatine-kinase MB or the proteins troponin I or troponin T, are a sensitive method for detecting the presence of MI in the acute setting, although the biomarker concentrations do not begin to rise until 4 – 6 hours after the onset of symptoms [24]. Additionally, these blood tests are insensitive to infarcts that are more than three days old, do not provide information on infarct location, and are only moderately accurate in determining infarct size [25]. Biomarkers only indicate the presence or absence of MI and do not identify ischemic conditions that may lead to infarction if left unresolved. If the biomarker tests are positive but there is no ST segment elevation, the MI is thought to be less severe. There may be a role for portable ultrasound to be used for the rapid detection of an ischemic wall motion abnormality in the acute stage when the ECG is inconclusive and before the four hour mark when blood biomarkers begin to rise. In the chronic setting, biomarkers and the ECG are not highly sensitive to MI and do not provide information regarding the transmurality of the infarct [23]; therefore, further tests are required.
Figure 1.2: Wall motion images of a human left ventricle acquired using MRI. Shown are 10 (a-j) of the 20 acquired images at difference phases of the heart cycle of a single short-axis slice. Each image is acquired at an effective temporal resolution of 50 ms. Image (c) shows the heart at end-diastole, while image (f) shows the heart at end-systole. The endocardial (inner) and epicardial (outer) contours drawn on the end-diastolic and end-systolic frames define the varying thickness of the LV wall, and are used to calculate the ejection fraction and the LV volumes and mass.

1.2.2 Non-invasive cardiac imaging

Non-invasive imaging of ischemic cardiac tissue is composed of three major components: an assessment of cardiac wall motion, perfusion, and viability. Note that in IHD, assessment of the patency of coronary arteries is also performed, normally via minimally invasive x-ray based angiography or increasingly with non-invasive x-ray computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Improving CTA and MRA is an active area of research; however, this thesis deals with assessment of cardiac tissue and not the coronary arteries. Additionally, while angiography is useful for determining whether an atherosclerotic plaque is present, it does not help determine the potential benefit of reperfusion to the myocardial tissue.

The first major component of myocardial tissue assessment in IHD is wall motion imaging. Wall motion imaging produces images of the heart throughout the cardiac cycle in order to visualize the contractility of myocardium (Figure 1.2). Wall motion images are used to determine the ejection fraction of the heart as well as the end-diastolic and
end-systolic volumes of the left ventricle (LV) and the mass of the LV. The fastest and most common method for estimating the EF is with ultrasound echocardiography [26]. Echocardiography is acquired in two standard views and manual tracings of the LV wall are applied to a 3D theoretical model of the heart to generate the EF and LV volumes. A nuclear medicine scan called a MUGA (multiple gated acquisition) and x-ray CT of the heart are alternatives to echocardiography for wall motion imaging. Magnetic resonance imaging (MRI) is now considered the gold standard for wall motion imaging [27] as MRI acquires true tomographic images at any orientation for full 3D coverage of the heart, and thus provides more accurate and more reproducible measures of EF and LV volumes [26]. A more detailed description of wall motion imaging with MRI can be found in Section 1.4.

The second component of myocardial tissue assessment is perfusion imaging to assess the delivery of arterial blood to capillaries in the myocardium. Perfusion imaging is used to detect microcirculatory damage and for an indirect assessment of the patency of the coronary arteries. Single-photon emission computed tomography (SPECT) is the most commonly used method for perfusion imaging [28]; images are acquired during the initial uptake of a thallium or technetium tracer. Positron emission tomography (PET) with a rubidium or nitrogen tracer can also be used for perfusion imaging. MRI first-pass perfusion imaging examines the initial wash-in of a gadolinium-based contrast agent. MRI perfusion images are most commonly used to qualitatively assess the presence or absence of a perfusion defect. Recently, there have been efforts towards calculating quantitative measures of perfusion using MRI [29]. However, it is difficult to obtain accurate quantitative perfusion estimates because the MRI contrast agent does not remain intravascular. Myocardial contrast echocardiography (MCE) can be used for the assessment of myocardial microcirculation using a microbubble contrast agent that remains completely intravascular [30]. MCE can be used to quantitatively calculate blood velocities and blood volumes. All of the methods mentioned above may be used during rest and/or during stress with a coronary vasodilator to test the perfusion reserve (the increase in perfusion in response to vasodilation) of the coronary arteries.
The third main component of myocardial assessment is viability imaging for the direct visualization of myocardial infarct. SPECT is the most widely used imaging modality for assessing myocardial viability [31]. SPECT viability imaging is performed by examining the redistribution pattern of the thallium or technetium tracer 3 – 4 hours after the initial injection. A focal defect in the redistribution pattern of the tracer indicates the presence of MI. Due to the low spatial resolution of SPECT imaging (10 mm isotropic), the sensitivity of this method for detecting MI is 64 – 72% and the specificity for MI detection is 45 – 88% [31]. SPECT has an extremely poor sensitivity (28%) for detecting infarcts with a transmurality of 50% or less [32].

Until recently, PET was considered the gold standard for viability imaging [33]. F-18-fluorodeoxyglucose (FDG) is the PET tracer used as a metabolic analog for viability assessment. The sensitivity and specificity of this method for detecting MI is 87% and 76% respectively [34]; the sensitivity is unlikely to improve unless the current spatial resolution of PET imaging (approximately 5 mm isotropic) is improved. Viability imaging with PET is not widely used because PET equipment is not available in most hospitals.

Echocardiography has been used in two ways to indirectly assess myocardial viability. The first method is stress echocardiography (measuring the contractility of the LV) during the infusion of dobutamine, a drug that increases contractility and cardiac output. The contractile reserve (the percent increase in LV wall thickening at various locations in response to dobutamine) is then assessed; an area of MI should have zero contractile reserve while an area of tissue with residual viability should retain some contractile reserve. However, this method fails to identify 45% of myocardial segments that ultimately regain contractile function after reperfusion [35]. While MCE with intravenous microbubbles can be used to quantify myocardial perfusion, the use of MCE perfusion imaging to indirectly assess viability is significantly limited because normal tissue perfusion does not rule out the presence of MI [36]. Additionally, the presence of a large perfusion defect does not always correspond to myocardial infarct [36].
Recently, MRI has come to be accepted as the gold standard for myocardial viability imaging, with a sensitivity of 99% (in acute MI) or 94% (in chronic MI) [25]. Due to a high spatial resolution (1 – 2 mm in-plane and 5 – 8 mm slice thickness), viability assessment with MRI can detect most small subendocardial infarcts (less than 25% transmurality) [32]. MRI viability imaging is discussed further in Section 1.5. Preliminary research is being performed to examine the use of CT for viability imaging [37]; however, this method has not yet been validated clinically.

MRI has become the gold standard for wall motion and viability imaging due to the strengths of cardiac MRI as discussed above. This thesis focuses on developing new MRI-based methods for wall motion and viability imaging to improve the characterization of myocardial tissue in the setting of MI. The rest of this chapter details the requirements for cardiac imaging with MRI and the current state of the art methods for MRI wall motion and viability imaging along with the existing limitations of these methods.
1.3 Cardiac MR imaging requirements

The left ventricular (LV) wall is approximately 10 mm thick in diastole and expands to 15 mm during systole. To visualize the systolic contraction and to assess infarct transmurality, the typical target spatial resolution for cardiac MR images ranges from 1 – 2 mm in-plane with a 4 – 8 mm slice thickness. The field of view used is approximately 32 cm to avoid aliasing of adjacent tissue into the imaging volume. Between 10 and 15 adjacent 2D slices are acquired for volumetric coverage of the entire LV.

To achieve the desired spatial resolution and field of view, the total image acquisition time with MRI normally exceeds 300 ms. It is generally accepted that there is a 200 ms window in diastole where there is no cardiac motion [38],[39]. A temporal resolution of 60 ms or better is required to effectively freeze the systolic wall motion in order to visualize the systolic contraction and to accurately measure the end systolic volume [40]. Cardiac MRI uses a segmented approach to address the issue of cardiac motion. Segmented imaging splits the data acquisition window over several heart beats, and the duration of each acquisition window is reduced appropriately. Segmented cardiac imaging is achieved by synchronizing the data acquisition windows to the same phase of the heart cycle using an electrocardiogram (ECG) signal; this is referred to as ECG gating (Figure 1.3).

Segmented imaging is typically acquired over 10 – 20 heart beats; therefore, breath holds are required to avoid respiratory motion artefacts. For longer segmented acquisition times, or to alleviate the need for breath holds, navigator echoes can be used. A navigator echo alternates the acquisition of cardiac images with an image of the position of the diaphragm. Cardiac data is accepted only if the position of the diaphragm is within certain prescribed limits to eliminate the influence of respiratory motion during a free breathing acquisition.
Figure 1.3: Diagram illustrating segmented cardiac imaging with MRI; in this example, segmented imaging is used for wall motion imaging. The heart cycle is split into 20 different phases, each at a specific time relative to the R-trigger of the ECG signal. During the first heart beat, 16 k-space rows (approximately 10% of the data required for an entire image) are acquired over a temporal window of 50 ms for each cardiac phase. During the second and subsequent heart beats, a different 16 k-space rows are acquired for each image. After 10 heart beats, a complete image is formed for each of the 20 cardiac phases. If only one image over the heart cycle is required (for viability imaging, for example), the temporal window can be extended to 200 ms in mid-diastole. Note that the diagram indicates that 16 k-space rows corresponds to a specific region on the image; in actuality, the 16 k-space rows acquired within one heart beat for one cardiac phase correspond to a region of data in k-space. When the entire k-space is filled (after 10 heart beats), a Fourier transform is used to generate the anatomical image.
1.4 Wall motion imaging with MRI

1.4.1 Overview

The acquisition of MRI wall motion images resolved over the cardiac cycle is referred to as cine MRI. Cine MRI is most commonly acquired in the short axis view; the ejection fraction (EF) and left ventricular (LV) volumes are calculated using manual contours of the end-systolic and end-diastolic short axis images (see Figure 1.2). Using a segmented approach, data is acquired over 10 – 15 heart beats to build up 20 images throughout the cardiac cycle at a single imaging plane. Therefore the acquisition of each imaging slice requires a 10 – 20 second breath-hold to avoid respiratory motion artefacts. Ten to fifteen short axis imaging slices are normally acquired to cover the entire LV. An entire stack of wall motion images takes approximately 10 minutes to acquire, allowing for some rest time between successive breath-holds. The spatial resolution of cine MRI is typically on the order of 1.5 x 1.5 x 8 mm, which is adequate to detect abnormalities in the thickening of the myocardial wall.

1.4.2 Contrast mechanism and pulse sequence

Characterization of cardiac wall motion requires a good delineation of the cardiac wall via images with a high signal-to-noise ratio, excellent contrast between the wall and the LV blood, and a high temporal resolution. This is best achieved with a steady-state free-precession (SSFP) imaging sequence. Cine MRI using a segmented SSFP pulse sequence is routine on all clinical MRI scanners [27]. The SSFP sequence yields images with a high contrast-to-noise ratio (CNR) between myocardium and the blood pool (~25) with an effective temporal resolution of approximately 50 ms [41]. The CNR is measured as the difference in signal intensities between two different tissues (myocardium and blood in this example) divided by the noise in the image.

SSFP refers to a method for sampling the magnetization that forms the signal for magnetic resonance images. First described in 1958 by Carr [42], SSFP is a gradient
Figure 1.4: Magnetization behaviour during an SSFP pulse sequence. (a) The magnetization begins at (1) and is tipped by $\alpha$ ($45^0$ in this case) onto the transverse plane (the x-axis) at (2), followed by $T_1$ and $T_2$ relaxations during the 3 ms repetition time, causing the magnetization to move to (3). (b) Another RF pulse (-45$^0$) moves the magnetization to (4), and a series of alternating ±45$^0$ pulses are applied. (c) After 50-100 RF pulses, the magnitude of the transverse magnetization reaches a steady state at ±$M_{ss}$.

An SSFP readout can also be used to sample magnetization without reaching a true steady state, such as during an inversion recovery pulse sequence (see Sec 1.4.2).
1.5 Viability imaging with MRI

1.5.1 Contrast mechanism

Myocardial viability imaging with MRI is performed anywhere from 10 to 30 minutes after an intravenous injection of a bolus of contrast agent [44]. The contrast agent used for cardiac MRI is Gd-DTPA (Gadolinium diethylene triamine pentaacetic acid). The delay prior to imaging allows the Gd-DTPA to exit the blood vessels and freely diffuse throughout the extravascular, extracellular space. In an acute MI, the loss of cell membrane integrity allows Gd-DTPA to enter the intracellular space [45], leading to an increased concentration of the contrast agent in regions of acute infarct [46],[47]. In chronic MI, the presence of collagen fibres in scar tissue increases the extracellular volume leading to an increase in the concentration of Gd-DTPA [45],[47],[48]. The increased accumulation of Gd-DTPA in infarcted tissue is also influenced by delayed wash-in and wash-out kinetics caused by a decreased capillary density [49].

Prior to discussing how differences in Gd-DTPA accumulation are used to create images with contrast between healthy myocardium and MI, a brief discussion of the physics behind Gd-DTPA is required. Gadolinium (Gd$^{3+}$) is the most common contrast agent used in MRI [50]. Free Gd$^{3+}$ is toxic, but upon chelation to DTPA (diethylene triamine pentaacetic acid), it becomes a non-toxic, paramagnetic contrast agent that is cleared via the kidneys [31]. Gd-DTPA has a molecular size of 550 Da and is hydrophilic, and therefore does not enter viable cells because it cannot cross through hydrophobic cell membranes [51]. However, Gd-DTPA is small enough to exit the vasculature and diffuse throughout the extracellular space. Gd-DTPA shortens the $T_1$ of tissue, along with a slight decrease in $T_2$, through the interaction of unpaired Gd electrons with hydrogen nuclei. Gd is an extremely effective metal for use as an MRI contrast agent because it has seven unpaired electrons. The change in the $T_1$ relaxation rate of tissue is in direct linear proportion to the concentration of the contrast agent [50]:

$$\frac{1}{T_{1,observed}} = \frac{1}{T_{1,inherent}} + R_1 \times C$$ (1.2)

where $T_{1,observed}$ is the $T_1$ rate with the contrast agent, $T_{1,inherent}$ is the inherent tissue relaxation rate, $R_1$ is the relaxivity of Gd-DTPA (roughly 4.5 L·mmol$^{-1}$·sec$^{-1}$), and C is
the concentration of Gd-DTPA. This relationship exists only when the exchange of water between the intra and extra-cellular compartments is fast compared to the $T_1$ of each compartment, which has been shown to hold true for myocardial tissue [52].

As discussed above, 10 to 30 minutes after a bolus of Gd-DTPA, an increased concentration of Gd-DTPA is found in infarcted tissue compared to healthy myocardium. This causes a difference in the $T_1$ of infarcted versus healthy myocardium, which is exploited with MRI to create images where the MI appears bright and healthy myocardium appears dark. Since the image acquisition is delayed after the administration of the contrast, viability imaging with MRI is referred to as delayed enhancement MRI (DE-MRI).

### 1.5.2 Standard pulse sequence for viability imaging

The pulse sequence used clinically for standard DE-MRI scans is an inversion-recovery gradient echo (IR-GRE) sequence [53]. The pulse sequence diagram for the IR-GRE sequence is shown in Figure 1.5. IR-GRE is a segmented acquisition that requires 10 – 20 heart beats to reconstruct a single image, depending on the imaging parameters chosen. The sequence starts off with a non-selective inversion pulse at a trigger delay (TD) time after the R peak of the ECG signal. The inversion pulse inverts all of the magnetization in the imaging slice. The longitudinal magnetization ($M_z$) then recovers towards its initial magnetization according to that tissue’s longitudinal relaxation rate ($T_1$) (Figure 1.6). At the specified inversion time (TI), a gradient echo readout is applied $n$ times to acquire $n$ rows of k-space. The inversion time is chosen so that the data acquisition window is centered on the null point of healthy myocardium (Figure 1.6a). The resulting image has no signal in areas of healthy myocardium, and appears bright in regions of MI (Figure 1.6b).

The number of gradient echo radiofrequency (RF) pulses applied during each heart beat ($n$ in Figure 1.5) is referred to as the views per segment (VPS). The VPS is typically 16 – 24. The TR (approximately 6 – 10 ms) and VPS of each gradient echo readout defines
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Figure 1.5: Pulse sequence diagram for the inversion-recovery gradient echo sequence. After a trigger delay (TD) time after the R peak of the ECG signal, a non-selective 180° inversion pulse is applied. At the appropriate inversion time (TI), chosen to null the signal from healthy myocardium, a series of gradient echo readout pulses ($\alpha_1$ to $\alpha_n$) are played out to fill $n$ rows of k-space. The TD time is chosen such that the readout pulses and data acquisition occur in diastole to avoid cardiac motion. This process is repeated over 16 heart beats to build up a single delayed enhancement image. A complete list of pulse sequence parameters for the IR-GRE sequence can be found in the text.

Figure 1.6: (a) Simulated signal recovery curves for healthy myocardium and infarct. Infarct has a shorter $T_1$ due to the increased Gd-DTPA concentration compared to healthy myocardium. If the inversion time (TI) is chosen so that the data is acquired around time = 300 ms (orange arrow) in this example, the resulting image has no signal in areas of healthy myocardium while infarcted tissue appears bright. Note that 10 – 20 minutes after the contrast injection, blood has a similar $T_1$ to infarct. (b) IR-GRE image from a patient showing a thin infarct (green arrows) as a hyperenhanced region and healthy myocardium (blue arrow) as a region with no signal intensity. The blood pool appears bright (red arrow); some regions of infarcted tissue have a similar signal intensity to that of the blood pool.
the temporal acquisition window. This temporal window is kept to 150 – 200 ms in diastole to avoid the influence of cardiac motion. The flip angle ($\alpha$) used is 20\(^\circ\) and the bandwidth is ±31.5 kHz. IR-GRE images are normally acquired with an imaging matrix of 192 x 192 over a 32 cm field of view yielding a spatial resolution of 1.7 x 1.7 x 8 mm. For the sequence shown in Figure 1.5, data is acquired every heart beat, and the entire k-space is filled twice and averaged together to boost the signal-to-noise ratio (SNR). Alternatively, data can be acquired every second heart beat to allow the magnetization to more fully recover before the next inversion pulse, alleviating the need to fill k-space twice; the effective imaging time remains the same.

The optimal TI to null the signal from healthy myocardium varies from patient to patient, and also varies depending on the elapsed time between the injection of Gd-DTPA and the image acquisition. The TD time is chosen so that the combination of TD and TI times yields a data acquisition window in mid-diastole (Figure 1.6) where there is no cardiac motion. A stack of 10 – 15 DE-MRI images are normally acquired in the short axis view to cover the entire left ventricle. Each image requires a 10 – 20 second breath-hold, and allowing for some resting time between breath-holds, an entire IR-GRE stack takes on the order of 10 minutes to acquire.

### 1.5.3 Analysis of viability images

Analysis of IR-GRE images is typically performed with manual contours of enhanced regions on each imaging slice to determine the overall size of the infarct. Additionally, short axis images can be split into six segments [54], and the transmurality of any MI can be assessed qualitatively for each segment. Transmurality is grouped into five categories: no enhancement, 1-25%, 25-50%, 50-75%, or 75-100%.

For a more accurate quantitative analysis of total infarct volume, various semi-automatic algorithms have been proposed. These algorithms all compare the signal intensity of each voxel to the signal intensity characteristics of remote voxels in a manually drawn region of healthy myocardium. Initially, MI was defined as any voxel with a signal intensity greater than two standard deviations away from the mean signal intensity of
remote voxels; using this definition, ex-vivo DE-MRI images in a canine model of infarction were shown to accurately measure the size of the infarct compared to histology [55]. A more recent study showed that using a full-width at half-maximum (FWHM) approach yielded a better correlation with post mortem data [56]. The FWHM method defines infarct voxels as any voxel with a signal intensity greater than 50% of the brightest signal intensity of all infarct voxels in that image. Both methods are semi-automatic as they require manual contours of the endocardial and epicardial borders, and both require a user to manually segment out random pixels in healthy myocardium (not adjacent to the core infarct) that are incorrectly classified as infarct by their respective algorithms.

A more automated and intelligent algorithm for infarct sizing, called the FACT (feature analysis and combined thresholding) algorithm, has been developed [57]. This method combines both the two standard deviation and FWHM thresholds, and uses region-based feature analysis to eliminate false positive voxels in healthy myocardium. One drawback to this algorithm is that it still requires manual input of the endocardial and epicardial contours, which can be difficult when the blood-infarct border is hard to visualize (see Sec 1.4.5).

### 1.5.4 Relationship to cardiac arrhythmias

The presence of infarcted tissue may result in the formation of reentry circuits that can cause ventricular tachycardia (VT) (see Sec 1.1.2). These reentry circuits occur when there is a mixture of viable and non-viable (infarcted) cells in close proximity. There have been recent efforts towards using MRI viability images to characterize scar tissue to predict whether or not a patient will be inducible for VT. While one group found that the total infarct size as defined by DE-MRI was predictive of inducibility for VT (with $p = 0.02$ comparing infarct mass between inducible and non-inducible patients) [58], another group found that inducibility did not correlate with infarct size (with $p = 0.17$) [59].
Figure 1.7: (a) Conventional DE-MRI image of a human heart using an IR-GRE pulse sequence showing an antero-septal infarct. (b) The DE-MRI image with the infarct separated into the infarct core (green voxels) and gray zone (yellow voxels), based on each voxel’s signal intensity. (c) Simulated inversion recovery curves for infarct, the gray zone (“mixed” tissue), and healthy myocardium, showing why heterogeneous infarct has a lower signal intensity on DE-MRI images than completely infarcted tissue.

In a porcine model of chronic infarction, the reentry circuit (the site of VT activation) was characterized by a small volume of viable myocardium bound by scar tissue on high resolution, ex-vivo 3D DE-MRI images [60]. This is consistent with the appearance of reentry circuits observed with histopathology [14].

When small regions of viable and non-viable tissue co-exist, the infarct appears heterogeneous at a macroscopic level. It has been postulated that this heterogeneous infarct can be detected as a “gray zone” on in-vivo DE-MRI images [59],[61], as illustrated in Figure 1.7. Two different methods have been used to separate the infarct core (assumed to be fully infarcted tissue) from the gray zone (assumed to be heterogeneous infarct), but both use the relative signal intensities of enhanced infarct voxels to voxels in healthy myocardium. A complete description of the methods used for defining the infarct core and gray zone can be found in Chapter 3. The size of the gray zone has been shown to correlate with all-cause post-MI mortality [61] and with inducibility for VT [59]. The limitations of using IR-GRE-derived gray zones to predict VT, including a high sensitivity to image noise, are examined further in Chapter 3.
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Figure 1.8: (a) IR-GRE patient image where the infarct-blood border is hard to distinguish because the blood pool and MI have similar signal intensities. (b) A patient where a thin subendocardial infarct was not identified in this imaging slice because it appeared to be part of the blood pool.

1.5.5 Limitations of viability imaging with MRI

At the time when DE-MRI images are acquired, blood and infarcted tissue have almost identical $T_1$ values [46]. Therefore with IR-GRE imaging, where a single image is acquired at the null point of healthy myocardium, blood appears bright and has similar signal intensity as infarct (Figure 1.8). This occurs because during the first ten minutes after a bolus injection, the concentration of Gd-DTPA in the blood pool is decreasing exponentially while the concentration in the myocardium is increasing more slowly [62]. Ten minutes after a bolus of Gd-DTPA, two studies have measured the $T_1$ of blood and myocardium and shown them to be identical [63] or have a difference of only 20 ms [64]. This can make it difficult to delineate the infarct-blood border and may cause thin subendocardial MI (MI at the endocardium, or adjacent to the blood pool, with a very small transmurality) to go undetected [65]. This problem is seen more often with chronic MI, when the ventricular wall and infarct remodels and thins out; this is likely the reason why the sensitivity of DE-MRI is lower in chronic infarcts (96%) than in acute infarcts (99%) [25]. The analysis for determining the gray zone on IR-GRE images requires manual segmentation of the blood pool. This is performed so that bright voxels that are part of the blood pool are not counted as part of the infarct core or gray zone. However, it can be difficult to accurately segment out the blood pool when the infarct-blood border is hard to visualize.
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Figure 1.9: Signal intensity curves illustrating the signal intensities at various TI times. At the time $T_{I\text{short}}$, healthy myocardium and infarct have the same signal intensity as the two curves cross. At $T_{I\text{optimal}}$, the signal from healthy myocardium is zero while infarct has a positive signal intensity. At $T_{I\text{long}}$, infarct is still brighter than myocardium although the difference in signal intensities between the two is reduced.

To obtain accurate imaging results, the appropriate TI ($T_{I\text{optimal}}$) needs to be selected (Figure 1.9). This is because IR-GRE images are displayed as magnitude images and therefore a negative magnetization during the inversion recovery process becomes a positive signal intensity. At $T_{I\text{optimal}}$, the contrast between healthy myocardium and infarct is near its maximum. If the TI is too short, the contrast drops off rapidly; there is a given TI ($T_{I\text{short}}$) where there is no contrast between healthy myocardium and infarct (Figure 1.9). This occurs when the signal intensity recovery curves of healthy myocardium and infarct cross each other. At longer TI times ($T_{I\text{long}}$) the contrast drops off more slowly; however, it is still advantageous to use $T_{I\text{optimal}}$, where healthy myocardium is perfectly nulled, in order to eliminate variations in the signal intensity of healthy myocardium due to coil shading.

Determining $T_{I\text{optimal}}$ is not a trivial process because the actual $T_1$ of healthy myocardium varies from patient to patient, and depends on the elapsed time from the injection of the GD-DTPA contrast agent [25]. For clinical viability scans, the $T_{I\text{optimal}}$ is determined through a trial-and-error process by acquiring a series of IR-GRE images at various TI times just prior to the acquisition of the stack of images covering the left ventricle. This process is referred to as “TI surfing”. TI surfing adds additional breath-holds to the MRI scan and lengthens the time required to complete a cardiac viability scan.
The acquisition of TI surfing images, an IR-GRE stack of viability images, and a stack of cine SSFP wall motion images requires a total of 20 – 35 separate breath-holds. This can tire the patient out, especially for elderly patients or patients with advanced heart disease. Some patients may not be able to adequately hold their breath for the 10 – 20 seconds required for each image acquisition; it has been reported that 33% of cardiac patients display some drift in their respiratory position throughout their breath-holds [66]. When combined with other image acquisitions (such as perfusion imaging), the large number of repeated breath-holds leads to long scan times for completion of a cardiac examination with MRI.

The IR-GRE sequence also requires ECG gating in order to apply the inversion pulse at the correct time so that the data is consistently acquired in diastole. This limits the patient population that can be successfully scanned with the IR-GRE sequence; specifically, patients with atrial fibrillation have a highly irregular ECG signal and are not suitable for conventional viability and wall motion scans with MRI. Even in patients with a steady heart beat, a clean ECG signal can sometimes be difficult to achieve when the patient is within the large static magnetic field used in MRI.

1.5.6 Alternate pulse sequences for viability imaging

A number of alternate pulse sequences for DE-MRI have been proposed to improve upon the standard 2D IR-GRE method. The simplest variation on the IR-GRE sequence is the use of phase sensitive inversion recovery (PSIR) to restore the polarity (negative values) of the signal intensities during the inversion recovery [67]. PSIR is performed by acquiring IR-GRE T\textsubscript{1}-weighted data (forming a standard infarct-enhanced image) and reference phase data in alternating heart beats. Subtraction of the reference phase image from the phase of the T\textsubscript{1}-weighted image on a voxel-by-voxel basis allows the signal polarity to be restored. Restoring the signal polarity increases the dynamic range of the signal intensities and reduces the variation in the apparent infarct size due to an incorrect choice of the TI.
To shorten the overall scan time for full coverage of the left ventricle, 3D IR-GRE pulse sequences have been developed [68]-[70]. A similar 3D sequence, using an SSFP readout following an inversion recovery pulse, has also been described [71]. Although 3D methods reduce viability imaging to a single breath-hold, this breath-hold is longer than typical 2D breath-holds and can be difficult to achieve in certain patients [69]. However, the overall time savings is significant, reducing viability imaging from 12 minutes to 24 seconds [68]. In order to cover the entire LV in a single breath-hold, these 3D sequences are acquired at a lower spatial resolution compared to 2D sequences. For MRI acquisitions, the SNR of the image increases as the spatial resolution decreases (meaning larger voxel sizes); therefore these 3D sequences have a higher SNR than 2D acquisitions. The time window for data acquisition is longer (300 ms) with the 3D sequences, and data is acquired every heart beat with NEX = 1, reducing the CNR between infarct and healthy myocardium. However, the increased overall SNR of the 3D images compensates for the reduced CNR. The central k-space ordering of the 3D acquisition results in a low pass filtering effect of the images and a corresponding loss of detail. Even with these limitations, 3D IR-GRE sequences show great promise for reducing the scan time for viability assessment and are becoming available on clinical MRI systems. To alleviate the requirement of breath-holds, 3D IR-GRE data can be acquired during free breathing with the use of navigator echoes [72],[73]. Navigator echoes monitor the position of the diaphragm and are used to gate the data acquisition to times when the respiratory position is consistent. Navigator echoes have also been applied to the conventional 2D IR-GRE sequence to eliminate breath-holds [74].

Three different methods have been described to improve the contrast between infarct and the blood pool. The first method acquires two separate images, one at a short TI corresponding to the null point of infarct, and one at the standard TI at the null point of myocardium [75]. By subtracting these two images, the contrast between infarct and blood is improved by 250%. However, this method requires doubling the number of images acquired and still produces bright-blood images. Another approach uses a double-preparation scheme by applying a slice-selective saturation pulse followed by a non-slice-selective inversion pulse to decouple the recovery curves of infarct and blood
This sequence yields a black-blood delayed enhancement image with a six-fold improvement in the CNR between infarct and blood. One drawback to this sequence is that it is sensitive to the timing between the saturation pulse and the inversion pulse, and two separate timing parameters have to be determined empirically for each patient being scanned. Finally, a delayed enhancement sequence that acquires both T1 and T2 contrasts within a single acquisition has been described [65]. The T2-weighted image provides a high contrast between myocardium (healthy or infarcted) and blood. Manual tracings of the endocardial border on the T2-weighted image can be copied to the T1-weighted image to help visualize subendocardial infarct enhancement. This method improves the detection of small subendocardial infarcts, but requires manual post-processing. All three of these methods require repeated breath-holds and ECG gating.

Single-shot DE-MRI pulse sequences have been developed as an alternative to navigator echoes to alleviate the requirement of breath-holds. Instead of acquiring data in a segmented acquisition over multiple heart beats with a gradient echo readout, an SSFP readout is used to acquire an entire image within a single heart beat [77],[78]. A large number of consecutive readout pulses (128 to 256) are required to form a single-shot DE-MRI image. An SSFP readout is used because consecutive SSFP readout pulses do not alter inversion recovery curves as significantly as gradient echo pulses do; however, to date there has not been any description of the influence SSFP pulses have on T1 recovery curves in the setting of delayed enhancement imaging. In the original single-shot sequences, the time window of the acquisition was longer (350 – 400 ms) than the time window for segmented IR-GRE imaging (150 – 200 ms) [77],[78]. When the spatial resolutions of the two sequences were matched, the CNR between infarct and myocardium in the single-shot SSFP images was reduced by 22% compared to the IR-GRE images [78].

More recently, parallel imaging has been applied to single-shot SSFP DE-MRI sequences to reduce the temporal window used for data acquisition [79],[38]. Even with parallel imaging, the spatial resolution of the single-shot sequence (2.9 x 1.9 mm in-plane) is lower than the segmented IR-GRE sequence (1.8 x 1.4 mm in-plane) in order to match
the 200 ms time window used for IR-GRE acquisitions [38]. The single-shot SSFP sequence was found to have a lower CNR between both infarct and healthy myocardium and infarct and blood compared to the IR-GRE sequence; this led to a reduction in the overall sensitivity for detecting MI, from 98% with IR-GRE imaging to 87% with single-shot imaging. The reduced CNR between infarct and the blood pool led to a large reduction of 34% in the sensitivity of the single-shot sequence for detecting infarcts with less than 50% transmurality [38]. To compensate for the reduced CNR, a series of single-shot acquisitions at the same imaging slice can be acquired during free-breathing and averaged together after motion compensation to boost the SNR [79]. Both rigid body [79] and nonrigid registration [80] have been used for motion compensation within this framework. With averaging, the CNR between infarct and myocardium was improved three-fold, back to the equivalent CNR seen in segmented IR-GRE images [79]; however, the improvement in the CNR between infarct and blood was not reported. The registration does not compensate for through-plane motion, which is not expected to be large for short axis images but can be significant for long axis images.

The 3D, dark-blood, and single-shot sequences all require an accurate estimation of the correct TI to acquire images with decent contrast between MI and myocardium. T$_1$-mapping sequences have been developed [81],[82] and evaluated in patients with MI [83] in order to alleviate this requirement. The T$_1$-mapping sequence developed by Messroghli et al. [82] uses three separate inversion recoveries with three or five single-shot SSFP readouts applied during each inversion recovery. The resulting 11 images, all at different TI times, are used with a data fitting procedure to create a quantitative map of the T$_1$ value of each voxel. Each single-shot readout is acquired over a 300 ms time window at a resolution of 1.6 x 2.3 mm. The T$_1$ maps can be used to detect infarcted tissue without the need to estimate the TI for nulling myocardium. Of note, the three earliest TI times are 100 ms, 200 ms, and 350 ms, while the other eight TI times vary from 900 ms to 3500 ms. Infarct and myocardium have T$_1$ values of approximately 280 ms and 380 ms ten minutes after the injection of Gd-DTPA [64]. Therefore, only the three earliest TI times are relevant for the T$_1$ data fitting because at the later time points the recovery curves have already reached their plateau.
All of the pulse sequences mentioned above describe alternate methods for viability imaging with various advantages over the standard IR-GRE imaging; however, wall motion imaging with a separate series of breath-holds using a cine SSFP sequence is still required. Delayed enhancement images are normally interpreted with the cine wall motion images immediately adjacent [84]; the cine images provide anatomical information such as the diastolic wall thickness in order to help evaluate the transmurality of any enhanced infarct. When cine and DE-MRI images are acquired in separate breath-holds, images at the equivalent slice prescription may be at different anatomical positions because of inconsistencies in the position of the breath-hold; this has been shown to complicate the interpretation of the viability images [65]. A pulse sequence, called cine delayed enhancement (cine DE), has been developed to address this problem [85]. Cine DE yields both viability and wall motion images in a single breath-hold. This sequence acquires a series of single-shot SSFP images with a variable delay time after the R peak of the ECG signal, but at a fixed TI. Cine DE yields 15 images, each with the same infarct enhancement (and no signal from myocardium), but at various phases of the cardiac cycle. This allows simultaneous visualization of wall motion and viability information. However, the temporal window of each single-shot acquisition is approximately 300 ms, which is much larger than the 60 ms temporal resolution required for systolic wall motion visualization [40]. The cine DE sequence was reported to have an accuracy of 71% for wall motion scores using conventional cine SSFP as the gold standard [85].

The goals of this thesis are to develop new methods for viability and wall motion imaging to address certain limitations existing MRI-based methods have not adequately addressed. These limitations include separate acquisitions for wall motion and viability imaging, the bright blood pool in viability images, the sensitivity to the choice of the inversion time, and the requirements of cardiac gating and repeated breath-holds. Furthermore, an improved method for detecting heterogeneous infarct is presented with the goal of being able to predict which patients with MI may go on to develop cardiac arrhythmias.
1.6 Overview of the thesis

In Chapter 2, simulations are performed to examine the influence of an SSFP readout during an inversion recovery process in the setting of delayed enhancement MRI. Based on these simulations, an optimized pulse sequence was developed that simultaneously produces multiple viability images (with varying image contrast) and wall motion images; this sequence, referred to as multi-contrast delayed enhancement (MCDE), was tested in a series of patients with MI and compared to the conventional IR-GRE and cine SSFP pulse sequences.

Chapter 3 describes an image processing pipeline for determining regions of heterogeneous infarct from a series of MCDE images. Imaging and the corresponding analysis was performed in 15 patients and the results are compared to the standard gray zone analysis based on conventional delayed enhancement imaging. In addition, the variability in the gray zone analysis due to several factors, such as image noise, is examined.

In Chapter 4, a pulse sequence called real-time delayed enhancement (RT-DE) is described which is also based on the use of an SSFP readout following an inversion recovery pulse. This pulse sequence alleviates the requirements of breath-holds and cardiac gating in the conventional IR-GRE acquisition. RT-DE and IR-GRE images were compared in 23 patients with chronic MI.

Finally, Chapter 5 discusses future directions and planned studies aimed at further improving myocardial viability imaging with MRI and expanding applications of the techniques developed in Chapters 2 to 4. Preliminary data is shown in Chapter 5 for some of the planned studies that are underway.
Chapter 2

2 Multi-contrast delayed enhancement imaging

2.1 Background

There is increasing interest in inversion recovery (IR)-prepared steady-state free precession (SSFP) imaging for use in $T_1$ quantification [86]-[88] or for myocardial delayed enhancement magnetic resonance imaging (DE-MRI) [77]-[79]. DE-MRI aims to differentiate healthy from infarcted myocardial tissue based on differences in their $T_1$ values 10-30 minutes after the injection of Gd-DTPA [55]. Inversion recovery images are acquired at an inversion time (TI) tuned to null healthy myocardium, showing infarcts as areas of hyperenhanced signal. Conventional DE-MRI uses a gradient echo readout, and is referred to as inversion recovery gradient echo imaging (IR-GRE). An SSFP readout following an inversion pulse is desirable because it can provide a higher signal-to-noise ratio than a gradient echo readout, and can be used to sample the magnetization throughout the entire inversion recovery process without significantly altering the dynamics of the signal recovery [86]. Previously, an SSFP readout after an inversion recovery pulse (referred to as IR-SSFP) has been used to acquire single-shot viability images [77],[78], reducing the time required for image acquisition.

In this chapter an in-depth analysis is performed to examine the effects of an SSFP readout on magnetization behaviour after an inversion recovery pulse in the setting of DE-MRI. In particular, the effects of varying the SSFP flip angle are examined. A segmented and cardiac-gated inversion recovery-SSFP sequence is developed with optimized parameters for infarct visualization based on computer simulations. This sequence, referred to as multi-contrast delayed enhancement (MCDE), provides cardiac-phase-resolved images at multiple inversion times. The goal of this sequence is to

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provide cine images of the heart with varying contrast in order to simultaneously visualize myocardial wall motion and detect infarcted tissue. MCDE produces viability images with multiple image contrasts with the potential to more easily differentiate infarcted tissue from healthy myocardium and blood. This new method was applied to eleven patients with ischemic heart disease, and the resultant images were compared to conventional SSFP cine images and IR-GRE delayed enhancement images.

2.2 Theory and simulations

2.2.1 Theory

The SSFP pulse sequence [42] uses a train of $\pm \alpha$ pulses with fully balanced gradient moments. With conventional SSFP imaging, $\alpha$ pulses are applied without any magnetization preparation; after a number of pulses a steady state signal is achieved that is $T_2/T_1$-weighted. When an SSFP readout is used during an inversion recovery process, the magnetization is being sampled during the transition from $T_1$ recovery to its true steady state value. The evolution of the magnetization during an SSFP readout can be calculated using the recursive equation described by Markl et al. [89]:

\[
M_n = R_x(\pm \alpha)[E_2(TR,T_1,T_2)M_{n-1} + E_1(TR,T_1)]
\]

(2.1)

where $M_n$ is the magnetization vector $[M_x \ M_y \ M_z]^T$ directly after the $n^{th}$ pulse and $R_x(\pm \alpha)$ is a rotation matrix about the x-axis in the rotating frame corresponding to an RF excitation with flip angle $\alpha$. $E_1$ and $E_2$ are matrix representations of $T_1$ and $T_2$ relaxation:

\[
E_1(TR,T_1) = \begin{bmatrix} 0 & 0 & M_0(1-e^{-TR/T_1})^T \end{bmatrix}
\]

\[
E_2(TR,T_1,T_2) = \begin{bmatrix} e^{-TR/T_2} & 0 & 0 \\ 0 & e^{-TR/T_2} & 0 \\ 0 & 0 & e^{-TR/T_1} \end{bmatrix}
\]

(2.2)

Note that this formulation neglects off-resonance effects. An inversion pulse can be added between any two pulses via:

\[
M_{\text{inv}} = R_x(\pi)M_n
\]

(2.3)

where $M_{\text{inv}}$ is the magnetization vector directly after the inversion pulse, and $R_x(\pi)$ is the rotation matrix about the x-axis for a $180^0$ inversion pulse.
Figure 2.1: Simulated $T_1$ recovery of myocardium and blood after an inversion pulse with and without SSFP pulses (SSFP flip angle of $60^0$). Note that the $M_z$ recovery curves for both myocardium and blood are affected by the SSFP readout. The recovery curve for myocardium is affected to a greater degree due to its low $T_2/T_1$ ratio.

2.2.2 Simulations

Simulations were performed in Matlab (Mathworks, Natick, MA) to model the signal behaviour of blood, healthy myocardium, and infarcted myocardium undergoing IR-SSFP in the setting of delayed enhancement imaging. Immediately after the inversion pulse, six linearly ramped dummy pulses [90] from $\alpha/6$ to $\alpha$ were applied to minimize signal oscillations, followed by $\pm\alpha$ SSFP readout pulses. The simulations use a TR = 3.4 ms. The inversion pulse is assumed to be non-slice selective, meaning blood entering the imaging slice after the inversion pulse will still follow an inversion recovery behaviour. An ejection fraction of 60% is assumed in the simulations, meaning that after systole 60% of the blood pool is replaced by blood that has not been exposed to any prior SSFP pulses. The $T_1$ and $T_2$ values of the different tissues used in the simulations are from previously published reports for a magnetic field strength of 1.5T [64],[91], assuming a ten minute delay between Gd-DTPA injection and imaging. The parameters used in the simulations are: $T_{1,myo} = 380$ ms, $T_{2,myo} = 45$ ms, $T_{1,inf} = 280$ ms, $T_{2,inf} = 40$ ms, $T_{1,blood} = 260$ ms, $T_{2,blood} = 180$ ms. Figure 2.1 shows a comparison between the natural $T_1$ recovery of blood and myocardium and the actual recovery when undergoing IR-SSFP imaging with $\alpha = 60^0$. The signal behaviour with an SSFP readout follows an exponential recovery with a time constant $T_1^*$ that is shorter than the true $T_1$ [87].
Figure 2.2: Simulated magnetization recovery during a single-shot IR-SSFP sequence, with an SSFP flip angle of (a) $\alpha = 30^0$ (b) and $\alpha = 60^0$. Note in (a) that myocardium is nulled at a TI = 240 ms with infarct and blood having approximately the same magnetization at the null point. In (b), the null point is shifted to a TI = 200 ms, at which time blood is also nulled.

The SSFP readout confers a $T_2$-weighting to the $T_1^*$ curve according to the following equation [87]:

$$
T_1^* = \left( \frac{1}{T_1} \cos^2 \alpha \left(\frac{1}{2} + \frac{1}{T_2} \sin^2 \alpha \right) \right)^{-1}
$$

(2.4)

The $T_1^*$ shortening effect is more pronounced for myocardium and infarct ($T_2/T_1 \approx 0.1$) than for blood ($T_2/T_1 \approx 0.7$), and varies with the SSFP flip angle. The $T_1^*$ effect alters the dynamics between the tissues of interest during the inversion recovery process.

One method previously described for DE-MRI is a single-shot IR-SSFP sequence [77],[78] where all phase encoding lines for a single image are acquired within one heart beat. The effects of changing the SSFP flip angle in the context of a single-shot IR-SSFP sequence are shown in Figure 2.2. With a 30$^0$ flip angle, the simulations show that at TI = 240 ms, normal myocardium will have no signal while infarcted tissue and blood will have the same magnitude of signal ($M_{z,inf} = M_{z,blood} = 0.17$). This agrees with what has been seen experimentally [77]. However, for $\alpha = 60^0$, myocardium is nulled earlier (at TI = 200 ms), at which point infarct has a small positive signal ($M_{z,inf} = 0.095$) but blood has no signal ($M_{z,blood} \approx 0$). This means that with $\alpha = 60^0$, a black blood appearance is achieved, but the contrast between healthy myocardium and infarct is reduced by 44%.
Thus, in the setting of DE-MRI, an SSFP readout affects the optimal TI and image characteristics.

A difficulty with the single-shot technique is that blurring is introduced due to cardiac motion over the 250 – 400 ms required for a single acquisition. Simulations were performed to examine the signal behaviour of IR-SSFP during a segmented DE-MRI sequence. A segmented approach acquires data during a small time window in each cardiac cycle; therefore, multiple inversion pulses (one per heart beat, followed by an SSFP readout, over multiple heart beats) are used to form a single image. The data acquired throughout the entire signal recovery is segmented and used to build up 20 different images, each at a different effective TI. Therefore, this sequence yields images with varying contrast between healthy myocardium, infarct, and blood; for this reason the segmented IR-SSFP approach will be referred to as multi-contrast delayed enhancement (MCDE). A diagram illustrating the MCDE acquisition is shown in Figure 2.3.

After the first inversion pulse, the signal behaviour would follow that of the single-shot IR-SSFP sequence (Figure 2.2). The SSFP pulses, if played out continuously, would limit the regrowth of $M_z$ based on the SSFP flip angle and the $T_2/T_1$ ratio of a particular tissue. Thus the magnetization of myocardium, infarct and blood just prior to the second and all subsequent inversion pulses are not equal (Figure 2.4). This alters the $M_z$ recovery curves of the three tissues relative to each other. Figure 2.4 shows that for $\alpha = 30^\circ$, after the second inversion pulse, blood is nulled at approximately the same time point as myocardium; this suggests that an image acquired with these parameters would be a black blood delayed enhancement image. Figure 2.4 also shows that when $\alpha = 60^\circ$, blood has a large negative magnetization at the null point of myocardium. Using a 60° flip angle, blood would appear bright on a magnitude image acquired at the null point for healthy myocardium. The simulations have shown that for any $\alpha$, the $M_z$ recovery curves are consistent after the second and all subsequent inversion pulses. This holds true only if SSFP pulses are played out continuously between successive inversion pulses and for $T_1$ values post-contrast. For pre-contrast tissue, the number of dummy inversion pulses would need to be increased before a consistent steady-state value would be achieved.
Chapter 2: Multi-contrast delayed enhancement imaging

Figure 2.3: Diagram illustrating the segmented MCDE acquisition scheme. Data is acquired continuously after an inversion pulse (shown at 1000 ms) and the data is segmented to a particular image number (from one to 20) based on the elapsed time from the inversion pulse. The inversion and subsequent SSFP readout pulses are repeated 10-15 times in order to build up data for all 20 images. Shown on top are six of the 20 images output by the MCDE sequence at early inversion times showing varying contrast between infarct, healthy myocardium, and blood.

Figure 2.4: Simulated magnetization recovery after the first two inversion pulses during a segmented IR-SSFP sequence (MCDE) for (a) $\alpha = 30^0$ and (b) $\alpha = 60^0$. Note that the first inversion pulse is played out at time $= 0$ ms, and the second inversion pulse at time $= 1000$ ms. After the second (and all subsequent) inversion pulses, an SSFP readout of $\alpha = 30^0$ results in the signal from myocardium and blood being nulled at approximately the same time point. With $\alpha = 60^0$, blood has a large negative $M_z$ at the null point for myocardium.
Figure 2.5: Simulated differences in signal intensity between (a) infarct and myocardium ($\Delta S_{\text{inf-myo}}$) and (b) infarct and blood ($\Delta S_{\text{inf-blood}}$) for the MCDE sequence (with flip angles between 16° and 50°), a gradient echo (GRE) sequence ($\alpha = 20°$), and a single-shot SSFP (SS-SSFP) sequence ($\alpha = 30°$).

Alternatively, a longer SSFP readout window can be used, for example by playing out the inversion pulse every other heart beat instead of every heart beat. It was observed that the inversion recovery behaviour and dynamics did not change significantly with changes in the value of 60% used for the ejection fraction.

2.2.3 Simulations: Optimization and pulse sequence comparison

It is apparent from the simulations that the appearance of DE-MRI images will be affected by the readout scheme (gradient echo, single-shot SSFP, or segmented SSFP) and the readout flip angle. Further simulations were performed to determine the optimal flip angle for visualizing infarcted tissue using the segmented MCDE sequence. The optimization examined the effect of various SSFP flip angles on the signal intensity differences between infarct and myocardium ($\Delta S_{\text{inf-myo}}$) and between infarct and blood ($\Delta S_{\text{inf-blood}}$) at the time point where the signal from healthy myocardium is zero. The results were compared to simulated signal intensity differences for gradient echo and single-shot SSFP readouts (Figure 2.5). The simulations assume a consistent total imaging time for each of the three types of sequences. The results indicate that for the MCDE scheme, $\alpha = 30°$ yields a maximum for both $\Delta S_{\text{inf-myo}}$ and $\Delta S_{\text{inf-blood}}$. Note that this applies only to the one MCDE image at the TI where the signal from healthy
myocardium is zero. MCDE produces multiple images at various effective TIs, each with a different contrast between myocardium, infarct, and blood. These results are relatively insensitive to the TR of the SSFP pulses, with a range of TRs from 2.5 ms to 3.5 ms changing the optimal flip angle by $2^0$. A $30^0$ flip angle also produces recovery curves where blood and myocardium are nulled at the same time point (Figure 2.4), meaning in the myocardium-nulled image blood would also have no signal.

The cost of using the MCDE approach is that $\Delta SI_{\text{inf-myo}}$ is reduced by 56% compared to a gradient echo readout and 36% compared to a single-shot SSFP readout. However, each segmented image (acquired over a temporal window of approximately 50 ms) will have less blurring due to cardiac motion, and the signal-to-noise ratio can be boosted by averaging over multiple excitations. It has already been noted that by using a segmented approach, multiple images are acquired over the cardiac cycle at different TIs. One of the images will be the equivalent of a conventional delayed enhancement image (with nulled myocardium and bright infarct); however, all of the images at early TIs (from zero to 300 – 500 ms) will display contrast between infarct, healthy myocardium, and blood. Images at later TIs will have a more traditional SSFP contrast and can be used to visualize myocardial wall motion because all of the images are cardiac-phase-resolved. It is expected that visually tracking the $T_1$ recovery of myocardium and infarct over the early MCDE images will help compensate for the lower myocardium-to-infarct contrast in the myocardium-nulled image.

For $\alpha = 38^0$ and higher, and for a gradient echo and single-shot SSFP readout, $\Delta SI_{\text{inf-blood}}$ is small and negative (Figure 2.5), meaning that blood would have a similar (or slightly greater) signal intensity compared to infarcted tissue. With IR-GRE or single-shot IR-SSFP, where only a single image at the myocardial null point is produced, the bright blood pool can mask the presence of subendocardial infarct. The multiple MCDE images with varying contrast can be used to discriminate between the blood pool and tissue because blood has a much different signal recovery curve relative to both infarct and healthy myocardium in the setting of MCDE (Figure 2.4).
Figure 2.6: Pulse sequence diagram for the MCDE sequence. The first inversion pulse is used to set up a consistent starting point for the second and all subsequent inversion pulses. The inversion-prepared, segmented SSFP readout is then repeated multiple times to build up k-space data to reconstruct multiple images over the cardiac cycle, each at a different effective TI.

2.3 Methods

A pulse sequence diagram of the MCDE sequence is shown in Figure 2.6. The first heart beat is used to set up a consistent signal for the ensuing heart beats. After the second and all subsequent inversion pulses, imaging is performed via a segmented SSFP-based acquisition. The inversion pulses are triggered off the patient’s ECG trace. The position of the inversion pulse within the R-R interval is determined by the user. The goal is to place the inversion pulse such that the images that show the best contrast between viable and non-viable tissue occur in mid-diastole, while ensuring that systolic images are acquired when the image contrast is no longer changing. An inversion time is not required for MCDE imaging because the sequence will produce multiple images each at a different effective TI.

Eleven patients with suspected myocardial infarcts resulting from ischemic heart disease (age = 64 ± 17, six females and five males) undergoing myocardial viability MRI scans were included in this study. The protocol was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, and informed consent was obtained. MR imaging
was performed on a 1.5T scanner (CV/i, GE Healthcare, Milwaukee, WI). Delayed enhancement imaging was performed 10-30 minutes after the injection of 0.2 mmol/kg of Gd-DTPA (Magnevist, Berlex Inc., Wayne, NJ). Between eight and 11 short-axis images were acquired with a conventional IR-GRE sequence and the MCDE sequence to cover the entire left ventricle (LV). Cine images were also acquired at the same anatomical locations with a conventional segmented SSFP sequence.

Parameters for the IR-GRE sequence were: $\text{BW} = \pm 31.5$ kHz, readout flip angle = $20^\circ$, views per segment (VPS) = 20, $\text{TR/TE} = 6.0/3.0$ ms, FOV = 320 mm, slice thickness = 8 mm, 192 x 192 imaging matrix and NEX = 2. The TI was tuned for each patient to optimally null myocardium, and ranged from 175 to 250 ms; the delay time (TD) was chosen to yield images in mid-diastole. The IR-GRE sequence required 20 heart beats (an 18-second breath-hold on average) to produce a single DE-MRI image. Parameters for the MCDE sequence were: $\text{BW} = \pm 125$ kHz, readout flip angle = $30^\circ$, VPS = 16, $\text{TR/TE} = 2.7/1.3$ ms, FOV = 320 mm, slice thickness = 8 mm, TD = 500 ms, 192 x 192 imaging matrix and NEX = 1. The MCDE sequence took 13 heart beats to acquire (one to establish the steady state, and 12 for data acquisition), leading to an 11-second breath-hold on average. MCDE produced 20 images over the cardiac cycle. Conventional cine imaging via a segmented SSFP approach used the same imaging parameters as the MCDE sequence.

The contrast-to-noise ratio between normal myocardium and infarct ($\text{CNR}_{\text{myo-inf}}$) and between infarct and blood ($\text{CNR}_{\text{inf-blood}}$) were compared for the two DE-MRI methods employed. The MCDE image that best depicted the infarct for each imaging slice was used for CNR analysis. However, because the MCDE sequence produces multiple images showing infarcted tissue, two visual scores were also graded by a cardiologist in a blinded fashion after all patient scans were completed. The two scores were a measure of how easily distinguishable infarcted tissue was from healthy myocardium, and from the blood pool (1 = no differentiation, 2 = poor differentiation, 3 = acceptable differentiation,
4 = good differentiation, 5 = excellent differentiation). Visual scores were made for each IR-GRE and MCDE imaging slice where infarcted tissue was detected by both methods.

The size of enhanced infarct was measured on the IR-GRE images with manual contours, using the equivalent cine SSFP image as a reference to help visualize the border between myocardium and the blood pool. The infarct size was also measured with manual contours on the MCDE images; all of the cine MCDE images throughout the T$_1$ recovery were used to visualize the infarct and the blood pool. The infarct sizes were compared between IR-GRE and MCDE images at the same anatomical location. All manual contours were drawn with the OCCIViewer software (OCCI, Toronto, Ontario, Canada) after all patient scans were completed, and separately from the visual scoring. The ejection fraction (EF) of each patient was calculated using the conventional cine SSFP and the MCDE images using MASS software (MASS plus 5.0, Medis, Leiden, The Netherlands).
Table 2.1: Contrast-to-noise ratios (CNR) and visual scores for IR-GRE and MCDE images.

<table>
<thead>
<tr>
<th></th>
<th>IR-GRE</th>
<th>MCDE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct-to-myocardium</td>
<td>CNR</td>
<td>20.8 ± 6.6</td>
<td>13.5 ± 2.8</td>
</tr>
<tr>
<td>Visual score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.5 ± 0.6</td>
<td>4.3 ± 0.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Infarct-to-blood</td>
<td>CNR</td>
<td>9.6 ± 4.2</td>
<td>11.2 ± 3.9</td>
</tr>
<tr>
<td>Visual score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.2 ± 1.1</td>
<td>4.8 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>visual score on a scale of 1-5 describing how easily distinguishable infarct was from myocardium or blood, with one being no differentiation possible to five being excellent differentiation.

### 2.4 Results

Myocardial infarcts were detected in six of the eleven patients examined. Figure 2.7 shows selected frames from the MCDE acquisition at early TIs showing varying contrast between infarct, myocardium, and blood, along with the corresponding IR-GRE image in a 70-year old patient with an anterior infarct. Multiple delayed enhancement contrasts with MCDE can be visualized in Figure 2.7; Figure 2.7c shows how blood and healthy myocardium are nulled at the same time point. Figure 2.8 shows selected images in a 47-year old male patient at early and late TIs, illustrating how the MCDE sequence is used to visualize viability and wall motion information. Infarcts were detected with the MCDE images in all 26 imaging slices (across six patients) where enhancement was seen in the IR-GRE images. There were two basal, adjacent imaging slices in one patient where MCDE detected infarcted tissue but IR-GRE did not. In the remaining 63 imaging slices, no infarcted tissue was detected in both IR-GRE and MCDE images. The contrast-to-noise ratios and visual scores for the IR-GRE and MCDE images are shown in Table 2.1. IR-GRE displayed a higher CNR<sub>inf-myo</sub> than MCDE (p = 0.03) while the two methods had an equivalent CNR<sub>inf-blood</sub> (p = 0.39). IR-GRE and MCDE had equivalent scores for distinguishing between infarct and healthy myocardium (p = 0.13), while IR-GRE had lower scores than MCDE for visualizing the infarct-to-blood border (p < 0.001).
Figure 2.7: Eight consecutive short-axis MCDE images (a-h) acquired in a 70-year old female patient with an anterior infarct, with the corresponding IR-GRE image (i). The infarct can be visualized as an area of fast $T_1$ recovery (hypoenhanced in (a-b), and hyperenhanced in (c-e)). Note the simultaneous nulling of healthy myocardium and blood in image (d).

Figure 2.8: Eight (of 20) MCDE images with their corresponding inversion time (TI) from a 47-year old male patient. The images at early TIs (98 ms – 245 ms) show the infero-lateral infarct enhancement, while at later TIs (343 ms – 931 ms) have more traditional SSFP contrast and allow the myocardial wall motion to be visualized. Manual contours on the end-diastolic frame (at 343 ms) and end-systolic frame (at 735 ms) are used to calculate the ejection fraction of the left ventricle.
Figure 2.9: Comparison between IR-GRE and MCDE for measuring (a) infarct size with (b) the corresponding Bland-Altman analysis. The infarct sizes measured with the two methods were statistically equivalent (slope = 0.93 ± 0.06) and highly correlated (R = 0.90), and no bias was observed (mean = 0.7 mm$^2$, 2•SD = 47 mm$^2$).

Figure 2.9 shows the infarct sizes measured using IR-GRE and MCDE. These measurements are strongly correlated (R = 0.90) with a paired t-test showing no difference between the two methods (p = 0.94). The Bland-Altman analysis (Figure 2.9) shows a lack of bias between the two measurements. For each imaging slice, wall motion could be visualized in 13 of 20 MCDE cine images where $T_1$-based signal changes were small. The ejection fractions measured with standard cine SSFP and MCDE imaging are shown in Figure 2.10. These measurements are also strongly correlated with a unitary slope (R = 0.98, slope = 0.98 ± 0.07) with no difference detected using a paired t-test (p = 0.31); no bias was detected using a Bland-Altman analysis (Figure 2.10). Signal recovery curves for healthy myocardium, infarct, and blood were extracted from a set of MCDE images and are shown in Figure 2.11. $T_1^*$ recovery curves were fitted to the data using a method described in [87].
Figure 2.10: Comparison between standard cine SSFP and MCDE for measuring (a) ejection fraction (EF) with (b) the corresponding Bland-Altman analysis. The ejection fractions measured with the two methods were statistically equivalent (slope = 0.98 ± 0.07) and highly correlated (R = 0.98), and no bias was observed (mean = 1%, 2•SD = 5%).

Figure 2.11: Signal recovery curves of infarct, healthy myocardium, and blood, (a) extracted from MCDE images and (b) from computer simulations (same curves as the second inversion recovery curves in Figure 2.3a). $T_1^*$ recovery curves (solid lines) were fit to the experimental data using methods described in [87].
2.5 Discussion

A new DE-MRI pulse sequence for simultaneously acquiring viability and wall motion images has been developed and optimized based on theoretical computer simulations. The MCDE sequence produces images with multiple contrasts, helping to more easily distinguish infarcted tissue from the surrounding anatomy. MCDE has simultaneous nulling of signal from healthy myocardium and blood. MCDE can be used to accurately determine infarct sizes and left ventricular ejection fractions. Additionally, viability and wall motion information is acquired within a single breath-hold using MCDE.

Excellent qualitative agreement is observed between the experimental $T_1^*$ recovery curves and computer-simulated recovery curves. Figure 2.11 illustrates the correlation between the experiments and simulations with respect to the behaviour of the inversion recovery curves for the tissues of interest. The $T_1^*$ recovery curves illustrate how infarcted tissue can be differentiated from myocardium and blood in multiple images. The visual scores for distinguishing infarct from healthy myocardium (Table 2.1) also show that the multi-contrast images produced by the MCDE sequence compensate for the reduced CNR compared to IR-GRE. The infarct-to-blood CNRs were equivalent between MCDE and IR-GRE; however, MCDE received higher qualitative scores for visualization of the infarct-blood border. This again is a result of the multi-contrast images and the black-blood appearance in one of the infarct-enhanced MCDE images (Figure 2.7d), while IR-GRE has bright infarct adjacent to a bright blood pool. These results illustrate the pitfalls of using CNR as the only measure of quality for image characterization. Comparisons of CNR alone cannot capture the relative ease of visual identification of the infarct-blood border using MCDE (black blood adjacent to bright infarct) versus IR-GRE (bright blood adjacent to even brighter infarct). Due to the improved visualization of the infarct-blood boundary with MCDE, small subendocardial infarcts may be more easily identified and infarct transmurality may be more easily assessed.
Another advantage of the MCDE approach is that viability and wall motion information is acquired in a single sequence and thus a single breath-hold. This reduces the amount of time for a cardiac MRI scan and avoids the potential for slice misalignment between separate cine and viability acquisitions due to inconsistent breath-hold positions. Conventional DE-MRI methods also require “TI surfing” to determine the optimal inversion time to null myocardium. TI surfing is usually a trial-and-error process involving two to four additional acquisitions at different TIs. The optimal TI varies from patient to patient, and can vary over the 5-10 minutes during which a stack of short axis images is acquired, leading to reduced contrast in some of the images. Phase sensitive reconstruction [67] reduces the need to find an accurate optimal TI; however, this method requires post-processing to produce the final image and still yields a bright-blood viability image. The MCDE sequence avoids this issue entirely by producing images at multiple TIs.

Inversion recovery-prepared SSFP sequences have been used [77]-[79] in order to avoid the breath-holds required with IR-GRE. These methods use a single-shot acquisition and yield a single bright-blood viability image. A cine DE-MRI method has been recently developed by Setser et al. to simultaneously acquire wall motion and viability images [85]. This sequence uses multiple single-shot inversion recovery-prepared SSFP acquisitions (one acquisition per heart beat) with a varying trigger delay to produce DE-MRI images throughout the heart cycle. The images are all acquired at the same TI to provide consistent contrast; this means that the optimal TI still needs to be empirically determined. The temporal window for each image acquisition with this method is approximately 300 ms, which is not adequate for visualizing systolic wall motion abnormalities. The segmented MCDE method described in this paper has a temporal window of approximately 50 ms (depending on the heart rate), allowing even small wall motion abnormalities to be detected. A segmented, cardiac-gated inversion recovery SSFP sequence has been previously described (16); however, the purpose of that implementation was the determination of the optimal TI for myocardial nulling. No attempt was made to use the images for detection of infarcts or for wall motion visualization. In that study an SSFP flip angle of 50° was used, and every other heart beat
was skipped to allow the magnetization to fully recover. In the present work, continuous SSFP pulses never allow the magnetization to fully recover, and the flip angle was optimized to $30^\circ$ to modify the image contrast to suppress the blood pool signal.

The MCDE method also produces images that can be used for an accurate estimation of the ejection fraction compared to conventional SSFP imaging. During the $T_1^*$ recovery portion where the image contrast is varying drastically in the MCDE images, wall motion is difficult to visualize. However, this only affects seven of the 20 cine images per acquisition. Throughout this study the placement of the inversion pulse relative to the ECG signal was optimized to ensure that the infarct-enhanced images are acquired in mid-diastole, while systolic images are acquired when $T_1$-based signal changes are small. One limitation of the MCDE sequence is that diastolic dysfunction may not be detected because of the reduced visualization of wall motion during diastole.

Patients with heterogeneous or “patchy” infarcts are at a higher risk of arrhythmias due to re-entry circuits [13], and increased infarct heterogeneity as assessed by conventional DE-MRI is independently associated with a higher risk of mortality [61]. Infarct heterogeneity gives rise to partial volume effects, where both healthy and infarcted tissues are found within a single voxel. The current definition of infarct heterogeneity uses signal-intensity-based thresholds of IR-GRE images, which can be sensitive to image noise and coil sensitivity patterns. $T_1^*$ maps generated from a set of MCDE images may provide a robust method for determining infarct heterogeneity by comparing the $T_1^*$ values of the peri-infarct region to those of healthy myocardium and the infarct core. Once generated, the $T_1^*$ maps may also be helpful in assessing a wide range of cardiomyopathies that can be detected with DE-MRI [92].
2.6 Conclusions

In this chapter, a segmented, cardiac-gated MCDE sequence for combined myocardial viability and wall motion imaging was described. MCDE is comparable to IR-GRE for measuring infarct size and comparable to cine SSFP for calculating the left ventricular ejection fraction. MCDE yields multiple image contrasts, including simultaneous nulling of signal from healthy myocardium and blood, which improves visualization of infarcted tissue compared to conventional IR-GRE imaging.
Chapter 3

3 Measuring infarct heterogeneity using multi-contrast delayed enhancement imaging

3.1 Background

Delayed enhancement MRI (DE-MRI) can be used to identify myocardial infarct (MI). Enhanced infarct on DE-MRI images can be separated into the infarct core and the “gray zone”; characterization of the gray zone in patients with ischemic heart disease has been shown to correlate with all-cause post-MI mortality [61] and with inducibility for ventricular tachycardia (VT) [59]. It is postulated that this gray zone represents heterogeneous infarct, an area with a mixture of viable and non-viable peri-infarct myocardium.

Conventional DE-MRI is acquired with an inversion-recovery gradient echo (IR-GRE) sequence that yields a single image at an inversion time chosen to null the signal from healthy myocardium. The definition of the gray zone on IR-GRE images depends on the signal intensity characteristics in a region of remote myocardium, and manual contours are required to segment out the blood pool as blood can have similar signal intensities to infarct [59]. Random noise, along with the use of remote regions and manual contours, may alter each voxel’s categorization as infarct core, gray zone, or healthy myocardium. To date, there has been no description of the influence of these factors on the variability in the size of the gray zone.

A new method for DE-MRI referred to as multi-contrast delayed enhancement (MCDE) has been developed (see Chapter 2) that produces infarct-enhanced images at multiple

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inversion times in a single breath-hold. In this chapter, an algorithm to achieve automated segmentation and classification of infarct zones using MCDE images is described. The infarct core and gray zones detected by the IR-GRE-based and MCDE-based methods were compared and correlated in a spectrum of patients. It is hypothesized that the MCDE-based classification will yield a more reproducible measure of the gray zone and thus the variability in the size of the gray zone using both DE-MRI methods is examined.

3.2 Methods

3.2.1 MCDE segmentation pipeline

MCDE is a segmented MRI pulse sequence using a steady-state free precession (SSFP) readout during the inversion recovery process. MCDE produces 20 images over the cardiac cycle, each at a different inversion time. The images at early inversion times have varying contrast where MI can be visualized as an area of fast $T_1$ recovery. Between six and eight images (at the earliest inversion times) were used to extract the signal intensity (SI) recovery for each pixel within the left ventricle (LV), including the blood pool pixels (Figure 3.1). The time window over which the signal recovery is tracked depends on the number of images used and the heart rate. The SNR for each pixel was calculated and the noise bias (due to the combination of the eight receiver coils) was removed [93]. This is especially important for data points near the null point (where the SI is small) that have a large noise bias. Matlab software (The Mathworks, Natick, MA) was used to perform weighted non-linear regression to fit the signal intensities to the following equation [87]:

$$SI(time) = SS \cdot [1 - 2 \exp(-time/T_{1}^*)]$$

(3.1)

where $SI$ is the signal intensity as a function of time, $SS$ is the steady-state plateau of the recovery curve and $T_1^*$ is the apparent $T_1$ relaxation (shorter than the true $T_1$ due to the continuous SSFP readout) [87]. The weights used for the regression were the relative SNR values for each data point.
Figure 3.1: (a-f) MCDE images (52 ms apart) and (g) an IR-GRE image (at an inversion time of 225 ms) from a 57-year old patient with an antero-septal infarct. The infarcted tissue can be seen as an enhanced area on the IR-GRE image and as an area of fast $T_1^*$ recovery on the MCDE images. Note that only the first six MCDE images after the inversion pulse are shown (out of 20 total acquired).

From the regression analysis, steady-state and $T_1^*$ parameter maps were created. Pixels with poor statistical fits (defined as having a regression residual more than five standard deviations away from the average residual for all pixels) were excluded from further analysis. Pixels outside of the left ventricle (either in the right ventricular blood pool or in air) were easily visualized on the parameter maps and were manually segmented out. A scatter plot showing the $T_1^*$ versus steady-state value for each pixel was used as the input to the fuzzy C-means algorithm to automatically characterize each pixel as infarct, healthy myocardium, or blood. The fuzzy C-means algorithm minimizes the following equation [94]:

$$
\sum_{i=1}^{c} \sum_{k=1}^{N} (u_{ik})^2 D_{ikA}^2
$$

where $\mu_{ik}$ is the probability of pixel $k$ belonging to cluster $i$ and $D_{ikA}^2$ is the squared inner-product distance norm. The Gustafson-Kessel modification of the fuzzy C-means algorithm [95] was used to allow for clusters with different geometrical shapes, leading to the following definition of $D_{ikA}^2$:

$$
D_{ikA}^2 = (x_k - v_i)^T A_i (x_k - v_i)
$$

where $x_k$ is the location of pixel $k$, $v_i$ is the cluster prototype for cluster $i$ and $A_i$ depends on the covariance matrix of cluster $i$. The cluster prototype ($v_i$) is the geometric centre of
all pixels belonging to cluster $i$. This fuzzy clustering algorithm determines the probability of each pixel belonging to each of the three clusters based on a distance metric derived from the scatter plot. Pixels with probabilities greater than 75% for belonging to infarct or healthy myocardium were classified as infarct core and healthy myocardium, respectively. Pixels with a heterogeneous mixture of viable and scar tissue (the gray zone) should have a significant probability for belonging to both the infarct and healthy myocardium clusters. Thus, pixels with less than a 75% probability of belonging to one of those clusters and greater than 25% probability for belonging to the other cluster were defined as the gray zone. Color maps were created based on the clustering results to display the spatial distribution of the blood, healthy myocardium, infarct core, and gray zones. The total size of the infarct core and gray zone (expressed in grams of tissue) was determined for each patient by summing the results for all slices where infarct was detected.

In the first five patients examined in this study, the amount of cardiac wall motion over the six to eight images used for the MCDE analysis was determined. This wall motion analysis was performed because the MCDE algorithm tracks signal recoveries on a pixel-by-pixel basis without any motion compensation. An automated algorithm for determining the epicardial and endocardial contours on cine wall motion images was applied [96]. The amount of translation and change in LV wall thickness over the diastolic time window used for the MCDE analysis was determined from the resulting contours. The translation and wall thickening was determined for the region of infarcted myocardium and adjacent pixels and for remote (healthy) regions of myocardium.

In a subset of six patients, the regression and fuzzy clustering analysis was repeated four times (for each imaging slice, and with different initial starting points for the non-linear regression) in order to determine the variability introduced by the analysis procedure. The variability is present because non-linear regression algorithms do not always converge to the same result when different initial starting points are used. The subset of patients was selected in order to include patients with antero-septal infarcts (four patients) as well as one inferior and one lateral infarct. In the same subset of patients, simulated
data sets were created by adding random noise to each pixel according to its own SNR value. Four separate simulated data sets were created for each imaging slice and the image analysis was performed for each simulated data set in order to determine the variability in the gray zone size due to random image noise. Note that manual contours of the epicardial and endocardial surfaces were not required for the MCDE image analysis.

3.2.2 IR-GRE segmentation

For each IR-GRE image, manual epicardial and endocardial contours were drawn to isolate pixels within the LV. A remote region in healthy myocardium was drawn and the mean (Mean\text{remote}), peak (Peak\text{remote}), and standard deviation (SD\text{remote}) of the signal intensities within the remote region were calculated. Two methods for determining the cut-off values for the infarct core and gray zones were used. The first method defines the infarct core and gray zone pixels as [61]:

\[
\text{SI}_{\text{core}} > \text{Mean}_{\text{remote}} + 3\times\text{SD}_{\text{remote}} \\
\text{Mean}_{\text{remote}} + 2\times\text{SD}_{\text{remote}} < \text{SI}_{\text{gray\_zone}} < \text{Mean}_{\text{remote}} + 3\times\text{SD}_{\text{remote}}
\]

where \text{SI}_{\text{core}} is the signal intensity of a pixel classified as the infarct core, and \text{SI}_{\text{gray\_zone}} is the signal intensity of a pixel classified as the gray zone. This method will be henceforth referred to as the “SD method” (for standard deviation).

The second method uses a full-width half-maximum (FWHM) approach [59], with the following definitions:

\[
\text{SI}_{\text{core}} > 0.5 \times \text{Peak}_{\text{infarct}} \\
\text{Peak}_{\text{remote}} < \text{SI}_{\text{gray\_zone}} < 0.5 \times \text{Peak}_{\text{infarct}}
\]

where \text{Peak}_{\text{infarct}} is the peak signal intensity of all infarcted pixels. This second method will be henceforth referred to as the FWHM method. As with the MCDE analysis, the total size of the infarct core and gray zone for each patient was expressed in grams of tissue.
In a subset of six patients (the same subset used for the MCDE subset analysis), four different remote regions were drawn (all in areas free of artifact) and the average change in the size of the gray zone due to the varying remote region statistics was determined. In the same subset of patient images, two different users drew epicardial and endocardial contours. The level of agreement between the two manual contours was determined by calculating the Cohen’s kappa value. Using the same SI cut-off values, the average difference in the size of the gray zone due to the different manual contours was determined. Finally, in the same subset of six patients, four simulated images were created by adding random noise to each pixel according to its SNR value. Using the same manual contours and remote region location, the average difference in gray zone size across the four simulated images was calculated to determine the variability introduced by random image noise. Note that the variability in gray zone sizes was determined separately for the SD and FWHM methods. The variability is expressed as the average variation in the gray zone size as a percentage of the average value of the total size of the gray zone. All measures were compared using correlation coefficients and a two-sided paired Student’s t-test.

3.2.3 Imaging protocol

Fifteen patients (11 men, mean age 64 ± 11 years) with chronic MI (resulting from ischemic heart disease) referred for cardiac MRI scans were included in this study. The average heart rate during MR imaging was 64 ± 14 beats per minute (range: 49 to 96). The protocol was approved by our Research Ethics Board and informed consent was obtained. MR imaging was performed on a 1.5T scanner (CV/i, GE Healthcare, Milwaukee, WI) using an 8-channel cardiac coil. Delayed enhancement imaging was started 10 minutes after the injection of 0.2 mmol/kg of Gd-DTPA (Magnevist, Berlex Inc., Wayne, NJ). Between eight and ten short-axis images were acquired to cover the entire left ventricle with the conventional IR-GRE sequence and the MCDE sequence. The order of the two sequences was randomized.
Parameters for the IR-GRE sequence were: bandwidth (BW) = ±31.5 kHz, readout flip angle = 20°, views per segment (VPS) = 20, TR/TE = 6.6/3.1 ms, FOV = 320 mm, slice thickness = 8 mm, 192 x 192 imaging matrix and NEX = 2. The inversion time (TI) was tuned for each patient to optimally null healthy myocardium, and ranged from 175 to 250 ms. A single image required a breath-hold of approximately 15-18 seconds. The parameters for the MCDE sequence were: BW = ±125 kHz, readout flip angle = 45°, VPS = 16, TR/TE = 2.7/1.3 ms, FOV = 320 mm, slice thickness = 8 mm, 192 x 192 imaging matrix and NEX = 1. The inversion pulse was placed such that the infarct-enhanced images are acquired during diastole. MCDE required a breath-hold of approximately 12-15 seconds for each imaging slice.

3.3 Results

3.3.1 Infarct segmentation

IR-GRE and MCDE images from a 57-year old male with an antero-septal MI were shown in Figure 3.1. The infarct can be seen as an area of fast T₁* recovery in the MCDE images (hypoenhanced in the first image and hyperenhanced in the next five images). Signal recovery curves extracted from MCDE images for a single pixel within infarct, healthy myocardium, and blood are shown in Figure 3.2. Figure 3.2 also shows the steady-state and T₁* parameter maps for all pixels resulting from the regression analysis. Note that the two dark pixels in the center of the infarcted tissue were pixels with large residuals after statistical fitting that were excluded from further analysis. A scatter plot of T₁* versus steady-state values, used as the input to the fuzzy clustering algorithm, is shown in Figure 3.3. A spatial map of the clustering results (Figure 3.3b) shows the infarct core, infarct gray zone, healthy myocardium, and blood.
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Figure 3.2: (a) Extracted signal intensities for a pixel within infarcted tissue, healthy myocardium, and blood (from the patient images shown in Figure 3.1), along with the recovery curves determined using Equation 3.1. Data fitting for all pixels in the left ventricle yield parameter maps of the (b) steady-state and (c) $T_1^*$ values. Note that the infarct can be seen in the $T_1^*$ parameter map as a dark region corresponding to smaller $T_1^*$ values.

Figure 3.3: The (a) scatter plot of $T_1^*$ versus steady-state (SS) values (data from the same patient shown in Figure 3.2) for all pixels within the left ventricle, and (b) the corresponding spatial map of the various tissue types classified using automated fuzzy clustering analysis. The clusters are color coded as infarct (green), healthy myocardium (blue), and blood (red). The gray zone (yellow) was defined as pixels that have a significant probability of belonging to both the infarct and healthy myocardium clusters.
The MCDE image and corresponding image analysis successfully identified scar tissue in all 15 patients that were examined. The average ejection fraction (EF) across all patients was 36 ± 10%, and the average heart rate during MR imaging was 63 ± 14 beats per minute (range: 47 to 96). The average sizes of the infarct core and gray zones detected using each of the three methods are shown in Table 3.1. Figure 3.4 compares the results of the infarct classification from a single imaging slice using the SD, FWHM, and MCDE methods. The relationships between the MCDE-derived and IR-GRE-derived measures of infarct core and gray zone sizes are shown in Figure 3.5. Comparing the MCDE and FWHM-based methods, there was some agreement in the infarct core size (r = 0.53) and good agreement in the size of the gray zone (r = 0.89), with no statistical difference between the two methods for either measure using a paired Student’s t-test (p = 0.10 for infarct core and p = 0.86 for gray zone). The SD-based method tended to characterize the infarct as having a larger infarct core than MCDE (overall average of 20.6 ± 6.1 g versus 14.8 ± 4.1 g, p < 0.001, r = 0.68) and thus a smaller gray zone (overall average of 3.0 ± 1.4 g versus 7.9 ± 3.1 g for MCDE, p < 0.001, r = 0.61). Coil sensitivity correction is built into the MCDE sequence, and no spatial sensitivity was noted in the raw MCDE images.
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Figure 3.4: Comparison of infarct core (green pixels) and gray zone (yellow pixels) classifications using (a) the MCDE-based method, (b) the FWHM-based method, and (c) the SD-based method in the same imaging slice from a 57-year old patient. The FWHM and MCDE methods detected similar gray zone sizes while the SD method detected fewer gray zone pixels compared to the other two methods.

Figure 3.5: Correlations in infarct core and gray zone sizes between (a,b) the SD (standard deviation) and MCDE (multi-contrast delayed enhancement) methods, and (c,d) the FWHM (full-width half-maximum) and MCDE methods.
Table 3.2: Variability in gray zone sizes.

<table>
<thead>
<tr>
<th>Effect</th>
<th>SD method</th>
<th>FWHM method</th>
<th>MCDE method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image noise</td>
<td>23%</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Data analysis</td>
<td>14%</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Manual contours</td>
<td>23%</td>
<td>12%</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac motion</td>
<td>-</td>
<td>-</td>
<td>3%</td>
</tr>
</tbody>
</table>

3.3.2 Analysis of cardiac motion

In the area of infarcted myocardium, there was no translation of the endocardial border in four of the five patients; in the other patient, the endocardial border was translated by one pixel (1.67 mm). There was no change in myocardial wall thickness over this time window in infarcted segments for all five patients. In remote regions of healthy myocardium, the average translation of the endocardial border was two pixels, with a maximum translation of four pixels.

3.3.3 Variability in segmentation results

Table 3.2 shows the results of the gray zone variability due to image noise, data analysis, the use of manual contours, and cardiac motion. Image noise had a smaller impact on gray zone variability using the MCDE analysis (4%) than either the SD (23%) or the FWHM (16%) methods. The variability from the data analysis stems from the variation in the location of the remote region for the SD method (14% variability) and the FWHM method (9% variability). For the MCDE analysis, the variability in gray zone size due to the non-linear regression and fuzzy clustering was 1%. The use of manual endocardial contours resulted in a gray zone variability of 23% for the SD method and 12% for the FWHM method, even though there was excellent statistical agreement when comparing the two manual contours to each other (Cohen’s kappa value = 0.84). Figure 3.6 shows one IR-GRE image with the endocardial contours from two users, and the associated infarct core and gray zones. Note the difference in the appearance of endocardial gray zone pixels, particularly in the septum, resulting from differences in the manual contours.
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Figure 3.6: (a) IR-GRE patient image with manual endocardial contours drawn by two different users (red and green contours), along with (b,c) the two gray zone maps derived using each of those contours. Note that slight differences in the contours at the blood-infarct border (particularly at the septum) result in differences in the appearance and size of the infarct core and gray zones.

The MCDE analysis did not require the use of manual contours to segment out the blood pool. There was on average 13 pixels excluded from each patient (across all images) in the region of the infarct because of large residuals from the data fitting procedure. The large residual is most likely due to cardiac motion. The 13 pixels corresponded to, on average, 3% of the total gray zone area. It is assumed that there is no cardiac motion over the 150 ms time window over which the IR-GRE images are acquired, although this was not explicitly tested.

3.4 Discussion

A new method for automatically segmenting and characterizing infarct zones using MCDE images has been developed. This image analysis and fuzzy clustering technique yields a more reproducible measure of the infarct gray zone than the signal intensity-based methods using conventional IR-GRE images. Image noise plays a much smaller role in determining the classification of each pixel using the MCDE analysis when compared to the IR-GRE approaches because MCDE uses statistical fits over eight images at different inversion times. The resulting classification for each pixel is therefore less sensitive to noise in any one image. The acquisition of multiple images during the $T_1$ recovery with MCDE is possible due to the greater efficiency realized when using an SSFP readout during an inversion recovery sequence. Note that the spatial resolutions for
the two imaging sequences were matched exactly, and the total acquisition time was approximately the same. Therefore the difference in the effect of noise on the gray zone classification is due to the differences in IR-GRE and MCDE pulse sequences and corresponding analysis.

The use of manually drawn remote regions also adds significant variability to the size of the gray zone. In a remote region of healthy myocardium where the true signal intensity is approximately zero, noise in the IR-GRE image plays a large role in determining the measured signal intensities. By changing the location of the remote region, the standard deviations and peak signal intensities can vary significantly due to repeatedly sampling the noise whose distribution has a large variance. This leads to different signal intensity cut-offs for defining the infarct core and gray zones, and leads to the high variability in gray zone sizes when using the SD or FWHM methods. The 1% variability due to data analysis using the MCDE approach is a result of small differences in the convergence of the statistical fit when repeating the non-linear regression.

Manual epicardial and endocardial contours, required for the IR-GRE analysis, cause additional variability in the gray zone size. Although statistically there was excellent agreement in the manual contours (kappa = 0.84), there was, on average, 103 pixels that were classified as blood pool by one user but myocardium by the other user. Differences in the endocardial contours are increased when the signal intensities of infarct and the blood pool are similar. These differences can affect the size of the gray zone by determining the presence or absence of endocardial gray zone pixels (as seen in Figure 3.6). A major advantage of using MCDE images is that, with the corresponding image analysis described above, a manually drawn endocardial contour is not required. The multiple image contrasts provided by the MCDE sequence have already been shown to provide superior discrimination of the infarct-blood border (see Chapter 2). The clustering analysis further demonstrates the excellent delineation of the blood pool on MCDE images as the clustering algorithm successfully segmented the blood pool from surrounding myocardial tissue in all images. While reproducibility across multiple repeat analyses of the same data set (or data sets differing only by random noise) is much
improved with the MCDE method, a critical remaining question is reproducibility across repeat studies. Such studies are planned so that one can establish the potential of the new method to detect small changes in infarct heterogeneity in longitudinal studies.

The MCDE approach showed a decent correlation with the SD and FWHM methods for defining the infarct core and gray zones (Figure 3.5, correlation values ranging from 0.53 to 0.89). The SD method segmented the tissue into larger infarct cores and correspondingly smaller gray zones compared to the FWHM method. The larger gray zones detected using the FWHM method may help explain why the FWHM method was able to distinguish between inducible and non-inducible patients in a recent study [59] but the SD method did not distinguish the two patient populations. The MCDE analysis yielded results more closely related to the FWHM approach in the current study; there was no statistical difference in the size of either the infarct core or gray zone when comparing these two methods. The lack of a higher correlation between the MCDE and FWHM methods may be due to the large variability associated with the FWHM-derived gray zone.

In general there was good qualitative agreement in the location of gray zones across the patients examined using the FWHM and MCDE analyses; however, the MCDE approach tended to detect more subendocardial gray zone. This could be due to manual blood pool contours on the IR-GRE images that can cut out subendocardial gray zone pixels. With the MCDE analysis, there may also be a partial volume effect at the infarct-blood border whereby a mixture of infarct and blood within a single voxel leads to an apparent gray zone that does not represent heterogeneous infarct. This would lead to a thin, single-pixel wide endocardial gray zone; in fact, this pattern was detected in some portion of the endocardial surface in all patients examined. Such single-pixel-wide regions could be isolated easily with post-processing and potential removed from subsequent analysis. However, in five other patients, endocardial gray zones greater than two pixels wide (and hence not likely associated with partial volume effects) were detected on the MCDE but not IR-GRE images; such gray zones may play a crucial role in VT inducibility because two-thirds of all reentry circuits leading to VT are found in the endocardium [97].
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The IR-GRE images and MCDE images also suffer from a partial volume effect at a sharp border between completely healthy myocardium and fully infarcted tissue. This effect should not alter the correlations in gray zone sizes between the methods examined because the spatial resolutions of the two imaging sequences were matched. As above, such a partial volume effect would lead to a baseline gray zone size that is not related to true infarct heterogeneity; any additional gray zone is postulated to be the result of a truly heterogeneous mixture of infarct and healthy tissue within a voxel. It is this heterogeneous area that is the known cause of reentry circuits leading to VT inducibility [13]. Further work is required to determine the relative contribution of each of these partial volume effects to the total gray zone size.

One limitation of the MCDE analysis is the lack of cardiac motion compensation prior to performing the pixel-by-pixel non-linear regression over the six to eight images at different inversion times. These images were acquired over a time window of 250 to 367 ms, depending on the number of images used and the heart rate of the patient. The inversion pulse is placed so that these images are acquired over diastole. It is generally accepted that there is a 200 ms time window in diastole with no motion [38],[39]. In the current study, the heart rate ranged from 49 to 96 beats per minute. At lower heart rates (such as 49 beats per minute), the time window of the MCDE images used in the analysis is longer (367 ms), but the diastolic no-motion window is also expected to be longer. At higher heart rates (i.e. 96 beats per minute), the diastolic window may be shorter, but the signal recovery is tracked over only 250 ms. The wall motion analysis performed as part of this study showed that in the region of infarcted tissue, where myocardial contractility is greatly reduced or eliminated, the diastolic window with little or no motion can be as long as 367 ms (in a patient with a heart rate of 49 beats per minute). Over this time window, there was either zero or one pixel of gross translation, and no change in myocardial wall thickness. There may be some cardiac motion over this time window in remote, healthy myocardium (on the order of two pixels); however, this results in the mixing of pixels of healthy myocardium with other pixels from healthy myocardium or blood, and will therefore not affect the resulting infarct core and gray zone segmentation.
If there is motion at the infarct border, the statistical fit will be poor because of the abrupt change in the signal recovery at a specific time point; the large residual would lead to the exclusion of that pixel from any further analysis. On average, a total of 13 pixels at the infarct border (across all acquired images) were excluded for each patient. This adds 3% to the variability of the gray zone size determined with the MCDE analysis, which should not significantly alter the correlation with the IR-GRE based methods. Due to the small variability caused by cardiac motion, motion compensation or tracking techniques were not implemented in the MCDE analysis. In hearts where there is a small infarct and cardiac contractility is only slightly reduced, the diastolic window with no motion may be reduced, especially at high heart rates. In this case, wall motion compensation techniques might be required. Note that although it was assumed that there was no cardiac motion over the 150 ms time window used for the IR-GRE acquisition, there may in fact be some motion if the trigger delay (the time between R-wave trigger and the inversion pulse) is not set correctly. This would lead to an unwanted partial volume effect that could lead to false positive or false negative gray zone pixels. With the IR-GRE imaging and analysis, there is no way to detect this motion; with the MCDE analysis, pixels that experience cardiac motion are explicitly excluded.

Another limitation of this study is that all of the infarcts examined were chronic infarcts in patients with no history of ventricular arrhythmias. In a similar patient population with no prior history of VT, a previous study has detected an average gray zone size of 13 ± 9 grams using the FWHM analysis of IR-GRE images [59]. The average gray zone size in the current study was 7.8 ± 3.2 grams (using the FWHM approach) or 7.9 ± 3.1 grams (using the MCDE analysis). The difference in average gray zone sizes between the two studies is likely a reflection of the smaller overall infarct size in the patients recruited for the current study (average total infarct size of 20.9 ± 6.5 grams, average EF of 36 ± 10%) compared to the previous study (average total infarct size of 34 ± 17 grams, average EF of 30 ± 10%). Further studies examining the gray zones detected by MCDE imaging in patients with known or suspected VT are currently ongoing.
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The signal intensity and probability cut-off values used to separate the gray zone from the infarct core for all three analysis methods are arbitrarily chosen. For the MCDE analysis, a linear relationship was observed between the gray zone size and the size of the window of probabilities chosen to correspond to the gray zone. This relationship suggests that, in studies comparing relative gray zone size, the absolute probability cut-off values may not be critical as long as they are consistent. Still, when predicting VT inducibility, one might expect some threshold effect identifying a minimum volume of infarct heterogeneity. In this study, there was no gold standard and thus the probability cut-offs (and signal intensity cut-offs for the SD and FWHM analyses) that best correspond to true infarct heterogeneity cannot be determined. Future studies in an animal model of inducible VT are planned. In these studies, the gray zone appearance at various probability and signal intensity cut-off levels will be compared to in-vivo electrophysiology measurements of action potentials.

3.5 Conclusions

In this chapter, new image analysis tools to segment the infarct core, gray zone, healthy myocardium, and blood on MCDE images were developed. Infarct characterization was performed in 15 patients with chronic infarct and the MCDE gray zone showed a good correlation with the gray zone detected on conventional IR-GRE images. Compared to the IR-GRE-based methods, the MCDE approach yielded a more reproducible measure of the infarct core and gray zone as it is less sensitive to noise and does not require manual contours to segment out the blood.
Chapter 4

4 Real-time delayed enhancement imaging

4.1 Background

Delayed enhancement MRI (DE-MRI) is the method of choice for detecting and measuring myocardial infarct (MI) [25]. DE-MRI is conventionally acquired with a segmented inversion-recovery gradient echo (IR-GRE) sequence. IR-GRE imaging requires repeated breath-holds which can be difficult to achieve in a patient population with cardiac disease. Breath-holds can be reduced or eliminated by using a single-shot readout [77],[78] or navigators [74]. These methods, however, still require cardiac gating, which can be problematic in patients with arrhythmias. In addition, these methods yield images where small subendocardial infarcts can be masked by the bright blood pool [65].

A method for real-time delayed enhancement (RT-DE) imaging has been developed [98] to alleviate the limitations of the IR-GRE sequence. RT-DE is a free-breathing, non-gated approach that consists of a continuous, real-time stream of images acquired using a series of single-shot steady-state free precession (SSFP) acquisitions [42] with intermittent inversion pulses [86] to create infarct-enhanced images. The RT-DE sequence is useful for rapidly assessing the presence or absence of infarcted tissue, or to allow for infarct assessment (including size and transmurality) in patients where cardiac gating or breath-holds are not possible. In this chapter, an understanding of the effects of the SSFP readout on the signal recovery after an inversion pulse is used to describe the appearance of RT-DE images. The RT-DE sequence is evaluated in a patient population with ischemic heart disease and compared to conventional IR-GRE imaging in terms of sensitivity and specificity for detecting MI, and for measuring infarct sizes.

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Figure 4.1: Schematic of the real-time delayed enhancement (RT-DE) sequence. The inversion pulse is applied (time = 0 ms in the figure), and a delay time (TD) is used during which no data is acquired. The delay time plus half of the imaging time for Image #1 is the effective inversion time (TI). Image #1 is the infarct-enhanced image, and four subsequent anatomical images are acquired before another inversion pulse is applied.

4.2 Methods

4.2.1 Pulse sequence

The RT-DE sequence (Figure 4.1) continually uses a non-slice-selective inversion pulse and variable delay time (TD) followed by single-shot SSFP readouts. The first image after the inversion pulse is the infarct-enhanced image, acquired with a full k-space acquisition. The four subsequent anatomical images are acquired while the magnetization recovers towards its steady state and use the same SSFP pulses but use view sharing to halve the imaging time for each anatomical image. Immediately after the acquisition of the fifth image, another inversion pulse is applied and the entire process is repeated. Note that the SSFP pulses are applied continuously and the magnetization never recovers to its initial magnetization (Figure 4.1). The effective inversion time (TI) is the sum of the delay time and half the acquisition time for the infarct-enhanced image. The images are continuously displayed on a real-time interface which can be used to manipulate the scan plane and control various sequence parameters [99], including the
delay time and the number of images acquired after each inversion pulse. The pulse sequence is applied during free-breathing, and is not triggered by the ECG signal.

RT-DE is a black-blood sequence whereby the signal from healthy myocardium and the blood pool is nulled at the same time point (see Figure 2.4 and Sec 2.2.2). This is a result of the continuous SSFP pulses that do not allow the magnetization to re-grow to its initial $M_0$. Due to the different $T_1/T_2$ ratios for blood and myocardium, the signal prior to and immediately following the inversion pulses for the tissues are different. The difference in the steady-state value between blood and myocardium depends on the SSFP readout flip angle and to a lesser degree the amount of blood that washes into the imaging slice over the time period between inversion pulses (typically $> 1$ s). From previous simulations (see Chapter 2), a flip angle of $30^\circ$ was shown to result in simultaneous nulling of the signal from healthy myocardium and blood, relatively independent of the amount of wash-in of blood.

4.2.2 Patient protocol

A total of 23 patients (19 males, average age of 66 ± 12 years, average heart rate of 66 ± 11 beats per minute) were examined under a protocol approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, and all patients gave informed consent. Patients with ischemic heart disease and suspected MI referred for a cardiac viability scan with MRI were included. Nineteen of the 23 patients had recent cardiac catheterizations that confirmed the presence of a coronary artery stenosis. Eight patients had a recent MI (defined as hospitalization for chest pain believed to be associated with an ischemic episode within the last two months). The other 15 patients had late chronic MI, with a median time since the patient’s first hospitalization for an ischemic-related episode of eight years (range from seven months to 18 years).

Imaging was performed starting 10 minutes after the injection of a solution of 0.2 mmol/kg Gadolinium-DTPA (Magnevist; Berlex, Inc., Wayne, NJ). An eight-channel cardiac coil (GE Healthcare, Milwaukee, Wisconsin), with four anterior and four posterior coils, was used for signal reception. All imaging was performed on a 1.5 T
scanner (Signa CV/i, GE Healthcare, Milwaukee, Wisconsin). Seven to twelve short-axis slices were acquired per patient with both IR-GRE and RT-DE to cover each patient’s entire left ventricle. The order in which the two sequences were acquired was randomized. The segmented IR-GRE sequence was acquired with 1.25 x 1.67 x 8 mm³ voxels covering a 32 x 32 cm field of view, TR = 7.7 ms, TE = 3.7 ms, 20⁰ flip angle and two averages. During each R-R interval, data was acquired over a time window of 154 ms during mid-diastole. Each slice was acquired with a 12-18 second breath-hold. The inversion time was optimized for each patient to null the signal from myocardium (range from 175-250 ms). RT-DE imaging was performed with the following parameters: 2 x 2 x 8 mm³ voxels covering a 32 x 32 cm field of view, TR = 2.7 ms, TE = 1.3 ms and SSFP flip angle of 30⁰. The temporal window for the viability image was 432 ms. The delay time was determined for each patient interactively with a slider bar on the real-time interface to obtain an optimal inversion time to null healthy myocardium (range of 200 – 250 ms). Since RT-DE is asynchronous to the cardiac cycle, RT-DE images were collected over 10-15 seconds in order to acquire at least some infarct-enhanced images near mid-diastole (the cardiac phase during which IR-GRE images were acquired). Conventional myocardial short axis cine images were acquired with a segmented SSFP sequence after viability imaging for the detection of wall motion abnormalities.

4.2.3 Data analysis

Each imaging slice was divided into six myocardial segments as per the recommendation of the American Heart Association [22]. Two independent readers determined the presence or absence of enhancement on a segment by segment basis for both IR-GRE and RT-DE in a blinded fashion. A third reader was used to resolve any discrepancies between the first two readers. Both readers read the IR-GRE images first and then the RT-DE images one week later. The order in which the studies were read during each session was randomized.

For each slice, the RT-DE image used for analysis was the single infarct-enhanced image of highest diagnostic quality acquired near mid-diastole. If enhancement was detected in a segment, it was then scored as either being transmural (transmurality of 50% or above)
or non-transmural (under 50%). Because the infarct-enhanced RT-DE images are black-blood, the RT-DE wall motion images acquired 200 ms before or after the infarct-enhanced image were used to help visualize the myocardial wall thickness. This information was used to help estimate infarct transmurality on the RT-DE images. A Cohen’s kappa value was calculated to determine the inter-observer variability in infarct transmurality for both the IR-GRE and RT-DE data. For each slice, a quantitative measure of the total MI size was determined with manual contours. For each patient, the infarct sizes from each imaging slice were summed and the total infarct size was expressed in grams of tissue.

A Bland-Altman analysis was performed to detect any bias in the RT-DE measure of infarct size. The contrast-to-noise ratios (CNR) between infarct and healthy myocardium and between infarct and blood were measured on the IR-GRE and RT-DE images, and the signal-to-noise ratio (SNR) of blood was also measured. For all statistical tests, a two-sided paired Student’s t-test was used, and tests were considered statistically significant at or below $p = 0.05$. 
4.2 A comparison of (a) IR-GRE and (b) RT-DE infarct-enhanced images in a 61-year old male patient. A small subendocardial infarct is visible in the IR-GRE image (arrow), though the infarct-to-blood border is hard to distinguish. A greater extent of subendocardial infarct can be visualized on the RT-DE image (arrows) due to the low signal from blood.

4.3 Results

Infarcts were detected in 19/23 patients in this study using the IR-GRE images. IR-GRE and RT-DE images in a selected patient are shown in Figure 4.2 illustrating the advantage of the black-blood RT-DE imaging. Figure 4.3 compares IR-GRE to RT-DE images in a patient who had difficulty with breath-holds. Example images in a patient with poor ECG gating and respiratory drift throughout the breath-hold are shown in Figure 4.4.

Eight patients had some respiratory drift (seen on the respiratory bellows) during the breath-holds required for an IR-GRE acquisition. Cardiac gating was suboptimal in four patients; in three patients the ECG trace was extremely noisy (reasons unknown), and one patient had atrial fibrillation. These difficulties led to seven patients whose IR-GRE images had some imaging artefacts, although only two slices from two patients were non-diagnostic. These two slices were excluded from the analysis. No other patients were excluded due to arrhythmias or breath-hold difficulties.
Figure 4.3: (a) Delayed enhancement image using IR-GRE in a 73-year old male patient who had difficulty holding his breath. Note the blurring and image ghosting that is introduced due to respiratory motion. (b) The RT-DE image at the same anatomical location does not suffer from this blur. Both images shown have a field of view of 32 x 32 cm.

Figure 4.4: (a) Delayed enhancement image using IR-GRE in a 76-year old male patient with respiratory drift and a poor ECG signal during the image acquisition. Note the image degradation causing poor visualization of the septal infarct. (b) The RT-DE at the same anatomical location does not suffer from this blur, and the enhanced infarct is easier to detect.
Figure 4.5: (a) Comparison of the total infarct size for each lesion, as detected by IR-GRE and RT-DE imaging, and (b) the corresponding Bland-Altman analysis. IR-GRE and RT-DE show excellent agreement in infarct sizes (slope = 1.02 ± 0.04, R = 0.97), and no bias was observed in the Bland-Altman analysis (mean = 0.29 g, 2•SD = 1.66 g).

RT-DE detected infarcts in 273/292 segments where enhancement was detected by IR-GRE, for a segmental sensitivity of 94%. RT-DE detected enhancement in all 19 patients with enhancement detected by IR-GRE. RT-DE had a specificity on a segment-by-segment basis of 98% (agreement in 617/632 segments). The 15 segments where enhancement was detected by RT-DE but not IR-GRE were all scored as non-transmural infarcts. Wall motion abnormalities were present in all 15 of these segments, detected in the separately acquired cine SSFP images at the corresponding slice locations. RT-DE did not show any enhancement in any of the four patients with no enhancement detected by IR-GRE. The infarct transmurality measured using the RT-DE images matched the transmurality measured using the IR-GRE images in 251/273 (92%) of the segments showing enhancement. There was excellent agreement between the two observers reading the IR-GRE images (Cohen’s kappa = 0.93) and RT-DE image (Cohen’s kappa = 0.89).

Agreement was observed between the two methods for the total infarct size (slope = 1.02 ± 0.04, R = 0.97), with no bias detected using a Bland-Altman analysis (Figure 4.5). The average time for DE imaging with IR-GRE (11.5 ± 1.9 minutes) was significantly longer than RT-DE (5.6 ± 0.9 minutes, p < 0.001). It took approximately 10-15 seconds to adjust the delay time to effectively null the signal from myocardium during RT-DE imaging. RT-DE exhibited a slightly lower CNR between infarct and healthy
myocardium than IR-GRE, though this difference did not reach statistical significance (9.3 ± 4.8 versus 12.7 ± 5.4, p = 0.06). However, the blood pool signal was suppressed in the RT-DE images (Figure 4.2) and thus RT-DE had a lower blood-pool SNR than IR-GRE (5.8 ± 3.1 versus 10.8 ± 5.6, p < 0.001); correspondingly, RT-DE exhibited a slightly higher CNR between infarct and the blood pool than IR-GRE, although this did not reach statistical significance (7.0 ± 4.9 versus 4.4 ± 3.0, p = 0.06).

4.4 Discussion

The results show that RT-DE is a highly sensitive and specific method for detecting MI when compared to conventional delayed enhancement imaging. There were 19 segments not detected on RT-DE images but seen on the corresponding IR-GRE image. These segments were all in imaging slices where the infarct core was detected by RT-DE imaging; however, the infarct extended into an adjacent region on the IR-GRE but not the RT-DE image. This is most likely due to different respiratory positions and these segments may have been detected if a number of the acquired RT-DE infarct-enhanced images (at different cardiac and/or respiratory phases) had been read in parallel. The reported specificity for RT-DE on a segmental basis is 98%; however, the 15 segments with enhancement on RT-DE not seen by IR-GRE are not necessarily false positives. RT-DE displayed a higher CNR between infarct and blood and a much lower blood pool SNR than IR-GRE because of the suppressed blood pool signal in RT-DE images. As a result, these “false positives” are likely small subendocardial infarcts that were detected by RT-DE but whose presence was obscured in the IR-GRE images by the bright blood pool (Figure 4.2). In all 15 segments with enhancement seen on RT-DE but not IR-GRE, wall motion abnormalities were detected in the cine SSFP images at the corresponding slice locations; this provides further evidence that these 15 segments are true positives on RT-DE. These results confirm a previous suggestion [65] that the current prevailing standard for DE-MRI may not be the best method for the detection of small, subendocardial infarcts. Two other methods have been described to improve the sensitivity of IR-GRE for detecting subendocardial infarcts obscured by the blood pool. The first acquires black-blood DE-MRI images by applying two inversion pulses; a slice-
selective inversion is followed by a non-selective inversion to decouple the recovery curves of blood and tissue [76]. This method requires an accurate estimate of two different inversion times to properly null the signal from blood while maintaining a high signal for infarcted tissue. The second method uses manual contours of the blood pool drawn on T2-weighted images and copied to the IR-GRE images in order to separate the blood pool from subendocardial infarct enhancement [65]. However, acquiring the T2-weighted images requires an increase in the scan time, and manual post-processing must be performed. Both of these sequences require cardiac gating and breath-holds. RT-DE acquires black blood delayed enhancement images without any additional imaging or post-processing.

Difficulties with breath-holding were encountered in 35% of the patients in this study. This is similar to the 33% of cardiac patients with inadequate breath-holds for coronary MR imaging as reported in a much larger study of 210 patients [66]. Cardiac gating was suboptimal in 17% of patients in this study; changes in the R-R interval during an IR-GRE scan due to a false ECG trigger may lead to imaging artifacts. No problems were experienced with RT-DE because this method is not gated or breath-held. The images in Figure 4.3 show how poor breath-holds can lead to IR-GRE images that are difficult to read, while the RT-DE image quality is not reduced during free-breathing. Another free-breathing method for DE-MRI using navigator echoes [74] has been recently described. This method tracks the position of the right hemidiaphragm and collects data only when there is a consistent respiratory position. The navigator-based method required five minutes to cover the entire LV, which was equivalent to the total time required for a stack of conventional breath-held images [74]. Alternatively, 3D IR-GRE sequences with a single breath-hold [68]-[71] or with navigators [72] can also be used to cover the entire left ventricle in a single breath-hold or during free breathing. However, all of these methods require cardiac gating and yield images with a bright blood pool. Using the RT-DE method, the entire left ventricle can be examined over a short time period with black-blood viability images, without any cardiac gating.
The RT-DE pulse sequence is similar to the inversion recovery single-shot imaging with SSFP proposed by Li et al. [77] and Huber et al. [78] and recently validated in a larger study by Sievers et al. [38]. The main difference with RT-DE is that it is not cardiac-gated or breath-held, yields black blood images, and RT-DE uses a continuous SSFP readout that provides anatomical SSFP images between successive viability images. The reason for the reduced blood pool signal with RT-DE is the continuous SSFP readout; the magnetization is not allowed to fully recover to $M_0$, and changes the starting position ($-M_z$) of the $T_1$ recovery curves of myocardium, infarct and blood relative to each other after each inversion pulse (see Figure 4.1).

Sievers reported a sensitivity/specificity of 87% / 96% [38] for detecting MI with a single-shot approach; RT-DE has a slightly higher sensitivity (94%) and a similar specificity (98%). The infarcts that were missed with the single-shot SSFP sequence were reported to be mostly subendocardial MI [38]; the elevated sensitivity using RT-DE is most likely a result of the dark-blood appearance in the RT-DE images leading to increased detection of these subendocardial infarcts. There were only four patients examined that did not have any MI in this study, and thus the per-patient specificity of the RT-DE method remains relatively untested.

Slight differences in the quantitative measures of enhancement between IR-GRE and RT-DE are expected because of the uncertainty in the cardiac and respiratory phase of the RT-DE images. In principle, ECG gating could be added to the RT-DE sequence to ensure that the infarct-enhanced image is acquired in diastole. However, the goal of this study was to evaluate the capabilities of a real-time sequence that does not require cardiac gating. RT-DE has a lower spatial resolution and more temporal blurring than IR-GRE; however, the results of this study show that the estimates of infarct size with the two methods are equivalent (slope = 1.02 ± 0.04). Even though RT-DE detected some subendocardial enhancement not detected by IR-GRE, the size of these areas of enhancement were small and thus they are not expected to significantly alter the relationship between infarct sizes measured with the two methods. These results are similar to the results of the study by Huber, who had a slope of 0.96 between infarct sizes
measured with single-shot SSFP sequence and IR-GRE [78], although Sievers [38] found that the single-shot SSFP images underestimated infarct size (slope = 0.69). The reason for the discrepancy between those two studies remains unclear.

The main limitation of the RT-DE method is the larger temporal window for acquisition compared to segmented IR-GRE sequences or other single-shot SSFP sequences that use parallel imaging. RT-DE did not use parallel imaging, although this could be added in future studies. It should be noted, however, that parallel imaging reduces the SNR of the resultant images. The SNR of enhanced infarct in DE-MRI using an SSFP readout is already reduced by a factor of 2.7 compared to a gradient echo readout [79]. The constant application of SSFP pulses yielded black-blood viability imaging; however, this comes at the cost of an even greater reduction in infarct SNR (see Chapter 2). A further reduction in SNR due to parallel imaging may lead to a reduced sensitivity for detecting MI, and therefore the temporal resolution of RT-DE was sacrificed in order to acquire black-blood viability images while maintaining a high sensitivity at a reasonable spatial resolution. Currently, the non-infarct-enhanced RT-DE images were used only to visualize the myocardial anatomy. The development a spiral SSFP imaging [100] version to replace the Cartesian-based readout in RT-DE is being pursued (see Chapter 5); with a spiral readout, the temporal resolution can be increased to 8-10 frames per second without substantial loss in SNR. This would result in cine images with sufficient temporal resolution to be used for wall motion visualization.

A major benefit of the RT-DE approach is that patients with atrial fibrillation (AF) can successfully undergo DE-MRI. This study had only one patient with AF; the benefits of the RT-DE approach would be further emphasized with more studies in patients with AF. Another limitation of this study was that there was no gold standard for infarct evaluation in patients where the IR-GRE results were non-interpretable or suboptimal.
4.5 Conclusions

In this chapter, a real-time delayed enhancement sequence was shown to be capable of detecting myocardial infarcts without cardiac-gating or breath-holds in a patient population with ischemic heart disease. RT-DE can be used to test for the presence of myocardial infarct in the entire left ventricle using a significantly shorter imaging time than the conventional IR-GRE sequence. In cases where breath-holding or cardiac-gating are suboptimal, RT-DE can be used to measure infarct sizes. The blood pool signal is suppressed in the RT-DE images and the results shown in this chapter suggest that this method may be able to detect small subendocardial infarcts more readily than conventional bright-blood DE-MRI techniques.
Chapter 5

5 Summary and future directions

5.1 Summary

In Chapter 2, simulations were performed to examine the effect of SSFP readout pulses on the signal evolution following an inversion recovery pulse. The effect of the SSFP flip angle on the apparent $T_1$-shortening was examined in the framework of a single-shot SSFP readout and for a segmented SSFP acquisition. Based on the simulations, an optimized, segmented multi-contrast delayed enhancement (MCDE) sequence was developed. The MCDE sequence produces wall motion images as well as viability images with varying contrast in a single breath-hold. This sequence was tested in patients and the results showed that MCDE could accurately detect myocardial infarct when compared to the conventional inversion-recovery gradient echo (IR-GRE) sequence. MCDE images also allowed for improved visualization of the infarct-blood border. The ejection fractions measured using MCDE images closely matched the ejection fractions derived from conventional cine SSFP images, showing that the MCDE sequence could be used to simultaneously evaluate viability and cardiac function. A United States patent application has been filed for the multi-contrast delayed enhancement sequence based on the work described in Chapter 2 (the patent description can be found in Appendix A).

In Chapter 3, an image processing pipeline was developed to analyze MCDE images. An automated algorithm for segmenting blood, healthy myocardium, the infarct core, and the peri-infarct gray zone was shown to be more reproducible than the gray zone segmentation methods used on IR-GRE images. The MCDE gray zone analysis is less sensitive to image noise and does not require manual contours of the blood pool. Two critical questions remain regarding the MCDE gray zone analysis. The first question is whether the improved robustness of the MCDE analysis will yield a stronger correlation between the gray zone characteristics and inducibility for ventricular tachycardia. The second question that remains is the determination of the relative amount of gray zone
from truly heterogeneous infarct versus the gray zone from unwanted partial volume effects at a sharp infarct-myocardium border. The influence of the spatial resolution of the acquired images on the size of the gray zone also requires investigation.

In Chapter 4, a real-time delayed enhancement (RT-DE) method was developed based on continuous single-shot SSFP imaging with intermittent inversion pulses. The RT-DE sequence was optimized based on simulations from Chapter 2 to provide black-blood viability images without requiring cardiac gating or breath holds. The RT-DE and IR-GRE sequences were compared in 23 patients with ischemic heart disease. The RT-DE sequence had a high sensitivity and specificity for detecting myocardial infarct (MI) and could be used to quantify the amount of MI.

After the completion of the study described in Chapter 4, another group looked at the application of single-shot inversion-recovery SSFP (IR-SSFP) imaging in a canine model of infarct, without breath-holds and with irregular heart rhythms [101]. Similar to the results in Chapter 4, that study concluded that fast, single-shot techniques could be used for viability imaging, and that the diagnostic accuracy was improved with their single-shot technique under free-breathing and when the ECG signal was irregular. However, RT-DE imaging still has the advantage of providing anatomical images 200 ms after the infarct-enhanced image, which facilitates the interpretation of the presence and transmurality of any infarct. Additionally, RT-DE has a higher sensitivity (94%) than the single-shot method under free-breathing conditions (82%) [101], most likely because of the black-blood appearance of RT-DE images.
5.2 Future directions: Protocol optimization

5.2.1 Pulse sequence development

To improve the temporal resolution of the RT-DE imaging sequence, a new real-time SSFP sequence with spiral readouts is under development. The current implementation of the RT-DE sequence uses a Cartesian readout which is limited to acquiring a single row of k-space during each TR. Using a spiral SSFP readout [100], a larger amount of k-space can be covered during each TR. With spiral SSFP readouts, images with an in-plane resolution of 2 x 2 mm can be acquired in 100 – 125 ms. This temporal resolution is limited by two factors: the gradient slew rate (which yields a TR of approximately 6 ms for the spiral readout used) and the number of spiral interleaves required to obtain an in-plane resolution of 2 x 2 mm. A temporal resolution of 100 ms should allow for a qualitative assessment of cardiac wall motion although some small systolic abnormalities might be missed. One trade-off of moving to spiral readouts is that off-resonance leads to blur in the image; the amount of blur and its effect on evaluating cardiac wall motion has yet to be assessed. Note that an improvement in the temporal resolution could also be achieved by maintaining a Cartesian readout but applying parallel imaging. However, parallel imaging results in a loss in SNR, and the parallel reconstruction algorithm is generally too slow to apply in a real-time environment. The spiral RT-DE sequence will also provide two to three images at early inversion times with varying contrast between infarct and healthy myocardium and blood, similar to the MCDE sequence. The temporal resolution of the $T_1^*$ sampling can be increased if the highly constrained backprojection (HYPR) algorithm is used [112]. The HYPR algorithm uses a composite image (in this case the first four or five images at early TI times) to constrain the reconstruction of temporally undersampled images (using a fraction of the 25 spirals used to fill k-space). However, the HYPR algorithm requires a sparse image which may cause the algorithm to fail when applied to images of myocardial tissue and blood. The spiral real-time sequence may be interleaved with a catheter tracking pulse sequence in order to guide an ablation catheter to the peri-infarct zone; this setup will be tested in a preclinical animal model of inducible VT (see Sec 5.3).
An improvement in the spatial resolution using the segmented MCDE sequence is also
desired. At an extremely high spatial resolution obtained with ex-vivo imaging, islands
of viable myocardium within infarcted tissue can be detected with a 3D IR-GRE
sequence [60]. In-vivo imaging is limited by cardiac motion and the breath-hold duration feasible in patients; therefore, heterogeneous infarct is likely limited to being detected via
a partial volume effect in the near future. The influence of unwanted partial volume
effects increases with decreasing spatial resolution, and thus a higher spatial resolution
for MCDE imaging should lead to a more accurate detection of truly heterogeneous
regions of infarct. However, the SNR that will be lost from going to a higher spatial
resolution needs to be compensated for in order to maintain a robust segmentation of the
infarct regions from healthy myocardium. Spiral SSFP readouts can be used for the
MCDE sequence to improve the spatial resolution. Maintaining a temporal window of 50
ms for every image during each cardiac cycle, a spiral MCDE sequence could achieve a 1
x 1 x 3 mm spatial resolution with an acquisition time of approximately 16 heart beats.

Another modification of the MCDE sequence would be to extend it to a 3D acquisition.
To maintain the spatial resolution required to detect the infarct gray zone, a 3D MCDE
sequence would likely need to be acquired during free-breathing with navigators, similar
to the high resolution 3D inversion recovery gradient echo sequence recently developed
to detect atrial ablation scars [102]. A 3D MCDE sequence would yield wall motion and
viability images covering the entire left ventricle with a single acquisition. The resulting
gray zone analysis may be more accurate because all voxels in the entire left ventricle
could be compared simultaneously, instead of voxels being compared only to other
voxels in the same 2D imaging slice. The target spatial resolution for the 3D MCDE
sequence would be 1 x 1 x 4 mm and using respiratory navigators the imaging time is
expected to be approximately 5 – 10 minutes per volume [102].
5.2.2 Contrast sensitivity

The MCDE sequence was shown in Chapter 2 to improve the visualization of enhanced MI compared to the IR-GRE sequence. It would be useful to determine in a large patient population how many cases of small endocardial infarct go unrecognized with IR-GRE imaging but are detected with MCDE. An example of such a case is shown in Figure 5.1, where the small subendocardial antero-septal infarct was not detected on the IR-GRE image due to infarct signal being isointense with the blood pool. The MCDE images with varying contrast allowed the small infarct to be easily visualized. It has already been shown that patients with small infarcts (1.4% of the total LV mass) experience a seven-fold increase in major adverse cardiac events compared to patients with no MI [5]. Long term follow up in patients where small subendocardial infarcts are detected with MCDE would be useful to determine if MCDE is an even more sensitive method for predicting which patients are at a higher risk for these adverse events; these patients can also be followed to determine if they are at a higher risk of ventricular arrhythmias.

In Chapter 3, it was shown that the MCDE sequence was four times less sensitive to image noise than the IR-GRE sequence for measuring the infarct core and gray zone sizes. The high sensitivity to noise in the IR-GRE images means that a large dose of Gd-DTPA (0.2 mmol/kg or higher) is required [25] and imaging must be performed within 30 minutes of contrast administration [44] in order to accurately detect MI. Even with these requirements, small areas of infarct may go undetected if the signal intensities of the
small number of infarcted voxels are near the noise floor of signal intensities of voxels in healthy myocardium. In addition, diffuse or patchy areas of MI are sometimes found in non-ischemic cardiomyopathies [103]. The MCDE sequence is expected to have an increased sensitivity to these small or diffuse infarcts. The increased sensitivity with MCDE may be used to lengthen the time window during which viability images can be acquired. MCDE may also allow for a reduction in the dose of Gd-DTPA without any loss in sensitivity to detect MI; this could be important because there are increasing concerns that Gd-DTPA might cause nephrogenic systemic fibrosis in patients with renal disease [104].

5.2.3 Quantification of infarct size

As discussed in Chapter 1, the quantification of infarct size is most commonly performed with manual contours on IR-GRE images. Semi-automatic methods using signal intensity thresholds to define each voxel as infarct or healthy myocardium have been shown to more accurately measure the size of MI when compared to histology [55],[56]. A more intelligent algorithm that uses signal intensity thresholds and region-based feature analysis to eliminate false positive voxels in healthy myocardium has also been developed [57]. However, all of these methods require manual contours of the endocardial border, which can be difficult on IR-GRE images when the infarct has the same signal intensity as the blood pool. The MCDE analysis is a fully automated segmentation algorithm that can be used to detect infarcted voxels without manual contours of the blood pool. The segmentation is robust for separating subendocardial infarct from blood pool voxels because of the combined $T_1^*$ and steady-state parameter maps. The MCDE analysis may therefore be a more accurate method for quantifying MI. The accuracy of the MCDE segmentation needs to be tested in an animal model of infarct where IR-GRE and MCDE images can be acquired. The results using the IR-GRE and MCDE segmentation algorithms can be compared to histology to determine if the MCDE analysis provides a more accurate and robust measure of infarct size.
5.2.4 Optimizing MCDE imaging to detect heterogeneous infarct

As discussed in Sec 5.2.1, the spatial resolution of viability images plays a role in the detection of the gray zone. It has been recently shown that high resolution 3D DE-MRI images had a 50% smaller gray zone than lower resolution 2D images in the same patient [105]. A comprehensive evaluation of the influence of spatial resolution on gray zone size is planned to address this issue. With the current MCDE sequence, images at the same anatomical position can be acquired at different resolutions, depending on the breath-hold capabilities of the patient being scanned.

Preliminary results illustrating the effect of spatial resolution on the gray zone are shown in Figure 5.2. The MCDE segmentation results are shown for the same imaging slice at three different resolutions. Note that a large gray zone in the antero-lateral wall (white arrows) is apparent at all three resolutions; however, the thinner septal gray zone (black arrows) is not seen in the image at the highest resolution (with a thinner slice thickness). With a fixed 8 mm slice thickness (Figure 5.2a-b), the gray zone size in the image with the lower in-plane resolution (2.02 g) was smaller than the gray zone with the higher in-plane resolution (2.45 g). At the higher resolution, there are more single voxel gray zones, likely due to the decreased SNR of the images leading to a larger variability in the parameter maps derived from the data fitting procedure. With a larger uncertainty, the fitted parameter values for a voxel composed of fully viable or fully infarcted tissue may be erroneously classified as gray zone. The gray zone was much smaller (1.40 g) in the high-resolution image with a 5 mm thick slice. A smaller gray zone is expected with a thinner slice thickness because partial volume effects are less pronounced.
Figure 5.2: Gray zone segmentation results from MCDE images of the same anatomical slice (in a 60-year old male patient) acquired at resolutions of (a) 1.8 x 2.7 x 8 mm, (b) 1.4 x 1.8 x 8 mm, and (c) 1.4 x 1.8 x 5 mm. The antero-lateral gray zone (white arrows) can be seen in all three images, while the septal gray zone (black arrows) was not detected at the highest resolution. The gray zone sizes in each slice are (a) 2.02 g, (b) 2.45 g, and (c) 1.40 g.

Any gray zone area that is a single voxel wide should be ignored when examining gray zone maps because it is likely caused by a partial volume effect at a sharp border between fully infarcted and healthy tissue, or by random noise effects. Further image processing of the MCDE maps to eliminate single-voxel gray zones can be applied to help remove this confounding effect. Larger areas of gray zone, on the order of 2 x 2 contiguous voxels or more, are more likely to correspond to a truly heterogeneous mixture of tissue types. With a slice thickness that is typically five times larger than the in-plane spatial resolution, small islands of viable myocardium found entirely within an infarcted voxel may go undetected. An isotropic resolution, with a slice thickness equal to the in-plane resolution, would be ideal for detecting heterogeneous infarct.

5.2.5 Multi-dimensional analysis

Characterization of myocardial tissue in the setting of ischemic heart disease is more complex than viable versus non-viable (or a mixture of both). Reduced blood flow can lead to ischemic yet viable myocytes. This region is referred to as the area-at-risk because the ischemic cells may undergo necrosis and become myocardial infarct. $T_2$-weighted MRI is able to detect this area-at-risk by detecting myocardial edema, which is a consistent feature of acute ischemia [106]. Such $T_2$-weighted imaging has been shown
to differentiate between acute and chronic infarcts [107] and has been used to determine
the fluctuations in hyperemia and cellular edema over time [108]. The $T_2$ signal is also
blood-oxygenation level dependent (BOLD), and has been shown to detect myocardial
ischemia related to severe coronary artery stenosis via signal changes between stress and
rest conditions [109],[110]. The BOLD effect can also be seen using an SSFP sequence
because the SSFP signal is proportional to the ratio of $T_2/T_1$ [111]. The addition of a $T_2$
or BOLD-related value as a third dimension to the MCDE segmentation described in
Chapter 3 might allow differentiation of healthy tissue from viable but ischemic tissue.
This data acquisition would have to be applied prior to the injection of the Gd-DTPA
contrast agent, and therefore accurate motion compensation techniques would be required
to align the images prior to performing any voxel-based analysis. A robust registration
algorithm could also be used to compensate for cardiac motion in the later MCDE images
in order to use more images for the data fitting procedure described in Chapter 3.

MR imaging with tissue tagging is used to examine the mechanical behaviour,
specifically the systolic strain, of the heart. It has been shown that the peak strain in the
infarct border zone is greater in patients inducible for VT versus patients that are not
inducible [114]. Therefore the strain measurements derived from a separate tissue
tagging sequence can be added as another dimension to the MCDE-based analysis. This
may help to more accurately segment regions of heterogeneous infarct to better predict
which patients are inducible. The fuzzy clustering framework currently used to define
the gray zone could easily be adapted to three or more dimensions for improved tissue
characterization. The number of defined clusters could also be increased to differentiate
between viable but ischemic myocardium (with a mechanical abnormality) from viable
and healthy myocardium (with normal wall motion behaviour).
5.3 Future directions: Preclinical studies

A large effort is underway toward a comprehensive evaluation of myocardial tissue in a swine model of myocardial infarct with inducible VT. One of the goals of this work is to further our understanding of the effect of infarct heterogeneity and ischemia on reentry circuits, and to link imaging characteristics to the underlying pathophysiology. A pig model is being used due to previous experience at our institution with this model, and because another institution has developed a swine model of MI that reliably demonstrates VT [60]. To that end, MCDE imaging and gray zone analysis is being performed and compared to histopathology. Preliminary results from the first animal included in this experiment are shown in Figure 5.3. The TTC (triphenyl tetrazolium chloride) stain shows a septal infarct (light pink), and a small tissue sample was extracted for H&E (hematoxylin and eosin) staining. H&E staining differentiates between viable and infarcted tissue, and fingers of viable myocytes extending into the infarct were detected. It is hypothesized that this is the pattern resulting in heterogeneous tissue that causes reentry circuits and VT. To further test this hypothesis, ex vivo high resolution MCDE and diffusion tensor imaging will be applied and compared to voltage-sensitive optical imaging to determine possible sites of reentry.
Another goal of this project is to design a framework for MR-guided RF ablation circuits. Gray zone maps will be derived from high resolution MCDE imaging and used as a reference for determining the site of RF ablation. A catheter can also be used to measure action potential voltages, and therefore it can be confirmed that the MCDE-derived gray zone accurately depicts an area with a reduced action potential, indicative of heterogeneous infarct. The real-time spiral RT-DE sequence, interleaved with a catheter tracking sequence [113], will be used to guide the catheter to the desired gray zone areas for voltage mapping and RF ablation. The success of the RF ablation can then be tested outside of the MRI magnet with an electrophysiology study.

5.4 Future directions: Clinical studies

5.4.1 Clinical validation of the MCDE sequence

The cardiologists who have reviewed the over 100 cases where MCDE images were acquired have noted the improved visualization and detection of myocardial infarct with the multi-contrast approach. Additionally, they have found it helpful to see the systolic wall motion along with the viability images in the same sequence during the same breath-hold. Therefore the clinical utility of this sequence is being further examined in a manuscript being prepared by Dr. Kim Connolly and myself. This manuscript is included as Appendix B.

The study described in the manuscript examines the accuracy of the MCDE sequence for estimating infarct size, the ejection fraction (EF), LV end-diastolic volume (EDV), and LV mass in a larger number of patients, using conventional IR-GRE and cine SSFP imaging as the gold standard. MCDE shows excellent agreement with the standard imaging sequences based on the results of this study. The inter-observer and intra-observer variability for the measurement of EF, EDV, and LV mass with MCDE was also tested and compares well to cine SSFP imaging. These results illustrate that the MCDE sequence can be used as a replacement for IR-GRE viability and cine SSFP wall motion imaging without any loss of information.
Figure 5.4: A series of spiral inversion-recovery SSFP images in a healthy volunteer (without Gd-DTPA). The temporal resolution of eight frames per second increases the number of images acquired during the $T_1$ recovery, and allows for improved wall motion visualization. The acquisition parameters for the images shown above are: TR/TE = 5.5 ms / 1 ms, field of view = 32 cm, 25 spiral interleaves, spatial resolution = 2.3 x 2.3 x 8 mm, bandwidth = 125 kHz and flip angle = 45\(^0\).

5.4.2 Real-time viability and wall motion imaging

A protocol is being developed to examine the spiral RT-DE sequence (see Sec 5.2.1) in patients with ischemic heart disease. Images from preliminary experiments using the spiral RT-DE imaging sequence in a healthy volunteer are shown in Figure 5.4. With the improved temporal resolution (approximately 8 independent frames per second), several images at the early times after the inversion pulse can be seen in Figure 5.4. In patients, this sequence will produce two to three images with varying infarct contrast, similar to the segmented MCDE sequence. The temporal resolution should allow for wall motion visualization and can potentially be used to estimate the ejection fraction. Because spiral acquisitions sample the centre of k-space during each readout, a sliding window reconstruction (temporal view sharing of data) facilitates a smooth interpolation of wall motion images. This sequence may allow for a comprehensive evaluation of viability and cardiac function during free-breathing and without cardiac gating. The spiral RT-DE sequence will be evaluated in any patients who have difficulty with breath holds, but the particular focus will be on patients with cardiac arrhythmias in whom conventional ECG gating (and therefore IR-GRE imaging) is not feasible.
5.4.3 Serial quantification of infarct heterogeneity

A study is underway to test the true reproducibility of the gray zone using both the IR-GRE and MCDE-based analyses. Patients with chronic infarcts are undergoing DE-MRI scans one week apart, with no changes in treatment in between successive scans. The infarct and gray zone should theoretically be identical in the two separate scans; therefore, the gray zones derived from the two IR-GRE analyses will be compared to determine the uncertainty in the gray zone size. The variability in the MCDE gray zone will be tested in the same manner. The first patient to be included in this study had gray zone sizes of 16.7 g and 15.2 g measured using the IR-GRE images from the two separate scans, a difference of 10%. The MCDE analysis yielded gray zone sizes of 16.9 and 17.1 g, a difference of only 1%. This reinforces the variability numbers derived in Chapter 3, although a larger sample size is required to state with certainty that the MCDE analysis is more reproducible than the IR-GRE analysis.

The reproducibility for measuring the gray zone size will determine how sensitive these methods are for detecting true changes in the gray zone. ICDs are not implanted until at least one month after an ischemic episode, because the infarct morphology changes dramatically in the first 4 – 6 weeks [3]. The evolution of the gray zone during the first month may be another method for predicting inducibility for VT. Therefore, a protocol is being developed to perform DE-MRI imaging in patients in the first week after a myocardial infarct, and 4 – 6 weeks later. The total gray zone size at both time points and the evolution of the gray zone will be correlated to outcomes and inducibility for VT.

5.4.4 Infarct characterization and ventricular arrhythmias

Another study has been initiated to test the correlation between the gray zone size and appearance (from both IR-GRE and MCDE images) and inducibility for VT. In patients post-MI, DE-MRI imaging is performed just prior to ICD implantation. Eight patients have been recruited so far to this study. It is too early to draw any conclusions because the patients are being followed for one year after ICD implantation to record the number of arrhythmic episodes they experience. The number of arrhythmic episodes will be
compared to gray zone size, infarct size and transmurality, and other measures such as the ejection fraction. It is hypothesized that the MCDE gray zone measurements will have a better correlation to arrhythmic events than the IR-GRE gray zone.

5.4.5 Further studies

The MCDE sequence is being used by Dr. Yuesong Yang at Sunnybrook Health Sciences Centre to test whether the multi-contrast images are more sensitive for detecting MI of the right ventricle (RV) [117] and of the papillary muscles (PM) [118]. The RV is thinner than the left ventricle, and the blood pool and pericardial fat often obscures the presence of RV infarct. MCDE and IR-GRE imaging were applied to seven pigs with induced MI (Figure 5.5). TTC staining confirmed the histological presence of a small region of RV infarction in all seven animals. Using IR-GRE images, the RV infarct was detected in only one of the seven pigs, while the RV MI was apparent in six of the seven pigs using MCDE imaging.

Papillary muscle infarction (PM-MI) can cause mitral regurgitation [115] and is another potential source of ventricular arrhythmias [116]. Twelve patients were examined with IR-GRE and MCDE imaging within one week of reperfusion for an acute MI. PM-MI was detected in only one of the twelve patients examined using IR-GRE imaging, but could be seen on four of the twelve patients on the MCDE images. Because the papillary muscles lie within the blood pool, they can appear to be part of the blood pool if they are infarcted and have the same signal intensity as blood on IR-GRE images (Figure 5.6). The multi-contrast MCDE images allow the papillary muscles to be easily visualized within the blood pool, making MCDE more sensitive for detecting PM-MI.
Figure 5.5: (a) IR-GRE short axis image and (b) MCDE short axis image in a pig model of infarct. The extension of the infarct in the RV wall was not detected using the IR-GRE image but was apparent on the MCDE image (white arrows). The presence of the RV MI was confirmed with TTC stained histopathology, shown in (c).

*Figure courtesy of Dr. Yuesong Yang.*

Figure 5.6: (a-d) MCDE short axis images in a 50-year old female patient showing a small subendocardial infero-septal infarct in (a) (red arrow); papillary muscle infarct can be seen in (b-c) (red arrows), but not in (d) because the blood pool signal is bright. (e) The IR-GRE image at the same location did not show the papillary muscle infarct because of the bright blood pool. Also note that the infero-septal MI is difficult to visualize on the IR-GRE image.
5.5 Final words

In this chapter, various pulse sequence optimizations have been described to improve the temporal and spatial resolutions of viability and wall motion imaging. A comprehensive evaluation of the various options presented (2D versus 3D, spiral and/or parallel imaging) is required to determine the optimal pulse sequence for characterizing ischemic and infarcted tissue. A large animal model (swine or canine) with a very small induced MI would be ideal to test the sensitivity of the proposed sequences for detecting infarct; however, such a model has not been realized to date. The pig model with MI that is inducible for ventricular tachycardia (Sec 5.3) will be useful for determining the optimal imaging sequence and parameters for defining the gray zone because the gold standard of action potential voltages or histopathology can be used for comparison. At the same time, these sequences will continue to be tested in patients with known or suspected cardiac arrhythmias. Long term follow up of these patients will help identify which imaging protocols are the most sensitive for predicting the onset of ventricular arrhythmias.

The methods developed and described in this thesis further the goal of merging anatomical and functional information for a more comprehensive characterization of cardiac tissue. The multi-dimensional analysis of each voxel of myocardial tissue can be theoretically extended to any number of dimensions to incorporate new information. For example, molecular imaging using carbon-13 is being developed to perform metabolic imaging of lactate in the heart [119]. The metabolic activity of each myocardial voxel could be used as another dimension to further characterize the functional ability of various regions of myocardium. Improved functional information can be used not only to determine the best course for treatment, but in the case ventricular tachycardia, to guide ablation therapy which may directly improve treatment results. Finally, tissue characterization with MRI could be used to evaluate novel treatments (such as stem cell therapy) for ischemia, infarct, heart failure, and arrhythmias.
Bibliography


[54] Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council


Bibliography


[102] Peters DC, Wylie JV, Hauser TH, Kissinger KV, Botnar RM, Essebag V, Josephson ME, Manning WJ. Detection of pulmonary vein and left atrial scar after


Appendix A – Patent application

PATENT APPLICATION FOR

MULTI-CONTRAST DELAYED ENHANCEMENT CARDIAC MAGNETIC RESONANCE IMAGING

By

Jay S. Detsky

Graham A. Wright
BACKGROUND OF THE INVENTION

[0001] The field of the invention is magnetic resonance imaging ("MRI") methods and systems. More particularly, the invention relates to delayed enhancement cardiac MRI.

[0002] When a substance such as human tissue is subjected to a uniform magnetic field (polarizing field $B_0$), the individual magnetic moments of the excited nuclei in the tissue attempt to align with this polarizing field, but precess about it in random order at their characteristic Larmor frequency. If the substance, or tissue, is subjected to a magnetic field (excitation field $B_1$) that is in the x-y plane and that is near the Larmor frequency, the net aligned moment, $M_z$, may be rotated, or "tipped", into the x-y plane to produce a net transverse magnetic moment $M_t$. A signal is emitted by the excited nuclei or "spins", after the excitation signal $B_1$ is terminated, and this signal may be received and processed to form an image.

[0003] When utilizing these "MR" signals to produce images, magnetic field gradients ($G_x$, $G_y$ and $G_z$) are employed. Typically, the region to be imaged is scanned by a sequence of measurement cycles in which these gradients vary according to the particular localization method being used. The resulting set of received MR signals are digitized and processed to reconstruct the image using one of many well known reconstruction techniques.

[0004] The measurement cycle used to acquire each MR signal is performed under the direction of a pulse sequence produced by a pulse sequencer. Clinically available MRI systems store a library of such pulse sequences that can be prescribed to meet the needs of many different clinical applications. Research MRI systems include a library of clinically proven pulse sequences and they also enable the development of new pulse sequences.

[0005] The MR signals acquired with an MRI system are signal samples of the subject of the examination in Fourier space, or what is often referred to in the art as "k-space". Each MR measurement cycle, or pulse sequence, typically samples a portion of k-space along a sampling trajectory characteristic of that pulse sequence. Most pulse sequences sample k-space in a raster scan-like pattern sometimes referred to as a "spin-warp", a "Fourier", a "rectilinear" or a "Cartesian" scan. The spin-warp scan technique is discussed in an article entitled "Spin-Warp MR Imaging and Applications to Human Whole-Body Imaging" by W.A. Edelstein et al., Physics in Medicine and Biology, Vol. 25, pp. 751-756 (1980). It employs a variable amplitude phase encoding magnetic field gradient pulse prior to the acquisition of MR spin-echo signals to phase encode spatial information in the direction of this gradient. In a two-dimensional implementation (2DFT), for example, spatial information is encoded in one direction by applying a phase encoding gradient (Gy) along that direction, and then a spin-echo signal is acquired in the presence of a readout magnetic field gradient (Gx) in a direction orthogonal to the phase encoding direction. The readout gradient present during the spin-echo acquisition encodes spatial information in the orthogonal direction. In a typical 2DFT pulse sequence, the magnitude of the phase encoding gradient pulse Gy is incremented ($\Delta G_y$) in the sequence of measurement cycles, or "views" that are acquired during the scan to produce a set of k-space MR data from which an entire image can be reconstructed.

[0006] There are many other k-space sampling patterns used by MRI systems. These include "radial", or "projection reconstruction" scans in which k-space is sampled as a set of radial sampling trajectories extending from the center of k-space as described, for example, in US Patent No. 6,954,067. The pulse sequences for a radial scan are characterized by the lack of a phase encoding gradient and the presence of a readout gradient that changes direction from one pulse sequence view to the next. There are also many k-space sampling methods that are closely related to the radial scan and that sample along a curved k-space sampling trajectory rather than the straight line radial trajectory. Such pulse sequences are described, for example, in "Fast Three Dimensional Sodium Imaging", MRM, 37:706-715, 1997 by F. E. Boada, et al. and in "Rapid 3D PC-MRA Using Spiral Projection Imaging", Proc. Intl. Soc. Magn. Reson. Med. 13 (2005) by K. V. Koladia et al and "Spiral Projection Imaging: a new fast 3D trajectory", Proc. Intl. Soc. Magn. Reson. Med. 13 (2005) by J. G. Pipe and Koladia.

[0007] An image is reconstructed from the acquired k-space data by transforming the k-space data set to an image space data set. There are many different methods for performing this task and the method used is often determined by the technique used to acquire the k-space data. With a Cartesian grid of k-space data that results from a 2D or 3D spin-warp acquisition, for example, the most common reconstruction method used is an inverse Fourier transformation ("2DFT" or "3DFT") along each of the 2
or 3 axes of the data set. With a radial k-space data set and its variations, the most common reconstruction method includes "regridding" the k-space samples to create a Cartesian grid of k-space samples and then perform a 2DFT or 3DFT on the regridded k-space data set. In the alternative, a radial k-space data set can also be transformed to Radon space by performing a 1DFT of each radial projection view and then transforming the Radon space data set to image space by performing a filtered backprojection.

Because it requires time to acquire a complete k-space MR data set, subject motion presents a problem in many clinical applications. Motion due to respiration and cardiac motion can produce image artifacts such as blurring or ghosting. There are many strategies used to suppress such artifacts. These include cardiac or respiratory gating techniques that acquire MR data only during certain phases of the cardiac or respiratory cycle. In gated cardiac MRI, for example, one or more k-space views of the heart ("segment") are acquired a preset time interval after the ECG triggered gating signal is produced. View segments for the image are acquired over a plurality of heart beats at the same preset time interval until sufficient data is acquired to reconstruct an image depicting the heart at that particular cardiac phase. By acquiring 8 to 16 views in each segment, a complete image can be acquired in one breath hold, thus eliminating respiratory motion issues. Typically, during a segmented cardiac MRI scan, segments of data will be acquired at a succession of cardiac phases during each cardiac cycle, or R-R interval, so that a plurality of images may be reconstructed at the conclusion of the scan which depict the heart at a corresponding succession of cardiac phases.

Delayed enhancement (DE) magnetic resonance imaging (MRI) is a cardiac MRI method for myocardial viability imaging. This method distinguishes healthy and infarcted myocardium. The identification of viable myocardium is useful for predicting which patients will have improved left ventricular (LV) ejection fractions and improved survival after revascularization. The transmural extent of infarcted tissue as determined by DE MRI has been shown to predict functional recovery post-revascularization procedures such as coronary bypass surgery.

DE MRI involves the injection of a bolus of a Gadolinium-based contrast agent called Gd-DTPA. Starting approximately ten minutes after the injection, Gd-DTPA preferentially pools in the areas of infarct due to differences in the wash-in times and distribution volumes between viable and non-viable tissue. The presence of a larger concentration of Gd-DTPA causes T1 shortening in infarcted tissue. The standard MRI pulse sequence for visualizing these infarcts is an inversion recovery gradient echo (IR-GRE) pulse sequence which takes advantage of the short T1 time of infarcted tissue to create images where viable tissue is nulled (dark) while infarcted tissue appears bright. A limitation of IR-GRE imaging for DE MRI is that blood in the left ventricle also appears bright. This makes it difficult to determine the border between blood and infarcted tissue and it can also result in the failure to detect small subendocardial infarcts that appear to be LV blood.

Cine imaging of the beating heart with MRI is performed during cardiac studies to visualize the wall thickness and systolic wall thickening throughout the cardiac cycle. With cine imaging complete k-space image data sets are acquired at a succession of cardiac phases so that the myocardium can be imaged throughout a complete cardiac cycle. Cine imaging is typically acquired with very short TR steady-state free precession (SSFP) imaging pulse sequences. These cine images are used to detect dysfunctional myocardium that may appear viable on DE MRI images. Cine imaging is also used to determine the LV ejection fraction to determine the overall pumping capacity of the heart.

DE MRI and cine images are acquired in a short axis view of the heart, and 10-15 slices are acquired during each scan to cover the entire left ventricle. Imaging a single anatomical slice for DE MRI or cine imaging requires a 10-20 second breath-hold. Currently, DE MRI and cine imaging are acquired separately, thus resulting in 20-30 of these breath holds. This can be quite difficult for some patients, and results in long scan times.

A real-time method for DE MRI imaging is disclosed by Guttman MA, Dick AJ, Raman VK, et al. "Imaging of myocardial infarction for diagnosis and intervention using real-time interactive MRI without ECG-gating or breath-holding", Magn Reson Med 2004; 42:354-61, to alleviate the requirements of breath-holding and cardiac gating. However, this real-time method has a lower spatial resolution than conventional DE MRI, and the temporal resolution of 2-6 frames per second is not adequate for analyzing wall motion, thus still necessitating a separate cardiac cine scan. A cardiac-gated cine delayed enhancement pulse sequence for acquiring viability and wall motion images simultaneously is disclosed in published U.S. Patent Application No. 20050245812 filed on November 3, 2005 and entitled "Acquiring Contrast-Enhanced, T1-Weighted, Cine Magnetic Resonance Images". This method uses a
single-shot acquisition over approximately 300 ms instead of a segmented acquisition, and thus blurring is introduced into the images, particularly during systole. This method also maintains the same tissue contrast throughout the cine images.

SUMMARY OF THE INVENTION

[0014] The present invention is a method for acquiring MR imaging data from a beating heart which enables the segmentation of healthy myocardium, infarcted myocardium and blood in reconstructed images and enables the visualization of wall motion and wall thickening over the cardiac cycle which enables calculation of ejection fractions. The entire scan is performed in a single breath hold.

[0015] The method includes performing a DE MRI scan in which a pulse sequence is used with an MRI system in which an inversion pulse is produced following a cardiac gating signal and a succession of steady-state free precession (SSFP) pulse sequence segments are produced throughout the remainder of each cardiac cycle. Image frames are reconstructed from the k-space data acquired during each segment, and the resulting successive image frames have different tissue contrast. Infarcted myocardium tissue is visualized in early segments in which blood and/or healthy myocardium tissue is suppressed and all the reconstructed image frames enable visualization of cardiac wall motion.

[0016] A general object of the invention is to acquire both myocardium viability images and wall motion information with a single pulse sequence. Twenty image frames may be produced from a single scan and the required tissue contrast information and wall motion information may be extracted from these. In addition, the succession of image frames enable the $T_1$ recovery curve to be calculated at each pixel location. This information may be employed to produce a $T_1$ map that in turn may be used to more accurately segment tissue types in the image frames.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Fig. 1 is a block diagram of an MRI system that employs the present invention;
[0018] Fig. 2 is a graphic representation of a preferred embodiment of a pulse sequence used to acquire MR data with the MRI system of Fig. 1;
[0019] Fig. 3 is a graphic representation of a $T_1$ recovery of myocardium and blood after an RF inversion pulse;
[0020] Figs. 4A and 4B are magnetization recovery curves during a single-shot IR-SSFP acquisition pulse sequence using an RF excitation pulse flip angle of $\alpha = 30$ degrees and $\alpha = 60$ degrees respectively;
[0021] Figs. 5A and 5B are magnetization recovery curves after the first two RF inversion pulses during a segmented IR-SSFP acquisition using the pulse sequence of Fig. 2 using an RF excitation pulse flip angle of $\alpha = 30$ degrees and $\alpha = 60$ degrees respectively; and
[0022] Figs. 6A and 6B are graphic representations of the differences in signal intensity between infarcted myocardium and normal myocardium and the differences between infarcted myocardium and blood respectively.

GENERAL DESCRIPTION OF THE INVENTION

[0023] An important aspect of the present invention is the discovery that SSFP pulse sequences may be employed in an inversion recovery acquisition to acquire a succession of image frames that depict different tissue contrasts. We have discovered that the effects of an SSFP readout on magnetization behavior after an IR pulse in the setting of DE MRI can predictably produce the desired tissue contrasts. In particular, the effects of varying the SSFP flip angle are examined. We present a segmented, cardiac-gated IR-SSFP sequence with optimized parameters for infarct visualization based on computer simulations. The goal of this sequence is to also provide cine images of the heart with varying contrast in order to simultaneously visualize myocardial wall motion and detect infarcted tissue.

[0024] The SSFP pulse sequence uses a train of $\pm \alpha$ pulses with fully balanced gradient moments. With conventional SSFP imaging, $\alpha$ pulses are applied without any magnetization preparation, and after a number of pulses a steady-state signal is achieved that is $T_2/T_1$-weighted. For IR-SSFP, an SSFP readout is used during IR, and thus the magnetization is sampled during the transition from $T_1$ recovery to its true steady-state magnetization value. The evolution of the magnetization during an SSFP readout can be calculated using the recursive equation:
\[ M_n = R_x(\pm \alpha) [E_2(\text{T}_1, \text{T}_2)M_{n-1} + E_1(\text{T}_1, \text{T}_1)] \]

where \( M_n \) is the magnetization vector \([M_x, M_y, M_z]^T\) directly after the nth pulse and \( R_x(\pm \alpha) \) is a rotation matrix about the x-axis in the rotating frame corresponding to an RF excitation with flip angle \( \alpha \). \( E_1 \) and \( E_2 \) are matrix representations of \( \text{T}_1 \) relaxation and \( \text{T}_2 \) decay, respectively:

\[
E_1(\text{T}_1, \text{T}_1) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & e^{-\frac{\text{T}_2}{\text{T}_1}} & 0 \\ 0 & 0 & e^{-\frac{\text{T}_2}{\text{T}_1}} \end{bmatrix} \\
E_2(\text{T}_1, \text{T}_2) = \begin{bmatrix} 0 & 0 & 0 \\ 0 & e^{-\frac{\text{T}_2}{\text{T}_1}} & 0 \\ 0 & 0 & e^{-\frac{\text{T}_2}{\text{T}_2}} \end{bmatrix}
\]

[0025] Note that this formulation neglects off-resonance effects. An inversion pulse can be added between any two pulses via

\[ M_{\text{inv}} = R_x(\pi) M_n \]

where \( M_{\text{inv}} \) is the magnetization vector directly after the inversion pulse, and \( R_x(\pi) \) is the rotation matrix about the x-axis for a 180 degree inversion pulse.

[0026] Simulations were used to model the signal behavior of blood, healthy myocardium, and infarcted myocardium undergoing IR-SSFP for DE imaging. Immediately after the inversion pulse, six linearly ramped dummy pulses from \( 0.7 \) to \( \alpha \) were applied to minimize signal oscillations, followed by \( \pm \alpha \) SSFP readout pulses. The simulations used a TR of 3.4 ms. The inversion pulse is assumed to be non-slice-selective, meaning that blood entering the imaging slice after the inversion pulse will still follow an IR behavior. An ejection fraction (EF) of 60% is assumed in the simulations, meaning that after systole 60% of the blood pool is replaced by blood that has not been exposed to any prior SSFP pulses. The \( T_1 \) and \( T_2 \) values of the different tissues used in the simulations were obtained from previously published reports for a 1.5T magnet, assuming a 10-min delay between Gd-DTPA injection and imaging. The parameters used were \( T_{1,\text{myo}} = 380 \text{ ms}, T_{2,\text{myo}} = 45 \text{ ms}, T_{1,\text{inf}} = 280 \text{ ms}, T_{2,\text{inf}} = 40 \text{ ms}, T_{1,\text{blood}} = 260 \text{ ms}, \) and \( T_{2,\text{blood}} = 180 \text{ ms} \).

[0027] Fig. 3 shows a comparison between the natural \( T_1 \) recovery of blood and myocardium and the actual recovery when undergoing IR-SSFP imaging with \( \alpha = 60 \text{ degrees} \). The signal behavior with an SSFP readout follows an exponential recovery with a time constant \( T^* \) that is shorter than the true \( T_1 \). The \( T^* \) shortening effect is more pronounced for myocardium and infarct (\( T_2/T_1 \approx 0.1 \) for blood (\( T_2/T_1 \approx 0.7 \)), and varies with the SSFP flip angle. The \( T^* \) effect alters the dynamics between the three tissues of interest during IR-SSFP imaging compared to IR-GRE imaging.

[0028] One method which may be used is a single-shot IR-SSFP sequence in which all phase-encoding lines for a single image are acquired within one heartbeat. The effects of changing the SSFP flip angle in the context of a single-shot IR-SSFP sequence are shown in Fig. 4. With a 30 degree flip angle, the simulations show that at TI = 240 ms, normal myocardium will have no signal, while infarcted tissue and blood will have the same level of signal \( M_{z,\text{inf}} = M_{z,\text{blood}} = 0.17 \). This agrees with what has been seen experimentally. However, for a \( \alpha = 60 \text{ degrees} \), the myocardium is nulled earlier (at TI = 200 ms), at which point the infarct has a small positive signal \( M_{z,\text{inf}} = 0.095 \) but blood has no signal \( M_{z,\text{blood}} = 0 \). This means that with \( \alpha = 60 \text{ degrees} \), a black-blood appearance is achieved, but the contrast between healthy myocardium and infarct is reduced by 44%. Thus, in the setting of DE-MRI, an SSFP readout affects the optimal TI and image characteristics.

[0029] A difficulty with the single-shot technique is that blurring is introduced due to cardiac motion over the 250-400 ms required for a single acquisition. Simulations were therefore also performed to examine the signal behavior of IR-SSFP during a segmented DE-MRI sequence. A segmented approach acquires data during a small time window during each cardiac cycle; therefore, multiple inversion pulses (one per heartbeat, followed by an SSFP readout) are used to form a single image. After the first inversion pulse, the signal behavior would follow that of the single-shot IR-SSFP sequence (Fig. 4). The SSFP pulses, if played out continuously, would limit the regrowth of \( M_z \) based on the SSFP flip angle and the
The simulations show that for any α, the $M_z$ recovery curves are consistent after the second and all subsequent inversion pulses. This holds true only if SSFP pulses are played out continuously between successive inversion pulses. It was observed that the IR behavior and dynamics did not change significantly with changes in the value of 60% used for the EF.

[0031] It is apparent from the simulations that the appearance of DE-MRI images will be affected by the readout scheme (GRE, single-shot SSFP, or segmented SSFP) and the read-out flip angle. Further simulations were performed to determine the optimum flip angle for a segmented IR-SSFP sequence for visualizing infarcted tissue. The optimization examined the effect of various SSFP flip angles on the single intensity differences between infarct and myocardium ($\Delta S_{\text{inf-myo}}$) and between infarct and blood ($\Delta S_{\text{inf-blood}}$) at the time point where the signal from healthy myocardium is zero. The results were compared with simulated signal intensity differences for GRE and single-shot SSFP readouts (Fig. 6). The results indicate that for a segmented IR-SSFP scheme, $\alpha = 30$ degrees yields a maximum for both ($\Delta S_{\text{inf-myo}}$) and ($\Delta S_{\text{inf-blood}}$). These results are relatively insensitive to the TR of the SSFP pulses, with a range of TRs from 2.5 ms to 3.5 ms changing the optimum flip angle by only 2 degrees.

[0032] A 30 degree flip angle also produces recovery curves where blood and myocardium are nulled at the same time point (Fig. 5.), meaning that blood would have no signal in the corresponding DE-MRI image. For $\alpha = 38$ degrees and higher, and for a GRE and single-shot SSFP readout, $\Delta S_{\text{inf-blood}}$ is negative, meaning that blood would appear brighter than infarct. This yields DE-MRI images that can be difficult to interpret because the boundary between infarct and blood is difficult to visualize. The cost of using a segmented IR-SSFP approach is that $\Delta S_{\text{inf-myo}}$ is reduced by 56% compared to a GRE readout, and 36% compared to a single-shot SSFP readout. However, a segmented approach will have less blurring due to cardiac motion and the SNR can be boosted by averaging over multiple excitations. Furthermore, with a segmented approach, multiple images can be acquired over the cardiac cycle, as is done with cine SSFP cardiac imaging. One of the IR-SSFP images will be the equivalent of a conventional DE image (with nulled myocardium and bright infarct), while the other images can be used as a cine loop to visualize the motion of the heart. The IR-SSFP images have varying contrast because each image is acquired at a different effective TI. It is expected that visually tracking the $T_1$ recovery of myocardium and infarct over all the IR-SSFP images will help compensate for the lower myocardium-to-infarct contrast in the myocardium-nulled IR-SSFP image.

DESCRIPTION OF THE PREFERRED EMBODIMENT

[0033] Referring particularly to Fig. 1, the preferred embodiment of the invention is employed in an MRI system. The MRI system includes a workstation 10 having a display 12 and a keyboard 14. The workstation 10 includes a processor 16 that is a commercially available programmable machine running a commercially available operating system. The workstation 10 provides the operator interface that enables scan prescriptions to be entered into the MRI system. The workstation 10 is coupled to four servers: a pulse sequence server 18; a data acquisition server 20; a data processing server 22, and a data store server 23. The workstation 10 and each server 18, 20, 22 and 23 are connected to communicate with each other.

[0034] The pulse sequence server 18 functions in response to instructions downloaded from the workstation 10 to operate a gradient system 24 and an RF system 26. Gradient waveforms necessary to perform the prescribed scan are produced and applied to the gradient system 24 that excites gradient coils in an assembly 28 to produce the magnetic field gradients $G_x$, $G_y$ and $G_z$ used for position encoding MR signals. The gradient coil assembly 28 forms part of a magnet assembly 30 that includes a polarizing magnet 32 and a whole-body RF coil 34.

[0035] RF excitation waveforms are applied to the RF coil 34 by the RF system 26 to perform the prescribed magnetic resonance pulse sequence. Responsive MR signals detected by the RF coil 34 or a
separate local coil (not shown in Fig. 1) are received by the RF system 26, amplified, demodulated, filtered and digitized under direction of commands produced by the pulse sequence server 18. The RF system 26 includes an RF transmitter for producing a wide variety of RF pulses used in MR pulse sequences. The RF transmitter is responsive to the scan prescription and direction from the pulse sequence server 18 to produce RF pulses of the desired frequency, phase and pulse amplitude waveform. The generated RF pulses may be applied to the whole body RF coil 34 or to one or more local coils or coil arrays (not shown in Fig. 1).

The RF system 26 also includes one or more RF receiver channels. Each RF receiver channel includes an RF amplifier that amplifies the MR signal received by the coil to which it is connected and a detector that detects and digitizes the I and Q quadrature components of the received MR signal. The magnitude of the received MR signal may thus be determined at any sampled point by the square root of the sum of the squares of the I and Q components:

\[ M = \sqrt{I^2 + Q^2} , \]

and the phase of the received MR signal may also be determined:

\[ \phi = \tan^{-1} \frac{Q}{I} . \]

The pulse sequence server 18 also optionally receives patient data from a physiological acquisition controller 36. The controller 36 receives signals from a number of different sensors connected to the patient, such as ECG signals from electrodes or respiratory signals from a bellows. Such signals are typically used by the pulse sequence server 18 to synchronize, or “gate”, the performance of the scan with the subject’s respiration or heart beat.

The pulse sequence server 18 also connects to a scan room interface circuit 38 that receives signals from various sensors associated with the condition of the patient and the magnet system. It is also through the scan room interface circuit 38 that a patient positioning system 40 receives commands to move the patient to desired positions during the scan.

The digitized MR signal samples produced by the RF system 26 are received by the data acquisition server 20. The data acquisition server 20 operates in response to instructions downloaded from the workstation 10 to receive the real-time MR data and provide buffer storage such that no data is lost by data overrun. In some scans the data acquisition server 20 does little more than pass the acquired MR data to the data processor server 22. However, in scans that require information derived from acquired MR data to control the further performance of the scan, the data acquisition server 20 is programmed to produce such information and convey it to the pulse sequence server 18. For example, during prescans MR data is acquired and used to calibrate the pulse sequence performed by the pulse sequence server 18. Also, navigator signals may be acquired during a scan and used to adjust RF or gradient system operating parameters or to control the view order in which k-space is sampled. And, the data acquisition server 20 may be employed to process MR signals used to detect the arrival of contrast agent in an MRA scan. In all these examples the data acquisition server 20 acquires MR data and processes it in real-time to produce information that is used to control the scan.

The data processing server 22 receives MR data from the data acquisition server 20 and processes it in accordance with instructions downloaded from the workstation 10. Such processing may include, for example: Fourier transformation of raw k-space MR data to produce two or three-dimensional images; the application of filters to a reconstructed image; the performance of a backprojection image reconstruction of acquired MR data; the calculation of functional MR images; the calculation of motion or flow images, etc.

Images reconstructed by the data processing server 22 are conveyed back to the workstation 10 where they are stored. Real-time images are stored in a data base memory cache (not shown) from which they may be output to operator display 12 or a display that is located near the magnet assembly 30 for use by attending physicians. Batch mode images or selected real time images are stored in a host database on disc storage 44. When such images have been reconstructed and transferred to storage, the data processing server 22 notifies the data store server 23 on the workstation 10. The workstation 10 may be used by an operator to archive the images, produce films, or send the images via a network to other facilities.
Referring particularly to Fig. 2, the present invention is a method for acquiring MR image data from a subject placed in the MRI system of Fig. 1 using a cardiac gated, inversion recovery segmented acquisition technique. A gating signal 150 is produced by the R wave of the ECG waveform to signal the start of each cardiac cycle. During the R-R interval between gating signals 150 a non-selective 180 degree RF inversion pulse 152 is produced to invert longitudinal spin magnetization throughout the heart. The R-R interval after the inversion pulse 152 is divided into a series of segments 154 that divide the cardiac cycle into a corresponding number of cardiac phases. During each segment 154 a plurality of SSFP MR pulses are performed to acquire a corresponding plurality of k-space views of the heart at the segment's cardiac phase.

A number of different SSFP pulse sequences can be used to direct the MRI system to acquire the data needed to practice the present invention. In the preferred embodiment a balanced SSFP pulse sequence is employed, such as the one shown in Fig. 2. It includes a selective RF excitation pulse 200 that is repeated at the start of each TR period as well as a slice select gradient pulse 202 that is produced concurrently with the RF pulse 200 to produce transverse magnetization in a prescribed slice. After excitation of the spins in the slice a phase encoding gradient pulse 204 is applied to position encode the MR signal 206 along one direction in the slice. A readout gradient pulse 208 is also applied after a dephasing gradient lobe 210 to position encode the MR signal 206 along a second, orthogonal direction in the slice. The MR signal 206 is sampled during a data acquisition window 212. To maintain the steady state condition, the integrals of the three gradients each sum to zero. To accomplish this, rephasing lobes 214 are added to the slice select gradient waveform, a rephasing lobe 216 is added to the readout gradient waveform 208 and a rewinder gradient lobe 218 is added to the phase encoding gradient waveform. As is well known in the art, each SSFP pulse sequence acquires a single k-space view of the subject and the pulse sequence is repeated and the amplitude of the phase encoding gradient 204 and its equal, but opposite rewinder 218 are stepped through a series of values to sample 2D k-space in a prescribed manner.

Referring still to Fig. 2, when the scan is initiated the subject is injected with a contrast agent and a period of 10 to 30 minutes is allowed to pass before MRI data is acquired. During the first cardiac cycle of the scan the inversion pulse 152 is produced at a preselected time after the gating signal 150 and then the RF excitation pulses 200 used in the SSFP pulse sequence are produced to establish a spin magnetization equilibrium. No MRI data is acquired during the first cardiac cycle. During the subsequent R-R intervals, the inversion pulse 152 is produced after the preselected delay and the SSFP pulse sequences are performed in their entirety to acquire MRI data. The inversion pulse 152 is set to a delay (TDEL) such that the image frames that show the best contrast between viable and nonviable myocardium occur in mid-diastole, while ensuring that systolic images are acquired when the image contrast is no longer changing.

The scan continues for a sufficient number of heart beats to acquire a k-space image data set at each cardiac phase segment 154 from which a two-dimensional image frame may be reconstructed. It should be apparent that the number of segments that are acquired and the number of SSFP repetitions performed during each segment 154 is a matter of choice. Longer segments 154 enable more SSFP repetitions during each segment so that total scan time (i.e., number of heart beats) is reduced. However, this reduces the number of image frames that are produced during each cardiac cycle and it increases cardiac motion artifacts. Typically 8 to 16 pulse sequences are performed during each segment 154 and this enables the scan to be completed in one breath hold.

Between 10 and 15 short-axis 2D images are obtained to cover the entire left ventricle of the heart. Scan parameters in one preferred embodiment are:

- bandwidth = ± 125 kHz
- RF pulse flip angle = 30 degrees
- views per segment = 16
- pulse sequence TR = 2.7 ms
- pulse sequence TE = 1.3 ms
- FOV = 320 mm
- slice thickness = 8 mm
- imaging matrix = 192 x 192
- NEX = 1
- TDEL = 500 ms

This embodiment requires 13 heartbeats to complete the scan (one to establish steady state and 12 to acquire MRI data). This requires an average breath-hold by the subject of 11 seconds.
This preferred embodiment yielded twenty image frames that are reconstructed from the k-space data sets acquired during each segment 154. The heart wall motion and thickness can be seen in all of these image frames enabling wall motion abnormalities to be seen and cardiac function values to be computed. Each segment 152 has a temporal window of approximately 50 ms, allowing even small wall motion abnormalities to be detected.

Because the present method acquires image frames in succession after the RF inversion pulse 152, the physician can select the particular images that provide the optimal tissue contrast characteristics during their respective T1 recoveries. This eliminates the requirement of conventional DE-MRI methods in which the optimal TI interval needed to null myocardium signal is done by a lengthy trial-and-error process involving two to four additional scans at different preset TI intervals. The optimum TI varies from patient to patient, and it can also vary over the 5-10 minutes during which a stack of short-axis images is acquired, leading to reduced contrast in some of the conventional DE MRI images.

Using the present method the physician is presented after a single scan with a series of image frames having different tissue contrast characteristics to choose from. It has been found that due to the improved visualization of the infarct-blood boundary, small subendocardial infarcts can be more easily identified and infarct transmurality can be more easily assessed when the present invention is used.

Another advantage of the present invention is that the T1 recovery of different tissue types can be observed in the succession of acquired image frames. From this information it is possible to produce a T*1 map of the imaged tissues. For each image pixel the magnitude of the MR signal is plotted as a function of recovery time of the successive segments 154. A T*1 recovery curve is fitted to these points using a method described by Schmitt, P, Griswold MA, Jakob PM, Kotas M, Gulani V, Flentje M, Haase A., "Inversion recovery TrueFISP: quantification of T1, T2 and spin density". Magn Reson Med 2004; 51: 661-667. The T*1 of the tissue is calculated from this curve. The calculated T*1 of each pixel determines the brightness of the corresponding pixel in the T*1 map.

T*1 maps generated from a set of acquired image frames provide a method for determining infarct heterogeneity by comparing the T*1 values of the peri-infarct region with those of healthy myocardium and the infarct core. Once generated, these T*1 maps may also be helpful in assessing a wide range of cardiomyopathies.

CLAIMS

1. A method for producing a series of cardiac gated magnetic resonance images of a subject's heart, the steps comprising:
   a) administering a contrast agent to the subject;
   b) producing a gating signal that indicates the start of the subject's cardiac cycle;
   c) producing an RF inversion pulse that inverts spin magnetization throughout a field of view a preset time after a gating signal is produced;
   d) acquiring a series of MR data segments after the RF inversion pulse is produced using a plurality of steady-state free precession pulse sequences (SSFP);
   e) repeating steps b) through d) until sufficient k-space data is acquired by the SSFP pulse sequences in each segment from which an image frame can be reconstructed; and
   f) reconstructing a series of image frames depicting the heart at a succession of cardiac phases using the k-space data acquired in each segment.
   
2. The method as recited in claim 1 which includes:
   g) performing a magnetization equalization pulse sequence during a cardiac cycle preceding the first acquisition of MR data segments.

3. The method as recited in claim 1 in which the preset time interval in step c) is determined such that images that depict best contrast between viable and nonviable myocardium are acquired during the mid-diastole of each cardiac cycle.

4. The method as recited in claim 1 which includes:
h) producing a $T^*_1$ map by fitting the magnitude values at corresponding pixels in the series of image frames to a $T^*_1$ curve and setting the magnitude of the corresponding pixel in the $T^*_1$ map to the $T^*_1$ value determined by the $T^*_1$ curve.

5. The method as recited in claim 1 in which the number of SSFP pulse sequences in each segment is selected such that sufficient k-space data is acquired for each segment during a single breath hold of the subject.

6. A method for producing a series of delayed contrast enhanced magnetic resonance images of a subject's heart, the steps comprising:
   a) producing a gating signal that indicates the start of the subject's cardiac cycle;
   b) producing an RF inversion pulse that inverts spin magnetization throughout a field of view a preset time after a gating signal is produced;
   c) acquiring a series of MR data segments after the RF inversion pulse is produced using a plurality of steady-state free precession pulse sequences (SSFP);
   d) repeating steps a) through c) until sufficient k-space data is acquired by the SSFP pulse sequences in each segment from which an image frame can be reconstructed; and
   e) reconstructing a series of image frames depicting the heart at a succession of cardiac phases using the k-space data acquired in each segment.

7. The method as recited in claim 6 which includes:
   f) performing a magnetization equalization pulse sequence during a cardiac cycle preceding the first acquisition of MR data segments.

8. The method as recited in claim 6 in which the preset time interval in step b) is determined such that images that depict best contrast between viable and nonviable myocardium are acquired during the mid-diastole of each cardiac cycle.

9. The method as recited in claim 6 which includes:
   g) producing a $T^*_1$ map by fitting the magnitude values at corresponding pixels in the series of image frames to a $T^*_1$ curve and setting the magnitude of the corresponding pixel in the $T^*_1$ map to the calculated $T^*_1$ value.

10. The method as recited in claim 6 in which the number of SSFP pulse sequences in each segment is selected such that sufficient k-space data is acquired for each segment during a single breath hold of the subject.

MULTI-CONTRAST DELAYED ENHANCEMENT CARDIAC MAGNETIC RESONANCE IMAGING

ABSTRACT OF THE DISCLOSURE

A series of MR image frames are acquired that depict a subject's heart at successive cardiac phases. Delayed enhancement of infarcted myocardium is depicted in some of the image frames by administering a contrast agent prior to data acquisition. Data acquisition is performed in a single breath hold by producing an RF inversion pulse followed by segments of SSFP pulse sequences during a succession of cardiac gated heart beats. The acquired MR image frames depict contrast between blood, viable myocardium and nonviable myocardium, and they depict left ventricle wall thickness and wall thickening throughout the cardiac cycle.

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Appendix B – Clinical validation of MCDE manuscript

Multi-contrast delayed enhancement imaging (MCDE) enables viability and wall motion assessment in a single acquisition with reduced scan times

Connelly KA, MBBS PhD\textsuperscript{1,3,4}; Detsky JS, BASc\textsuperscript{1,5}; Graham JJ, MD\textsuperscript{1}; Paul G, MD MSc\textsuperscript{1,2}; Vijayaragavan R\textsuperscript{1,2} MD; Wright GA PhD\textsuperscript{1,5}; Dick AJ MD \textsuperscript{1,2}

\textsuperscript{1}Department of Imaging Research and \textsuperscript{2}Department of Cardiology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; \textsuperscript{3}Keenan Research Centre in the Li Ka Shing Knowledge Institute, St. Michael’s Hospital and University of Toronto, Toronto, Canada; \textsuperscript{4}St Vincent’s Hospital Department of Medicine, Melbourne, Australia; \textsuperscript{5}Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

Short Title: MCDE imaging in ischemic heart disease

Corresponding author:
Dr Kim Connelly
St. Michael's Hospital
Room 8-005, 30 Bond Street
Toronto, Ontario M5B 1W8
Telephone: 416-864-6060 ext 4081, Fax: 416-867-3681
cnelly@medstv.unimelb.edu.au

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ABSTRACT
Background: Cardiac magnetic resonance (CMR) imaging is an important tool in the assessment of cardiac function and viability, with prognostic implications for patients with ischemic heart disease. Multi-contrast delayed enhancement imaging (MCDE) allows myocardial viability and wall motion to be assessed simultaneously by producing cardiac-phase-resolved images at multiple inversion times. This study compared MCDE imaging to the conventional wall motion and viability CMR pulse sequences.

Methods: Forty-one patients with suspected myocardial infarction were studied. All patients underwent assessment of cardiac function with cine SSFP, followed by delayed enhancement viability imaging using the conventional inversion recovery gradient echo scanning (IR-GRE) sequence and the MCDE sequence. MCDE was compared to cine SSFP in the assessment of ejection fraction (EF), left ventricular LV mass, and LV end-diastolic volume (EDV) and to IR-GRE for measuring infarct size.

Results: MCDE, IR-GRE, and SSFP imaging demonstrated excellent agreement in the assessment of EF (bias= -2% (95% CI: -8% to 4%)), LV infarct size (bias = 0.2 g (-1.5 g to 2.0 g)) and LV mass (bias = 0.2 g (-18 g to 18 g)). Agreement was clinically acceptable for LV EDV (bias = -7 mL (-30 mL to 16 mL)). Inter and intra-observer variability was low between SSFP / IR-GRE and MCDE imaging.

Conclusion: MCDE demonstrated excellent clinical agreement with conventional SSFP and IR-GRE imaging in the assessment of cardiac function and viability. MCDE provides wall motion and viability information during a single breath-hold with inherent spatial registration, as opposed to the cine SSFP and IR-GRE acquisitions which require separate breath-holds. MCDE imaging may be considered an alternative to conventional imaging.

INTRODUCTION
The quantitative assessment of cardiac function and left ventricular (LV) mass has become a requirement for cardiac imaging, as abnormal cardiac function and the presence of myocardial scar have been shown to predict poor outcomes. Cardiovascular magnetic resonance imaging (CMR) is currently the most powerful non-invasive tool for the accurate, reproducible assessment of cardiac function and mass. Furthermore, gadolinium-enhanced CMR imaging, known as delayed enhancement magnetic resonance imaging (DE-MRI) has significant clinical and prognostic implications, enabling the differentiation of viable from non-viable, infarcted tissue. As a result, CMR is widely accepted as the modality of choice to determine function, mass and viability.

Currently, two separate, breath-held imaging sequences are required to assess viability and LV function. Viability imaging is conventionally acquired with an inversion-recovery gradient echo (IR-GRE) sequence while wall motion imaging is performed with a segmented steady-state free-precession (SSFP) sequence. For each sequence, approximately 10-12 separate imaging slices are acquired to cover the entire LV in the short axis plane. This leads to a large number of required breath-holds to complete a CMR examination; while this is feasible in many patients, the development of an imaging sequence that enables both function and viability to be assessed simultaneously offers many advantages. Reduced overall scan time and number of breath-holds leads to improved patient comfort, along with the potential for further cardiac characterization using sequences which previously would not have fit into a typical one-hour scan time. Delayed enhancement images are normally interpreted with cine wall motion images immediately adjacent; the cine images provide anatomical information such as the diastolic wall thickness to help the reader evaluate the infarct transmurality. When cine and DE-MRI images are acquired in separate breath-holds, images at the equivalent slice prescription may be at different anatomical positions due to inconsistencies in the position of the breath-hold; this has been shown to complicate the interpretation of viability images. A technique that obtains viability and wall motion images in the same breath-hold avoids the issue of slice mis-registration. The IR-GRE sequence also yields images where the blood pool has a similar signal intensity to enhanced infarct, which can complicate the detection of small subendocardial infarction.

Our group has developed a novel cardiac-gated, segmented inversion recovery SSFP sequence, entitled multi-contrast delayed enhancement imaging (MCDE). The MCDE sequence allows myocardial viability and wall motion to be assessed simultaneously by producing images at multiple inversion times (TI), resolved throughout all phases of the heart cycle, with improved visualization of the infarct-blood border. The purpose of this study was to evaluate the accuracy and reproducibility of MCDE imaging compared to
conventional cine SSFP and IR-GRE imaging in the assessment of cardiac volumes, ejection fraction, mass and infarct size.

**MATERIAL AND METHODS**

**Study population**
Forty-one patients (65 years [IQR 59-72], 31 males) were enrolled in the study. All patients had suspected myocardial infarction (MI) and were referred for CMR viability scans. Subjects with typical contraindications to MRI, such as pacemakers and advanced renal dysfunction were excluded. The protocol was approved by our Research Ethics Board and informed consent was obtained prior to scanning.

**Imaging Protocol**
CMR imaging was performed on a 1.5 T scanner (CV/i; GE Healthcare, Milwaukee, WI) with an eight-channel cardiac array for signal reception. After localization, short axis SSFP cine images were acquired to cover the entire LV (between nine and 12 slices per patient). The parameters for cine SSFP imaging were: bandwidth = ±125 kHz, flip angle = 45°, views per segment (VPS) = 16, TR/TE = 3.7 / 1.6 ms, field of view (FOV) = 320 mm, acquisition matrix = 256 x 192, and slice thickness = 8 mm. The cine SSFP sequence produced 20 phase-resolved images over the heart cycle.

Delayed enhancement imaging was initiated 10 minutes after the injection of 0.2 mmol/kg of Gd-DTPA (Magnevist; Berlex Inc., Wayne, NJ). IR-GRE and MCDE images were acquired in the same imaging planes as the cine SSFP images. The order in which IR-GRE and MCDE imaging were acquired was randomized. The IR-GRE sequence used the following parameters: bandwidth = ±31.5 kHz, readout flip angle = 20°, VPS = 20, TR/TE = 6.0 / 3.0 ms, FOV = 320 mm, slice thickness = 8 mm, acquisition matrix = 192 x 192, one R-R, and number of excitations (NEX) = 2. The TI was tuned for each patient to optimally null myocardium, and ranged from 175 to 250 ms. The delay time was chosen to yield images in mid-diastole. The IR-GRE sequence required 20 heartbeats (an average breath-hold of 18 seconds) to produce a single viability image.

The MCDE sequence was performed as previously described. Briefly, the sequence was developed to enable the simultaneous acquisition of cine and multi-contrast viability images. The MCDE sequence applies an inversion pulse once every R-R interval, followed by a segmented SSFP acquisition. The 20 reconstructed images are each at a different effective TI and at a different cardiac phase. The inversion pulse is placed just prior to diastole to produce infarct-enhanced images (at early TIs) in diastole and cine images with normal SSFP contrast in systole. The parameters used for MCDE imaging were: bandwidth = ±125 kHz, readout flip angle = 45°, VPS = 16, TR/TE = 3.3 / 1.4 ms, FOV = 320 mm, slice thickness = 8 mm, 192 x 192 imaging matrix and NEX = 1. The MCDE sequence took 13 heartbeats to acquire, leading to an 11 second breath-hold on average.

**Data Analysis**
Blinded analysis was performed by two trained observers (KAC, JJG) using MASS software (MASS plus 5.0; Medis, Leiden, The Netherlands). The most basal image was defined as the image where >50% of the myocardium was seen during end-systole. The end-systolic and end-diastolic frames were independently chosen by each observer. The end-diastolic frame was defined as the image with the largest ventricular volume in each series, and the image with the smallest volume was chosen as the end-systolic frame. Endocardial and epicardial borders on both end-systolic and end-diastolic frames were then manually traced on both conventional cine SSFP images and MCDE images. From this data, ejection fraction, LV end-diastolic volume, LV end-systolic volume, stroke volume and LV mass were calculated. LV myocardial mass was calculated by multiplying the tissue volume by the specific density of myocardium (1.05 g/cm³). LV infarct size was determined by manual tracings of enhanced myocardium on IR-GRE and MCDE images. The infarct contours were performed by a single observer (JSD) blinded to the results of the cine analysis. Inter-observer variability was determined and is reported. Intra-observer variability was performed by one observer (KAC) by re-analyzing five data sets four weeks after the original analysis.

**Statistical Analysis:**
All data are presented as mean ± standard deviation (SD). Correlations were assessed using the Spearman correlation co-efficient, and Bland-Altman analyses were performed to determine bias. A two-sided
paired Student’s t-test was used where appropriate, and results were considered statistically significant at p < 0.05. The statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago, IL).

RESULTS
CMR imaging was well tolerated in all subjects. Images from two patients were excluded from the final analysis. One patient was excluded as an incorrect placement of the inversion pulse for the MCDE sequence prevented systolic frame identification. The second patient was excluded due to poor quality images (for all three sequences) resulting from improper gating due to a poor ECG signal.

Myocardial infarct was detected on delayed enhancement images in 24 patients, with associated wall motion abnormalities and a reduced EF. Three other patients had focal wall motion abnormalities and an EF under 50%, but with no infarct enhancement seen on the DE-MRI images. Selected MCDE images displaying viability and wall motion information in a patient with an infero-lateral MI are shown in Figure 1. SSFP, IR-GRE, and MCDE images in a patient with an antero-septal MI are shown in Figure 2. In one patient, an enhanced infero-septal infarct was detected on the MCDE images but not on the IR-GRE images (Figure 3); reduced wall motion was observed in the infero-lateral segment where enhancement was detected with MCDE, and the patient’s EF was 46%.

Table 1 shows the mean LV volume (mL), mass (g) and ejection fraction (%) determined using the SSFP and MCDE images across all patients. There were no clinically significant differences between the mean values of the two sequences. The Bland-Altman plots (Figure 4) demonstrate excellent agreement for EF (mean difference = -2%, 95% CI of -8 to 4%) and LV mass (mean difference = 0.2 g, 95% CI of -18 to 18 g). Agreement was clinically acceptable for LV EDV (mean difference = -7 mL, 95% CI of -30 to 16 mL). Excellent agreement was found between the IR-GRE and MCDE images in the LV infarct size (mean difference = 0.2 g, 95% CI = -1.5 to 2.0 g, Figure 4D).

The inter-observer variability for the SSFP and MCDE analyses is shown in Table 2. Excellent agreement was seen for LVEF and LV EDV determined from both SSFP and MCDE sequences. LV mass showed the least agreement between observers, with MCDE demonstrating a 2.6% difference compared to a 7.9% difference seen with conventional SSFP imaging.

Table 3 shows the intra-observer variability. No clinically or statistically significant variability was demonstrated for LVEF, LV EDV and LV mass. LV EDV as measured by MCDE demonstrated the greatest intra-observer variability.

DISCUSSION
This study demonstrates that MCDE imaging accurately and reproducibly assessed ejection fraction, LV volume and mass, as well as infarct size, across a range of patients with both normal and abnormal myocardial architecture and function. This data was acquired with half the number of breath-holds and in approximately half the time of the conventional sequences.

Cardiac MRI offers major advances when compared to echocardiography in the assessment of functional parameters, as excellent agreement and reproducibility enable enhanced accuracy. As a result, it is the tool of choice for both longitudinal patient follow-up and clinical research. One limitation has been the time required for full coverage of the LV, involving multiple acquisitions and repeated breath-holds for both wall motion and viability imaging. The development of a single sequence which incorporates both function and viability represents a significant advance. By combining these two imaging sets, MCDE reduces acquisition time, which improves patient tolerability and comfort, while providing a richer, more integrated data set. The time savings will potentially enable further characterization of myocardial properties such as valvular function and diastolic function within a clinically acceptable exam duration.

The acquisition of both DE-MRI and cine SSFP in a single breath-hold also yields wall motion and viability images that are inherently registered spatially. This assists clinicians in determining the transmurality of any infarct, and in visualizing the extent of a wall motion abnormality related to a
particular MI. This may facilitate the identification of myocardial segments whose function will improve after revascularization. Another sequence, called cine-DE, has been developed to produce viability and wall motion images within a single acquisition. However, the cine-DE method uses a single-shot readout to acquire images at a single fixed TI but with a varying delay time from the R-trigger; this yields wall motion images with a temporal resolution of approximately 300 ms. The MCDE sequence maintains the temporal resolution of cine SSFP wall motion imaging (approximately 50 ms), which enables the visualization of systolic wall motion abnormalities and the accurate calculation of the EF.

MCDE imaging offers advantages over conventional IR-GRE imaging in that “TI surfing” becomes obsolete. MCDE imaging automatically obtains several frames at different TIs, providing excellent contrast between viable and non-viable myocardium. We believe that the MCDE sequence may be more sensitive to small subendocardial infarcts as MCDE provides improved contrast between infarct and blood pool. In this study, there was one patient where the enhanced infarct was undetected on the IR-GRE images due to being a thin, subendocardial infarct that appeared to be part of the blood pool. The enhancement could be easily seen on a number of MCDE images at early inversion times (Figure 3). It is believed that this enhancement is a true positive because there is a wall motion abnormality at the site of the MCDE enhancement and the patient had a reduced EF of 46%. Additionally, upon re-examination of the IR-GRE images after viewing the MCDE images, it was determined that the infarct was present but simply masked by the adjacent blood pool.

Single-shot inversion recovery SSFP pulse sequences have been developed for CMR viability imaging to overcome the limitations imposed by multiple breath holds. While single-shot SSFP imaging holds promise, the images are acquired at a lower spatial resolution (to maintain a temporal window of 200 ms in diastole), and exhibit reduced contrast between infarct and healthy myocardium. Single-shot sequences also do not provide any functional information. A real-time delayed enhancement sequence has been recently shown to provide viability and anatomical images (during free-breathing and without cardiac gating) with improved contrast between infarct and blood; however, the temporal resolution of this method does not allow for the visualization of cardiac wall motion. MCDE imaging can be acquired at the same (or higher) resolution as IR-GRE imaging with the same temporal resolution as cine SSFP acquisitions.

Our results were consistent with the literature in regards to the reproducibility and accuracy of CMR. Ejection fraction was the most reliable parameter assessed, with both sequences demonstrating excellent agreement, as well as clinically acceptable inter and intra-observer variability. This has important clinical ramifications, as EF is commonly used as a surrogate endpoint for clinical research, as well as in the decision making for therapies such as implantable defibrillators. LV mass and end-diastolic volume demonstrated greater variability, both between observers and between sequences, which is also consistent with the literature. The likely explanation for differences in LV volume and LV mass with SSFP include poor border detection at the interface between the epicardium and the lungs, as well as chemical shift at the myocardial-epicardial fat interface. These problems affect MCDE as well as the conventional SSFP sequence. At this time, only experience and training appears to be able to overcome this limitation. MCDE imaging may slightly overestimate LV EDV, as the timing of the inversion pulse reduces the visualization of the endocardium in end-diastole. Despite this, our data suggests that the degree of underestimation is clinically acceptable, and the inter and intra-observer variability is consistent with other reports in the literature.

While clearly offering advantages for viability and systolic function assessment, the timing of the inversion pulse for MCDE imaging results in end-diastolic images with reduced visualization of the cardiac wall. This may limit the assessment of diastolic function. However, the temporal resolution of 50 ms with both MCDE and SSFP imaging already limits diastolic function assessment of load sensitive measures such early and late diastolic filling E and A waves. In order to accurately assess diastolic function, CMR tagging is currently preferred over wall motion imaging.

In conclusion, MCDE imaging reproducibly and rapidly enables both viability and functional imaging in a single acquisition. MCDE imaging is a useful alternative to conventional SSFP and IR-GRE imaging for the assessment of cardiac function and viability.
ACKNOWLEDGEMENTS
We would like to thank our MR technologist Rhonda Walcarius. This work is supported by grant number MOP36477 from the Canadian Institutes of Health Research and by research funding from GE Healthcare. Dr. Kim Connelly is supported by a TACTICS scholarship (Canada), an Australian NHMRC Neil Hamilton Fairley scholarship ID 440712, and a RACP “Pfizer” Overseas travelling grant. Jay Detsky is supported by funding from the Natural Sciences and Engineering Research Council of Canada.

Disclosures:
Jay Detsky and Graham Wright have filed a patent application on the MCDE pulse sequence. This work was partially supported by research funding from GE Healthcare. All authors disclose no other conflict of interest.

REFERENCES
Table 1: Comparison between SSFP and MCDE across all patients.

<table>
<thead>
<tr>
<th></th>
<th>SSFP</th>
<th>MCDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EF (%)</td>
<td>44 (17)</td>
<td>41 (16)</td>
</tr>
<tr>
<td>LV EDV (mL)</td>
<td>126 (62)</td>
<td>130 (58)</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>119 (64)</td>
<td>111 (65)</td>
</tr>
<tr>
<td>Infarct size (g)</td>
<td>6.6 (11.7)</td>
<td>6.8 (11.5)</td>
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</table>

Table 2: Inter-observer variability

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>Mean</th>
<th>Mean difference</th>
<th>Difference (%)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF; SSFP (%)</td>
<td>0.99</td>
<td>44</td>
<td>-2.6</td>
<td>5.9</td>
<td>-3.5 to -1.7</td>
</tr>
<tr>
<td>EF; MCDE (%)</td>
<td>0.99</td>
<td>41</td>
<td>-2.0</td>
<td>5.0</td>
<td>-3.0 to -1.1</td>
</tr>
<tr>
<td>EDV; SSFP (mL)</td>
<td>0.99</td>
<td>126</td>
<td>-1.8</td>
<td>1.4</td>
<td>-5.2 to 1.6</td>
</tr>
<tr>
<td>EDV; MCDE (mL)</td>
<td>0.99</td>
<td>130</td>
<td>-1.7</td>
<td>1.3</td>
<td>5.3 to 1.9</td>
</tr>
<tr>
<td>LV mass; SSFP (g)</td>
<td>0.95</td>
<td>119</td>
<td>9.5</td>
<td>7.9</td>
<td>6.1 to 13.0</td>
</tr>
<tr>
<td>LV mass; MCDE (g)</td>
<td>0.91</td>
<td>111</td>
<td>2.9</td>
<td>2.6</td>
<td>-1.9 to -7.7</td>
</tr>
</tbody>
</table>

MCDE is multi-contrast delayed enhanced imaging; EF is ejection fraction and EDV is end-diastolic volume; r is the Pearson correlation co-efficient; difference is mean value of observer 1 minus observer 2, expressed as a mean difference and percentage of mean.

Table 3: Intra-observer variability

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>Mean</th>
<th>Mean difference</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF; SSFP (%)</td>
<td>0.99</td>
<td>43.8</td>
<td>-2.2</td>
<td>-5.7 to 1.4</td>
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<tr>
<td>EF; MCDE (%)</td>
<td>0.95</td>
<td>40.1</td>
<td>-7.5</td>
<td>-17 to 2.7</td>
<td>0.111</td>
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<td>EDV; SSFP (mL)</td>
<td>0.99</td>
<td>127.5</td>
<td>0.5</td>
<td>-7 to 8</td>
<td>0.871</td>
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<tr>
<td>EDV; MCDE (mL)</td>
<td>0.99</td>
<td>110.5</td>
<td>11</td>
<td>-5.5 to 27.5</td>
<td>0.137</td>
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<tr>
<td>LV mass; SSFP (g)</td>
<td>0.93</td>
<td>87.9</td>
<td>-6</td>
<td>-20 to 7.9</td>
<td>0.293</td>
</tr>
<tr>
<td>LV mass; MCDE (g)</td>
<td>0.98</td>
<td>87.3</td>
<td>0.8</td>
<td>-11 to 12</td>
<td>0.866</td>
</tr>
</tbody>
</table>

MCDE is multi-contrast delayed enhanced imaging; EF is ejection fraction and EDV is end-diastolic volume; r is the Pearson correlation co-efficient; mean difference is reading 1 minus reading 2.
Figure 1: MCDE images (eight of 20 acquired images shown). The number on each image is the inversion time for that image. The top four images can be used to visualize the infero-lateral infarct (area with a more rapid signal recovery), while the bottom four images show cardiac wall motion. The image at 343 ms is at end-diastole, and the image at 735 ms is end-systole.

Figure 2: A comparison between (a) IR-GRE delayed enhancement image, (b) conventional SSFP end-systolic wall motion image, (c) conventional SSFP end-diastolic wall motion image with (d) MCDE infarct-enhanced image, (e) MCDE end-systolic image, and (f) MCDE end-diastolic image. Note that (d-f) are three of the 20 MCDE images acquired during a single breath-hold.
Figure 3: Images from two adjacent slices in a patient where the infero-septal enhanced infarct was not detected during the clinical reading of the IR-GRE images (a,e), but was detected on the MCDE images (b-d and f-h). The multi-contrast MCDE images with varying contrast allowed discrimination between the thin subendocardial infarct and the blood pool, while the infarct appeared to be part of the blood pool on the IR-GRE images. A wall motion abnormality was seen in the cine SSFP and MCDE systolic images in the region where the infarct was detected, and the patient’s EF was 46%. The arrows also show papillary muscle infarction that is not visible on the IR-GRE images.
Figure 4: Bland-Altman plots for comparing cine SSFP and MCDE for measuring (a) LV ejection fraction ($r = 0.98$, bias = -2\%), (b) LV end-diastolic volume ($r = 0.98$, bias = -7 mL), and (c) LV mass ($r = 0.99$, bias = 0.2 g). (d) Comparison between IR-GRE and MCDE measures of infarct size ($r = 0.99$, bias = 0.2 g).