INTERACTIVE, QUANTITATIVE 3D STRESS ECHOCARDIOGRAPHY AND MYOCARDIAL PERFUSION SPECT FOR IMPROVED DIAGNOSIS OF CORONARY ARTERY DISEASE

DISSERTATION

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By

Vivek Walimbe, B.E.

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Dissertation Committee:

Dr. Cynthia Roberts, Ph.D.

Dr. Raj Shekhar, Ph.D.

Dr. Robert Hamlin, Ph.D., D.V.M

Dr. Alan Litsky, M.D., Sc.D.

Approved by

Graduate Program in Biomedical Engineering
ABSTRACT

Coronary artery disease (CAD), which involves narrowing of the vessels supplying blood to the heart, is the leading cause of death in the United States. Complete recovery from CAD can be achieved by early and accurate diagnosis of the disease leading to timely and appropriate treatment. Stress testing is a common approach for diagnosing myocardial ischemia, a state of blood supply and demand imbalance resulting from CAD. Physical exercise or pharmacologic agents raise the heart’s oxygen demand, failure to meet which sets in myocardial ischemia leading to left ventricular (LV) dysfunction. Stress echocardiography (echo) and stress single photon emission computed tomography (SPECT), which provide complementary anatomical and perfusion information about the heart, remain the two most commonly prescribed cardiac stress testing procedures. Stress echo manifests the LV dysfunction as abnormal myocardial wall motion and thickening, whereas stress SPECT shows the myocardial perfusion defects. Despite their frequent clinical utilization, however, these two procedures remain limited in their sensitivity and specificity, and the diagnosis of CAD using either of these techniques individually is often ambiguous, necessitating costly invasive follow-up tests like cardiac catheterization. This dissertation focuses on development of accurate and automatic
image analysis techniques that will enhance the utility of these images and increase the diagnostic accuracy of cardiac stress testing using echo and SPECT.

Real-time three-dimensional (RT-3D) ultrasound is an emerging innovation in imaging that is capable of scanning the entire left ventricle along with its complex motion in a few cardiac cycles. The clinical feasibility of 3D stress echocardiography, based on the powerful RT-3D ultrasound, has previously been documented. The first hypothesis in this dissertation is that a truly quantitative 3D stress echo procedure, that utilizes advanced quantitative image analysis techniques together with RT-3D ultrasound, is capable of overcoming many of the limitations of conventional stress echo and therefore improving diagnostic accuracy. The current research builds on the preliminary work (interactive visualization and registration of 3D echo) done within the group, and describes the development of a novel interactive and quantitative stress echo software that combines, for the first time, fully automatic tools for accurate pre-/post-stress image alignment, LV myocardial segmentation and quantification of global and regional LV function for RT-3D echo images. Results of a study involving 15 subjects with known/suspected CAD indicate improved diagnostic performance of the newly developed method compared to that of conventional stress echo (reference data from angiography). The second hypothesis states that simultaneous improvement in sensitivity and specificity for detecting CAD can be achieved with a multimodality stress testing approach, wherein diagnosis is based on accurately correlated (temporally and spatially) complementary functional and perfusion information available from RT-3D echo and SPECT, respectively. This dissertation includes development of techniques, including a novel elastic image registration algorithm, for automatic multimodality fusion of RT-3D
echo and SPECT images. The quantitative analysis techniques developed for 3D stress echo are extended for the multimodality stress testing approach. A preliminary validation study involving 20 subjects evaluates the effectiveness of the quantitative multimodality stress testing approach as compared to that of the individual modalities for diagnosis of CAD.

The current work will potentially result in new diagnostic techniques – quantitative 3D stress echo and a multimodality cardiac stress testing procedure – for all patients suspected of having CAD, irrespective of race, gender or socioeconomic stature. The developed techniques require minimal deviation from existing clinical procedures, allowing easy introduction in the clinical workflow with minimal cost increase. In addition to early and accurate diagnosis, the methodologies developed in this research can be naturally extended in the long term for identifying regions of viable myocardium that stand to benefit from specific treatment options like medical therapy or revascularization, thus saving many lives and dollars in healthcare.
Dedicated to Aai-Baba and Devyani, for their love and support.
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VITA

March 26, 1980 . . . . . . . . . . . . . . Born – Satara, India

2001 . . . . . . . . . . . . . . . . . . . . . . . B.E., Instrumentation and Control Engineering, Govt. College of Engineering, Pune (University of Pune, India)

2001 – 2002 . . . . . . . . . . . . . . . . . University Fellow, The Ohio State University

2004 – 2006 . . . . . . . . . . . . . . . . . Predoctoral Fellow, American Heart Association

2002 – present . . . . . . . . . . . . . . . . . Research Assistant, The Ohio State University

SELECTED PUBLICATIONS

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**FIELDS OF STUDY**

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CHAPTER 1

INTRODUCTION

This dissertation discusses advanced image processing techniques for real-time three-dimensional (3D) echocardiography (echo) and single photon emission computed tomography (SPECT), aimed towards providing an improved diagnosis of myocardial ischemia with underlying coronary artery disease (CAD). The first chapter provides an introduction about the major problem being addressed, describes the motivation behind the study, outlines the specific research objectives and presents an overview of the dissertation.

1.1 What is the major problem being addressed?

Heart is arguably the most vital organ for normal functioning of the human body, with its most vital chamber being the left ventricle that is responsible for pumping oxygenated blood to various parts of the body. The ability of the heart (or the left ventricle) to function effectively to ensure adequate supply of blood and nutrition to the various parts of the body depends largely on the health of the left ventricular (LV) myocardium. Blood is supplied to the LV myocardium through three main coronary arteries – the left anterior
descending (LAD), the right coronary artery (RCA) and the left circumflex (LCx) (Figure 1.1). CAD is defined as the condition involving narrowing or occlusion of one or more of these three main coronary arteries or their branches supplying blood to the LV myocardium, resulting in reduced blood supply to the myocardium. In the early stages of CAD, the reduced blood flow might be enough to meet the metabolic demands of the contracting myocardium at rest. However, when stressed (or even at rest when the disease has progressed) the reduced blood supply leads to a supply-demand mismatch to the myocardium, a condition known as myocardial ischemia. CAD is responsible for over two thirds of heart failure cases in the United States (AHA 2006). Fortunately, early and accurate diagnosis of ischemic heart disease (caused by CAD) can potentially reduce mortality and morbidity in patients by identifying LV regions that could be revascularized before the corresponding myocardium becomes irreversibly scarred.

Stress testing is a common approach for diagnosing myocardial ischemia with underlying CAD, in which physical exercise or pharmacologic agents artificially ‘stress’ the heart and raise the oxygen demand, failure to meet which sets in myocardial ischemia leading to LV dysfunction. Ischemia manifests as abnormal wall motion and thickening in echo and as abnormal perfusion defects in SPECT. Stress echo and stress SPECT are the two most commonly prescribed ‘fist-step’ noninvasive cardiac stress testing procedures. Despite their frequent clinical utilization, stress echo and stress SPECT show limited accuracy for diagnosing ischemic myocardium - stress echo is more specific than stress SPECT (86% vs. 77%), but less sensitive (78% vs 83%) (O’Keefe, Barnhart et al. 1995).
Thus, the diagnosis of CAD using either of these techniques individually is often ambiguous, necessitating costly invasive follow-up tests like cardiac catheterization.

1.2 Goal of the research

The overall goal of the current research is to improve the diagnostic accuracy of common cardiac stress testing procedures for detecting CAD, viz. stress echo and stress SPECT. Towards achieving the overall research goal, this dissertation proposes (1) use of real-time 3D echo (RT-3DE), a recent innovation that for the first time enables almost instantaneous volumetric imaging of the beating heart in 3D, and (2) development of novel methodologies to enable and maximize potential of cardiac stress testing using RT-3DE alone and in combination with SPECT. Accordingly, the specific technical objectives of the current work can be summarized as below:

Specific objective #1: To develop a novel interactive, quantitative stress echo procedure that combines, for the first time, fully automatic image analysis tools for accurate pre-/post-stress image alignment, LV myocardial segmentation and quantification of global and regional LV function for cardiac stress testing using RT-3DE images.

Specific objective #2: To develop necessary advanced image processing techniques to enable a novel quantitative multimodality cardiac stress testing approach involving fused RT-3DE and SPECT images.
1.3 Significance of the study: Why is early and accurate diagnosis of CAD important?

CAD has emerged as the primary etiology of LV dysfunction and heart failure, the leading causes of hospitalization in the United States (AHA 2006). Among all patients suffering from LV dysfunction, mortality rate is highest among those with underlying CAD as opposed to other non-ischemic diseases. Fortunately, myocardial hypoperfusion with underlying CAD, leading to LV dysfunction, is not irreversible and normal heart function may be restored after medical therapy or revascularization. The selection of the most efficacious treatment option, critical for reducing current morbidity and mortality rates, depends on timely and accurate diagnosis of CAD as the cause of LV dysfunction. Thus, enabling early and accurate detection of underlying CAD at an early ischemic stage will allow physicians to make timely diagnosis followed by medical therapy/revascularization, and may lead to complete recovery in majority of cases. Moreover, even a modest 1% gain in sensitivity and specificity of diagnosis of CAD would have tremendous economic impact. An improvement in specificity of 1% would preclude unnecessary follow-up catheterizations in 1% of CAD patients – an annual saving of $539 million ($24,893 (average cost of catheterization) x 21,660 (1% of annual CAD discharges)). With 1% improvement in sensitivity, the same number of currently misdiagnosed CAD patients would receive appropriate treatment, saving $1.22 billion ($56,803 per patient) in morbidity and mortality costs (AHA 2006).
1.4 Overview of dissertation

This dissertation has six chapters including this introductory chapter. CHAPTER 2 provides background about cardiac stress testing using conventional stress echo and stress SPECT and summarizes the limitations of these stress-testing techniques. CHAPTER 2 also describes the advantages of the emerging RT-3DE modality and provides the rationale behind the proposed research, leading to the formal definition of the scientific challenges tackled by the current research. The relevant literature is surveyed in CHAPTER 3, which also includes a description of the preliminary work this dissertation builds upon. The development and validation of a novel quantitative 3D stress echo procedure is described in CHAPTER 4. CHAPTER 5 describes the techniques developed to enable the multimodality (RT-3DE + SPECT) stress testing approach and presents a study performed for preliminary validation of the proposed multimodality approach. The methods, results and future direction of the research are summarized in CHAPTER 6.
1.5 Figures

Figure 1.1 Coronary arteries supplying blood to left ventricle (Figure(Reference#1))
CHAPTER 2

BACKGROUND

This chapter contains background information about various concepts involved in this dissertation such as cardiac stress testing, stress echo and stress SPECT. The chapter initially introduces the concept of cardiac stress testing and the common clinical protocols involved in external induction of cardiac stress. Basic overview is provided about image acquisition and interpretation for stress echo and stress SPECT, the two cardiac stress testing procedures involved in this dissertation, followed by rationale behind focusing on stress echo and stress SPECT. Next, the shortcomings of conventional stress echo and stress SPECT procedures are outlined, leading to formal definition of two main hypotheses that motivate the current research.

2.1 What is cardiac stress testing?

Cardiac stress testing, a commonly used procedure for diagnosing myocardial ischemia with underlying CAD, involves artificially stressing the heart, through physical exercise or pharmacologic agents, and analyzing the resulting changes in electrophysiology, structure, function, perfusion and/or metabolic activity of the LV myocardium. In the
early stages of CAD, the reduced blood flow might be sufficient to meet the oxygen demand of the contracting myocardium during normal functioning, i.e. the “resting” state. “Stressing” the heart raises the myocardial oxygen (i.e. blood) demand, which cannot be met by the occluded coronary arteries. This ‘demand-supply mismatch’ elicits a number of symptoms: metabolic and perfusion abnormalities, abnormal LV wall motion and thickening, ST-segment depression in electrocardiogram (ECG), chest pain, etc. Figure 2.1 shows an illustration of different stress-induced manifestations of CAD, depending on the extent of disease. Detection of these stress-induced abnormalities is a good diagnostic indicator of existence of CAD. Common clinical protocols for inducing stress externally are described next.

2.1.1 Common clinical stress protocols

Common clinical protocols for inducing stress involve actual physical exercise or pharmacologic drugs.

**Exercise stress**

This protocol involves evaluation of state and response of LV myocardium immediately before and after the subject performs physical exercise. A common approach involves the patient exercising on a standard treadmill. The speed of imaging/signal acquisition at peak stress after the exercise is the critical aspect for this test. The primary disadvantage of this method is that monitoring is possible only before and after exercise – evaluation at intermediate levels is very difficult to almost impossible. So, any abnormality early in the
procedure may not be detected until termination of the exercise. The overall accuracy of this protocol is equivalent to peak exercise imaging/signal acquisition.

Bicycle ergometry, with patient in either upright or supine position, is another approach for exercise stress. It is less well tolerated among patients, so a lot of flexibility in terms of personalization of exercise is required. In upright method, a marked difference in workload and heart rate is achieved as compared to supine bicycle ergometry. With bicycle ergometry, imaging is usually done at sequential stages.

**Pharmacological stress testing**

In cases where a patient is unable to achieve sufficient level of physical exercise to stress cardiovascular system to the diagnostic endpoint, non-exercise method of stress induction is used. Dobutamine is one of the most frequently used drugs for this purpose. Graded infusion of dobutamine mimics the effects of exercise by increasing contractility, heart rate, and the blood pressure, thus resulting in a supply-demand mismatch. Sometimes atropine may be delivered intravenously to increase heart rate to more appropriate cardiovascular stress testing levels. The infusion of dobutamine is well tolerated with only self-limited side effects observed. Other pharmacologic agents include dipyridamole and adenosine, both potent coronary vasodilators, which are used at times as diagnostic agents with echo or SPECT for provocation of regional wall motion abnormalities or perfusion defects – a sign for presence of CAD.
2.2 Conventional stress echocardiography

Conventional stress echo involves evaluation of cardiovascular response to externally induced stress using two-dimensional (2D) ultrasound imaging. A typical clinical procedure involves acquisition of pre- and post-stress standard 2D cross-sectional views of the left ventricle using a 2D echo scanner, thus allowing evaluation of the structural and functional state of the heart to detect any abnormalities resulting from stress.

2.2.1 Standard 2D echo views

The standard cross-sectional images acquired and analyzed during 2D stress echo studies are shown in Figure 2.2. They are obtained from standard transducer positions – parasternal and apical – with the patient in the left lateral decubitus position (patient lying on the left lateral side with left arm stretched above the head and right arm beside the body). The parasternal long and short-axis views are obtained with the transducer placed in the left parasternal region between the third and fourth intercostal spaces. For obtaining the apical view, the transducer is placed at or very near the point where maximal apical impulse is localized. Pre- and post-stress cross-sectional images are manually acquired by sonographers and displayed side-by-side as digital cine-loops for diagnosis.

2.2.2 Interpretation of images

The analysis of a stress echocardiograph may range from the simple distinguishing of normal and abnormal states to the more detailed calculation of various parameters like ejection fraction, ventricular volume or the centerline chordal shortening. All these
techniques are targeted towards assessing the structure and function of the LV myocardium.

A normal response to stress includes increased myocardial thickening and a smaller cavity in systole as compared to diastole. Abnormality in function is usually symptomized in the form of regional wall motion abnormalities and/or deterioration in LV global function. Secondary changes observed include worsening of mitral or tricuspid regurgitation and development of or worsening of pulmonary hypertension. Common geometric deformations that occur as a result of myocardial ischemia include rounding of the apex or regional deformation in shape such that right-left symmetry of the left ventricle is lost. Calculation of LV volume in diastole and systole, from which ejection fraction and end systolic pressure-volume ratios can be derived, also provide additional information for detecting coronary disease.

2.3 **Conventional stress SPECT**

Stress SPECT involves the evaluation of perfusion abnormalities in the myocardium resulting from externally induced stress by studying the uptake of radionuclide tracers injected into the patient. The radionuclides used to study myocardial perfusion have especially good avidity for the myocardium, a good uptake and distribution in the myocardium that is proportional to the regional blood flow. The most widely used tracers are Thallium-201 (Tl-201) and Tecnetium-99m (Tc-99m)-labeled compounds like sestamibi (MIBI). Following intravenous administration, these radionuclides distribute into the patient’s body in proportion to the regional blood flow. Different radionuclides
have different half-lives; after time duration equivalent to half-life they transition to a more stable chemical form through process of electron capture. The photons emitted in the process are detected by special gamma sensors, which produce the output signal that is measured. The chemicals are eventually washed out of the body, predominantly via the kidneys. The gamma camera is the fundamental equipment for detection in SPECT, and consists of scintillation detectors that are transducers converting the emitted radiation energy into electronic impulses, which are then converted into digital signals. Thus, the intensity of digital signal detected in SPECT is proportional to the regional blood flow.

In the basic clinical stress SPECT protocol, pre-stress images are acquired 10-15 minutes after the patient is given an intravenous injection of 2.0-2.5 mCi of Tl-201. Following externally induced stress (exercise or pharmacologic), at peak stress, 20 mCi of Tc-99m MIBI is injected. Post-stress imaging usually starts 40-60 minutes after injection of MIBI, because MIBI undergoes minimal (about 20%) redistribution primarily within the first 20 to 60 minutes following injection.

2.3.1 Image acquisition in SPECT

For image acquisition, patient typically lies supine in a gantry. Modern SPECT scanners have two or three gamma cameras rotating inside the gantry. Raw tomographic projection image data is collected from multiple positions of the gamma cameras. Image acquisition can be summed or gated using the ECG into 8 or 16 phases of the cardiac cycle. Various reconstruction techniques, e.g. filtered backprojection technique and statistical reconstruction, are used to reconstruct 3D images that are used for diagnosis.
2.3.2 **Interpretation of images**

Summed images are used for normal perfusion analysis, whereas gated images are acquired and analyzed only if analysis of global LV function is desired. For perfusion analysis, the data for individual cardiac phases are summed together, reconstructed, and displayed in standard short axis, and vertical and horizontal long-axis slices (Figure 2.3). Myocardial regions with perfusion abnormalities are identified as regions of low signal intensity in the images. Typically, regions with newly developed post-stress perfusion abnormalities are identified as ischemic. Regions with persistent pre- and post-stress perfusion abnormalities are identified as infarcted/scarred. Exact scheme for diagnosis depends on the specific clinical protocol and the radionuclide used. Recently, analysis of global LV volume and wall motion using gated images is being used (Lee, Ahn et al. 2000; Bavelaar-Croon, America et al. 2001; Berk, Isgoren et al. 2005), though prognostic value of such an analysis in case of mild single vessel disease is still debatable.

2.4 **Why focus on stress echo and stress SPECT**

The onset of various symptoms of CAD during stress testing is related to the degree of ischemia. The abnormal perfusion defects in SPECT and abnormal LV wall motion and thickening in echo are observed earlier than changes in the ECG (see Figure 2.1). As seen in Figure 2.1, metabolic abnormalities tend to appear earlier during the disease progression than wall motion or perfusion abnormalities. Positron emission tomography (PET) is regarded as the gold standard for imaging myocardial metabolism (and health), and seems a better alternative to stress echo or SPECT for earlier diagnosis of CAD.
However, PET is not widely used because of the limited availability of radioisotopes such as 2-fluoro-2-deoxy-D-glucose (FDG)-18. The higher scan cost and limited reimbursement continue to prevent PET from competing favorably against echo and SPECT. Detection of diastolic abnormalities, which may also appear early during the disease in some cases, is not a very reliable marker since the etiology for diastolic abnormalities includes various other conditions besides CAD like chronic hypertension, aortic stenosis, restrictive cardiomyopathy, aging among others. Besides, even in patients with CAD, diastolic abnormalities may be masked by presence of mitral regurgitation (Tomimoto, Takeuchi et al. 1989). Consequently, stress echo and stress SPECT are the two most commonly prescribed ‘first-step’ noninvasive diagnostic procedures for detection of CAD, with more than 10 million combined scans/exams performed annually in the United States (AHA 2006).

In recent years, magnetic resonance imaging (MRI) has made significant strides in imaging the heart through the introduction of dedicated cardiac coils, pulse sequences and contrast agents. Cardiac MRI is capable of depicting both morphology and function of the heart. However, it remains limited to mostly research and very few clinical cardiac examinations utilize cardiac MRI. Moreover, stress MRI remains excessively expensive due to the length of the procedure and can only be performed using drugs, not exercise. MRI is further inappropriate for a large segment of CAD patients with pacemakers and implantable cardioverter defibrillators. Other alternatives are electron-beam computed tomography (CT) and multi-slice helical CT, which allow imaging of the heart, but are not sensitive for imaging myocardial ischemia. Cardiac CT exams are also more
expensive than echo and SPECT (Fischer, Fuchs et al. 2002). To summarize, stress echo and SPECT are not only the most clinically suitable, but also the most economically viable, modalities for cardiac imaging, both in the short-term and the foreseeable future. Thus, development of diagnostic techniques based on these two imaging modalities has potential for tremendous clinical impact.

2.5 Problems with stress echo and SPECT

Despite their frequent clinical utilization, stress echo and stress SPECT have certain specific limitations, leading to limited diagnostic accuracy.

2.5.1 Limitations of conventional stress echo

Conventional stress echo suffers from low sensitivity and specificity and high interobserver variability, in part because of the limitations of 2D echo (2DE) employed and related limitations of visual interpretation. To cover most regions of the LV wall using 2DE, imaging is necessary from multiple locations on the chest. A short 60–90-second window to complete this task makes post-stress imaging challenging, and the diagnostic utility of the images depends on the skills of the sonographer. Even with successful imaging within this narrow window, the acquired images do not cover the entire LV wall. Moreover, as a result of factors such as limitations in manually duplicating the exact transducer position and patient movement during image acquisition, pre- and post-stress views often do not correspond to the same anatomic plane. Finally, the 2D nature of images makes implementation of sophisticated visualization and quantitative image analysis tools difficult. In current clinical practice, the interpretation
of these images is predominantly based on visual interpretation, which leads to higher subjectivity and significant inter- and intra-observer variations for diagnosis of wall motion abnormalities (coefficient of variation, kappa ($\kappa$) = 0.45–0.55 (Hoffmann, Marwick et al. 2002)).

### 2.5.2 Limitation of SPECT: Attenuation artifacts

Interpretation of SPECT images is often hampered by attenuation artifacts observed in the images. Attenuation is the decrease in intensity of a photon signal along its path to the detector. During cardiac SPECT imaging, non-uniform attenuation occurs as photons pass through tissues of varying densities, such as the sub-diaphragmatic tissues, chest wall, spine, and breasts. This results in an attenuation artifact whose extent varies with location of soft tissue, overall patient body size, and depth of target organ (heart). Attenuation artifact leads to a loss of diagnostic accuracy as artifacts may be confused with true perfusion abnormalities, resulting in an increase in false-positives. There may also be cases of under-interpretation of true perfusion abnormalities as the observer may overestimate the effects of attenuation. Attenuation maps containing detailed information about density distribution in the body are required to make the appropriate attenuation correction to avoid intensity artifacts. Several reviews have shown that attenuation correction methods that are currently available on clinical cameras can introduce artifacts that may be difficult to identify and might inadvertently alter diagnoses and study outcomes. As a result, the attenuation correction option is often avoided in clinical practice, even in those centers that have all the necessary equipment (Celler, Dixon et al.
Thus, stress SPECT continues to provide diagnosis of CAD with high sensitivity, but very low specificity.

### 2.5.3 Limited diagnostic accuracy of stress echo and stress SPECT

A number of studies have reported the accuracy of the two procedures for various population cohorts and sizes and stress induction protocols (exercise vs. drugs). A notable meta-analysis of 44 studies published between 1990 and 1997 compared exercise echo with exercise myocardial perfusion SPECT using coronary angiography as the reference for diagnosing CAD (Fleischmann, Hunink et al. 1998). The analysis showed that the exercise echo had a sensitivity of 85% with a specificity of 77%, and that the exercise myocardial perfusion SPECT had a slightly higher sensitivity of 87% with a comparatively much lower specificity of 64%. Similar numbers have been reported for stress procedures using pharmacologic drugs. A similar meta-analysis of 11 studies (O'Keefe, Barnhart et al. 1995), not differentiating between exercise and drug protocols, reported higher sensitivity for stress SPECT (83% vs. 78%) and higher specificity for stress echo (86% vs. 77%). Accordingly, there is a definite need for improvement of diagnostic accuracy for these two imaging modalities.

### 2.6 Emergence of real-time 3D echocardiography (RT-3DE)

Echocardiography has traditionally relied on capturing 2D ultrasound images for the entire cardiac cycle. However, recent advances in computing and transducer technology have made it possible to acquire 3D volumetric images in real-time using ultrasound technology – real-time 3D ultrasound technology. Before real-time 3D ultrasound, 3D
images could only be acquired mechanically, i.e., sweeping a conventional probe over the volume of interest and stacking the 2D slices. Such 3D acquisition is unsuitable for cardiac imaging because it can take minutes to form a single volume (thus precluding instantaneous volumetric imaging necessary for tracking heart motion), and is susceptible to distortions due to organ motion and deformation. Real-time 3D ultrasound uses a 2D matrix of transducer elements to electronically steer an ultrasound beam anywhere within a pyramidal space (e.g., $65^\circ \times 65^\circ \times 15$ cm), and is capable of producing up to 25 volumes per second (Figure 2.4) (von Ramm and Smith 1990; von Ramm, Smith et al. 1995; Ota, Fleishman et al. 1999; Schmidt, Ohazama et al. 1999; Kisslo, Firek et al. 2000). RT-3DE that is based on these recent innovations in 3D ultrasound imaging enables, for the first time, almost instantaneous volumetric imaging of the beating heart in 3D. RT-3DE, in itself, promises to improve the diagnostic accuracy of stress testing compared with conventional 2DE, because with RT-3DE, it is possible to image the entire heart, as opposed to only a few representative planes, in the time of a single cardiac cycle (Figure 2.4). Besides, the 3D nature of data allows a range of image processing tasks to be accomplished, thus allowing a quantitative and more objective stress echo procedure compared to conventional stress echo. Additionally, combination of complimentary anatomical and perfusion information for the entire cardiac cycle available from RT-3DE and SPECT, respectively, also has the potential to allow simultaneous analysis of LV wall motion, thickening and perfusion quantitatively, thus minimizing ambiguity of diagnosis and allowing an improved diagnosis of CAD compared to the individual modalities. Image registration (alignment) is a vital task that needs to be accomplished before the echo and SPECT images can be meaningfully
combined. The volumetric data from RT-3DE would allow the possibility of a true, 3D-to-3D (volume-to-volume) image registration between echo and SPECT, which is considerably easier than 2D-to-3D (slice-to-volume) registration that would have been required using conventional 2DE.

2.7 Research hypotheses

Based on aforementioned observations, this dissertation proposes to take advantage of RT-3DE towards achieving the goal of improving accuracy of CAD diagnosis using stress echo and stress SPECT. To summarize, the research described in this dissertation is motivated by the following two main hypotheses.

**Hypothesis 1:** A truly quantitative 3D stress echo (3D-SE) procedure that utilizes RT-3DE together with advanced quantitative image analysis techniques is capable of overcoming many of the limitations of conventional stress echo and therefore providing a more objective and accurate diagnosis of CAD.

**Hypothesis 2:** Simultaneous improvement in sensitivity and specificity for detecting CAD can be achieved with a multimodality stress testing approach, wherein diagnosis is based on accurately correlated (temporally and spatially) complementary functional and perfusion information available from RT-3DE and SPECT, respectively.

The current research builds on the preliminary work (interactive visualization and registration of 3D echo) done previously (Shekhar and Zagrodsky 2002; Shekhar, Zagrodsky et al. 2004), and describes the development of a novel interactive and quantitative stress echo software that combines, for the first time, fully automatic tools
for accurate pre-/post-stress image alignment, LV myocardial segmentation and quantification of global and regional LV function for RT-3DE images. The current work further includes development of techniques, including a novel elastic image registration algorithm, for automatic multimodality fusion of RT-3DE and SPECT images. The quantitative analysis techniques developed for 3D-SE are extended for the multimodality stress testing approach. The dissertation also includes preliminary validation studies evaluating the two hypotheses.
Figure 2.1 Illustration of different stress-induced manifestations of CAD
Figure 2.2 Standard views acquired for 2DE studies. (1) Parasternal long-axis (2) parasternal short axis, (3) apical four-chamber, (4) apical long axis.
Figure 2.3 Standard SPECT image display for diagnosis
2D + Time $\rightarrow$ 3D + Time

Figure 2.4 2DE to RT-3DE: Sequence of 2D images to sequences of volumes
This chapter discusses the previous work related to 3D stress echo and multimodality cardiac stress testing involving combination of stress echo and stress SPECT. Next, the contribution of the current research is discussed in the context of the limitations of the previously reported studies, use of existing techniques/algorithms and new algorithmic developments as part of this dissertation.

3.1 Current state-of-art in real-time 3D echocardiography and its clinical utility

RT-3DE is steadily gaining acceptance in the cardiovascular imaging community. The first commercially available RT-3DE scanner (Volumetrics Inc., Durham, NC) suffered from image intensity artifacts and low spatial resolution. With improvements in transducer and computation technology, the currently clinically available 3D echo scanners (e.g. GE Vivid 7 Dimension, Milwaukee, WI; Philips SONOS 7500, Andover, MA) offer higher image resolution than the first-generation Volumetrics scanner (Figure 3.1). These newer-generation 3D echo scanners (e.g. GE Vivid 7 Dimension, Milwaukee, WI; Philips SONOS 7500, Andover, MA) acquire the full LV volumetric data in the form
of four conical subvolumes scanned during four-to-seven consecutive heartbeats (<4-6 seconds) from the same transducer position and then integrated into complete pyramidal image sets using ECG gating. The latest-generation scanner (Philips iE33, Andover, MA) can achieve full volume image acquisition in even less time using a wider sector angle (and hence needing fewer than four conical subvolumes to cover the left ventricle) and more efficient electronic beam-steering mechanisms. Thus, RT-3DE using these latest generation scanners performs almost instantaneous volumetric imaging of left ventricle over the entire cardiac cycle, providing an increased dimensionality in imaging compared with conventional 2DE, while still allowing high spatial resolution and retaining the real-time nature of the image acquisition. Since the introduction of RT-3DE in 1990 (von Ramm and Smith 1990; Salehian and Chan 2005), many studies have reported the feasibility of clinical RT-3DE imaging and the effectiveness of this imaging technology in accurately quantifying LV measures like volume (Fleming, Cumberledge et al. 2005), myocardial mass (Mor-Avi, Sugeng et al. 2004; Oe, Hozumi et al. 2005), valve motion studies (Salehian and Chan 2005), using mostly manual or semi-automatic image analysis tools.

3.2 Stress echocardiography using RT-3DE

3.2.1 Advantages of using RT-3DE

The advantages of RT-3DE in terms of increased dimensionality of imaging also make it more naturally suitable for stress echo procedures than 2DE, allowing the possibility of early and accurate detection of wall motion abnormalities and diagnosis of myocardial ischemia with underlying CAD (Table 3.1). Firstly, RT-3DE is capable of almost
instantaneous imaging of the entire left ventricle and the surrounding anatomy from a single transducer position, making post-stress imaging less problematic and successful imaging not contingent on high level of operator skill. Due to the availability of true volumetric data, any cardiac plane can be visualized off-line/post-acquisition, thus avoiding foreshortening of the ventricle that is common with conventional stress echocardiography. Further, anatomically matching pre- and post-stress views can be readily generated at any location or orientation in the 3D image space by spatially and temporally aligning pre- and post-stress volumetric images. In a recent review of the state-of-art in stress echocardiography, Armstrong et al. (Armstrong and Zoghbi 2005) have acknowledged RT-3DE as a vital new technological development, and stress echo using RT-3DE, i.e. 3D-SE – a clinically attractive solution.

3.2.2 Prior studies investigating 3D stress echocardiography

Due to the novelty of RT-3DE, only a countable few studies have evaluated viability of RT-3DE for the stress echo procedure (Collins, Hsieh et al. 1999; Ahmad, Xie et al. 2001; Matsumura, Hozumi et al. 2005). These studies have demonstrated that stress echo using RT-3DE is at least as effective as with 2DE by comparing wall motion analyses from 3D-SE and conventional 2D stress echo (2D-SE), either head-to-head or in reference to angiography or SPECT. Collins et al (Collins, Hsieh et al. 1999) have reported satisfactory performance of RT-3DE with reference to 2DE for assessment of regional wall motion abnormalities. Ahmad et al. (Ahmad, Xie et al. 2001) reported good agreement between RT-3DE and 2DE for detection of myocardial ischemia at peak dobutamine-induced stress, with RT-3DE offering advantages such as shorter scanning
times, improved inter-observer agreements and unique new views of left ventricle. Matsumara et al. (Matsumura, Hozumi et al. 2005) have recently reported comparable sensitivity, specificity and accuracy between RT-3DE and 2DE for assessment of ischemia using exercise TI-201 SPECT as the reference standard.

3.2.3 Limitations of prior studies

A significant limitation of the aforementioned studies has been that the wall motion analysis in 3D-SE was based on the limited information made available during diagnosis, in the form of either limited number of pre-extracted cross-sectional 3D views (Ahmad, Xie et al. 2001) or cropped anatomic rendered views (Matsumura, Hozumi et al. 2005), and thus did not encompass the entire available 3D information and did not fully utilize the inherent imaging superiority of RT-3DE. Also, the diagnosis was very subjective and based solely on visual interpretation of the images and the wall motion abnormalities, not involving any quantitative analysis. Subjective nature of diagnosis arising from the primarily visual analysis of images, a limitation of these previous studies, is also a problem that has plagued conventional 2D stress echo (high variability in diagnosis of wall motion abnormalities – coefficient of variation, kappa (κ) = 0.45–0.55 (Hoffmann, Marwick et al. 2002)). In part due to these limitations, these previous studies have been unable to extract maximum information from RT-3DE images, and so report no significant improvement in diagnostic performance using 3D-SE compared to 2D-SE. To summarize, key features missing from previous studies that are crucial for fully maximizing inherent imaging superiority of RT-3DE for improving stress echocardiography include (1) achieving interactive side-by-side visualization of
anatomically matching pre- and post-stress views at desired frame rate, and (2) evaluating and utilizing 3D quantitative information from the pre- and post-stress images for diagnosis.

3.3 Multimodality cardiac stress testing involving echo and SPECT

3.3.1 Summary of prior studies

Only three reported studies (from two independent research groups) have attempted simultaneous application of stress echo and stress SPECT for diagnosis of CAD, and measured the sensitivity and the specificity of the combined test against coronary angiography (Senior, Sridhara et al. 1994; Slavich, Guerra et al. 1996; Khattar, Senior et al. 1998). In these studies, independent diagnoses of CAD from the two tests were combined. Senior et al. (Senior, Sridhara et al. 1994) assumed that the combined test was positive when either of the two tests was positive, and negative when both were negative (Figure 3.2). Similar logic was used in their follow-up study (Khattar, Senior et al. 1998), leading to sensitivity and specificity numbers that followed a similar trend. In another study, designed to test feasibility and effectiveness of combining stress echo and stress SPECT in women specifically, Slavich et al. (Slavich, Guerra et al. 1996) adopted a different approach to combining test results, wherein the combined test was positive when both individual tests were positive, and negative when either test was negative (Figure 3.2).
3.3.2 Limitations of prior multimodality echo-SPECT studies

All prior studies used 2DE for stress echo diagnosis, leading to limitations/shortcomings in the stress echo diagnosis due to reasons discussed above. Furthermore, the approach adopted by these studies for combining results of independent diagnoses is inherently flawed in creating both a more sensitive and a more specific test. Whether the combined test is more sensitive or more specific depends on the arbitrary approach of combining the results. The combination logic employed by Senior et al. (Senior, Sridhara et al. 1994) and Khattar et al. (Khattar, Senior et al. 1998) – positive test, if either of the two tests was positive – resulted in more positives (true or false) and fewer negatives, leading to increased sensitivity and decreased specificity (Table 3.2). In the Slavich study (Slavich, Guerra et al. 1996), which employed a different approach (positive diagnosis, if both tests positive), the number of positives (true or false) decreased, lowering the sensitivity of the combined test, resulting in increased specificity due to higher number of negatives (true or false) (Table 3.2). Overall, compared to the single modality approach, the benefits of these reported combined stress procedures are arguable if sensitivity must be traded for higher specificity or vice versa, compared with a single-modality procedure. However, unlike these studies, a registration-based approach is proposed in this dissertation, which yields a unique diagnosis made using “fused” images. With the capability of diagnosis based on fused images, the “problem” cases – positive according to one test and negative according to another – will not occur and be more accurately diagnosed. Figure 3.2 illustrates the decision-making logic inherent to the multimodality approach. With this approach, a higher percentage of both true positives and true negatives can be expected, resulting in both a more sensitive and more specific test.
3.3.3 Prior work on echo-SPECT registration

The failure of prior studies in fusing cardiac echo and SPECT images indicates the difficulty of and a lack of appropriate techniques for performing multimodality cardiac image registration (Note: accurate temporal and spatial alignment between images through registration must precede image fusion). A few reported techniques are approximate at best and as such unusable for 4D (3D + time) spatiotemporal image fusion proposed here. For example, Rakotobe et al. (Rakotobe, Marek et al. 1994) registered 2D, end-diastolic apical 2- and 4-chamber echo views of the heart with the closest (in orientation) sagittal or frontal 2D slice of SPECT image by matching myocardial borders, traced manually in ultrasound images. This method has many problems: 1) registration is limited to two anatomical planes and a single cardiac phase, 2) the two images may not show the same anatomical cross-section to begin; and 3) the myocardial border tracing (manual or automatic) could be inaccurate. Although not involving ultrasound modality, Faber et al. (Faber, McColl et al. 1991) performed temporal and spatial (in 3D) registration of cardiac SPECT and MR images by matching LV endocardium. A potential problem with this, or any segmentation-based approach, is that the myocardial borders may not appear at the same location in images from different modalities. Savi et al. (Savi, Gilardi et al. 1995) attempted registration of many combinations of cardiac modalities, including echo and PET. A geometric transformation was applied to the 3D PET image so that the user-selected coplanar anatomic landmarks (papillary muscles and inferior junction of right ventricle) in the PET image corresponded with their counterparts in the 2D ultrasound image. This method also suffers from the inaccuracies of segmentation of
poorly defined landmarks and the dimensionality mismatch between the two types of images.

3.4 Contribution of the current work

As observed from the above discussion, in addition to the availability of RT-3DE, development of advanced image processing algorithms is also important to achieve the overall goal of improving diagnosis of CAD through (1) reducing subjectivity of diagnosis, especially in stress echo, and (2) achieving meaningful fusion of RT-3DE echo and SPECT images for a “true” multimodality diagnostic approach. Accordingly, this dissertation reports development of techniques for enabling two novel cardiac stress testing procedures (1) a fully automatic quantitative 3D-SE procedure, and (2) a fully automatic quantitative multimodality stress testing approach utilizing RT-3DE and SPECT. In order to achieve these objectives, the current research builds on the prior development performed within the research group for registration of pre- and post stress RT-3DE images (Shekhar, Zagrodsky et al. 2004), basic algorithm development for interactive visualization of RT-3DE data (Shekhar and Zagrodsky 2003) and initial development of endocardial segmentation in RT-3DE (Zagrodsky, Walimbe et al. 2005), and combines these algorithms with newly developed algorithms for LV myocardial segmentation and elastic image registration. The next two chapters describe in detail the development of the technical capabilities for enabling the novel stress testing procedures and also the preliminary validation of feasibility and clinical effectiveness of the novel techniques.
## 3.5 Tables

<table>
<thead>
<tr>
<th></th>
<th><strong>2D Echo</strong></th>
<th><strong>3D Echo</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Image quality</strong></td>
<td>Better than 3D</td>
<td>Improving rapidly</td>
</tr>
<tr>
<td><strong>Image data</strong></td>
<td>Incomplete – 3-4 standard cross-sectional views</td>
<td>Complete – True volumetric information</td>
</tr>
<tr>
<td><strong>Ease of acquisition</strong></td>
<td>Challenging - Separate acquisitions from multiple probe locations/orientations</td>
<td>Convenient - Complete image data acquired from single probe location</td>
</tr>
<tr>
<td><strong>Post-Stress imaging</strong></td>
<td>Image data corresponds to different stress levels</td>
<td>All image data indicated unique stress level, closer to peak stress</td>
</tr>
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Table 3.1 Comparison between use of 2DE and RT-3DE for stress echo procedure

<table>
<thead>
<tr>
<th>Test</th>
<th><strong>Senior study</strong></th>
<th><strong>Slavich study</strong></th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>Stress SPECT</td>
<td>95</td>
<td>71</td>
</tr>
<tr>
<td>Stress Echo</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>Combined</td>
<td>98</td>
<td>71</td>
</tr>
</tbody>
</table>

Table 3.2 Sensitivity and specificity of individual and combined tests reported for prior echo-SPECT studies.
3.6 Figures

Figure 3.1 Comparison of image quality: First-generation Volumetrics scanner (left panel) versus latest-generation iE33 scanner (right panel)
Figure 3.2 Decision-making logic for combined diagnosis from stress echo and stress SPECT; (a) and (b) shows logic in prior studies combining separate diagnoses of stress echo and stress SPECT; (c) indicates improvements with the current multimodality procedure that makes diagnosis based on “fused” images.
CHAPTER 4

INTERACTIVE, QUANTITATIVE 3D STRESS ECHO

This chapter discusses development of an interactive, quantitative 3D-SE approach for improved diagnosis of wall motion abnormalities with underlying CAD. Previously reported algorithms for interactive ‘any-plane’ visualization and registration of pre- and post-stress RT-3DE are summarized. Next, a novel segmentation algorithm is described that for the first time allows accurate and fully automatic delineation of LV myocardium (endocardium and epicardium) in RT-3DE image sequences. A convenient user-interface allows interactive and quantitative interpretation of images following completion of all the image processing operations. Finally, a small clinical study is presented for demonstrating the feasibility of the approach and providing a preliminary evaluation of the clinical effectiveness of the novel approach.

4.1 Overview of proposed quantitative 3D-SE procedure

As mentioned in the previous chapter (section 3.2.3), lack of interactive, quantitative image analysis methodologies for the diagnosis has been a limitation of prior studies investigating 3D-SE, thus failing to utilize the inherent advantages of RT-3DE. The
benefits to stress echo from the technological advances of RT-3DE imaging can be fully realized by providing tools for convenient interactive visualization and true 3D quantitative analysis of RT-3DE images, thus realizing their potential to improve the sensitivity, specificity, and accuracy of stress echo with largely reduced interobserver/interinstitution variability in diagnosis. Figure 4.1 shows a flowchart of the proposed interactive, quantitative 3D-SE procedure that utilizes, for the first time, interactive visualization along with fully automatic tools for accurate pre-/post-stress image alignment (registration) and automatic LV myocardial segmentation and quantitative analysis (structural and functional parameters) for diagnosis of wall motion abnormalities with underlying CAD. The clinical stress protocol, together with the RT-3DE imaging protocol, produce pre- and post-stress echo image sequences. The exact number of frames in the sequences depends on the patient heart rate and the rate of echo image acquisition. However, since post-stress heart rate is greater than the pre-stress rate, the number of frames covering a complete cardiac cycle is less in post-stress sequence than pre-stress sequence. The current work contributes the development of new and compilation of existing image processing algorithms that are used to process the RT-3DE image sequences before the physician performs diagnosis based on the interrogation of these images. A comprehensive and convenient user-interface has been developed that enables the physician to analyze the images interactively and with the aid of quantitative LV wall motion information. The following paragraphs discuss the existing and newly developed algorithms and features comprising the interactive, quantitative 3D-SE approach.
4.2 Summary of existing visualization and registration algorithms

4.2.1 Interactive, real-time visualization

‘Interactive’ and ‘real-time’ are two vital features for any visualization scheme designed for RT-3DE. Interactive nature of the visualization scheme is necessary so that the entire 3D image information is conveniently available through dynamic manipulation of the region being visualized. With real-time visualization, it is possible to assess the time-varying cross-sectional views (interactively selected at the anatomical location/orientation) at the original frame rate of image acquisition, usually 15-25 frames per second (fps). With the vast amount of image data in RT-3DE, a CPU-only implementation cannot meet the computational demands of such a dynamic interactive visualization. The current work utilizes a previously reported algorithm that includes custom data bricking and caching techniques (Shekhar and Zagrodsky 2003), utilizing the 3D texture memory in modern graphics boards available with most currently available PCs. For the current 3D-SE procedure, this visualization algorithm has been the basis to achieve dynamic, interactive reformatting of aligned pre- and post-stress 3D image sequences, which facilitates comprehensive spatial interrogation of 3D image sequences in real-time (Figure 4.12).

4.2.2 Pre- and post-stress image registration

For 3D-SE it is vital to account for the coordinate system mismatch between pre- and post-stress RT-3DE images resulting from probe placement differences and patient movement between the two scans. The current work utilizes a fully automatic mutual information (MI)-based rigid and nonrigid registration algorithm for RT-3DE images
(Shekhar and Zagrodsky 2002), previously reported and validated for registration of pre-
and post-stress RT-3DE images for stress echo (Shekhar, Zagrodsky et al. 2004). Figure 4.2 shows a schematic of the registration scheme. Temporal alignment, which is the first step of the registration process, helps in creating pre- and post-stress image pairs belonging to the same cardiac phase. A piecewise linear interpolation scheme is implemented to account for different number of pre- and post-stress images/frames in the cardiac cycle as well as unequal changes in duration of systole and diastole from pre- to post-stress. Next, for the phase-correlated pre- and post-stress image pairs, the two-step spatial registration algorithm ensures that coordinate system mismatch between the images is removed, while preserving stress-induced changes. Following spatial alignment of the phase-matched pre- and post-stress images, it is possible to navigate through anatomically equivalent pre- and post-stress views to accurately identify development of new or worsening LV wall motion abnormalities.

4.3 Development and validation of fully automatic algorithm for segmentation of LV myocardium

The availability of true volumetric image data from the left ventricle over the entire cardiac cycle from RT-3DE imaging makes it feasible to perform accurate quantitative analysis of LV structure and function. With RT-3DE, it is possible to accurately calculate parameters like wall thickness and wall strain (for LV structure), and LV volume, ejection fraction and 3D wall-motion (for LV function), without making the geometric assumptions necessary for a 2DE-based quantitative analysis. The quantitative analysis is
particularly useful from the standpoint of more accurate and objective diagnosis of various cardiovascular diseases as well as for evaluating the myocardial recovery following procedures like cardiac resynchronization therapy (CRT). Accurate true 3D segmentation of complete LV myocardium (both endocardial and epicardial borders) over the entire cardiac cycle is a vital image-processing task that needs to be accomplished before the accurate evaluation of the above-mentioned parameters for the left ventricle is possible. Manual segmentation of the endo- and epicardial surfaces in RT-3DE is very tedious due to the huge amount of image data (typically few hundred megabytes) involved. Moreover a method based on extensive manual interaction remains subjective and susceptible to inter-observer variability. Thus, an accurate, robust and automatic tool for segmentation of complete LV myocardium is absolutely necessary for improving clinical utility of RT-3DE. This section describes an algorithm developed as part of the current work for implementing fully automatic segmentation of the complete LV myocardium in RT-3DE, through simultaneous endo- and epicardium segmentation controlled by mesh-interaction forces. Two manuscripts describing the development of this segmentation algorithm have been published (Zagrodsky, Walimbe et al. 2005; Walimbe, Zagrodsky et al. 2006).

An overview of segmentation techniques for echo data can be found in (Bosch, van Burken et al. 1998). Recent notable solutions for segmentation of 2D echo have involved statistical shape models (Jacob, Noble et al. 2002) and active appearance models (Bosch, Mitchell et al. 2002). Corsi et al. (Corsi, Saracino et al. 2002) have reported segmentation of 3D echocardiographic images using level set techniques, whereas Papademetris et al.
(Papademetris, Sinusas et al. 2002) achieved segmentation of the LV in 3D by performing a series of 2D segmentations using active contours. Gerard et al. (Gerard, Billon et al. 2002) have reported integration of 3D deformable models (DMs) and a statistical heart motion model for segmentation of the ventricular cavity. However, all these methods require varying degrees of manual intervention to initialize segmentation (either for a single frame (Gerard, Billon et al. 2002) or for each frame of the cardiac sequence (Corsi, Saracino et al. 2002; Papademetris, Sinusas et al. 2002)).

The two most important distinctions of the methodology proposed in this dissertation are as follows: (1) segmentation is performed for full LV myocardium (endocardium + epicardium), compared to the endocardium-only approaches proposed previously, and (2) the method proposed here is fully automatic and does not require any manual intervention for initialization, thus allowing its seamless integration in clinical workflow.

4.3.1 Deformable model (DM)-based segmentation

DM-based segmentation of medical images is by far the most reliable and robust approach to image segmentation. DM-based segmentation starts with placing a template of the expected shape in the vicinity of the true borders. A second step, called energy minimization step, then refines the shape template appropriately under image-derived and shape integrity preserving constraints to make it snap to the true borders. DM-based segmentation is especially suitable for ultrasound images as they are robust to intensity dropouts and noise. However, initial placement of the DM is a challenge with this approach, and in previously reported algorithms this process remains mostly manual or
semi-automatic at best. The segmentation algorithm described here involves a DM-based approach for segmentation of LV myocardium in RT-3DE sequences (Zagrodsky, Walimbe et al. 2005; Walimbe, Zagrodsky et al. 2006), where the problem of initial placement of the DM template is tackled through a novel approach involving registration of the image being segmented with a “voxel + wiremesh” template. Registration-assisted initialization, a novelty of the segmentation algorithm, allows for the possibility of complete automation of the segmentation procedure. Figure 4.3 provides a flowchart of the segmentation algorithm. Following paragraphs contain details of the segmentation algorithm.

4.3.2 Dual wiremesh template

The algorithm employs a “voxel + wiremesh” template, which is essentially a RT-3DE volumetric image with the corresponding 3D wiremesh model for the LV myocardium. A ‘dual wiremesh’ template is used for the segmentation algorithm, and consists of separate 3D wiremeshes for endocardium and epicardium traced by an expert on the ‘voxel’ template, which is an end-diastolic volumetric image selected from a healthy subject (Figure 4.4). As shown in Figure 4.4, the epicardium wiremesh is considered to be a scaled version of the endocardium wiremesh. The actual relationship might not correspond to exact scaling, but the model represents only the initialization phase, and hence this simplistic assumption is acceptable. The endocardium and epicardium wiremeshes are joined at the base of the LV, in the mitral valve region. Initialization of the wiremesh template is performed through automated MI-based registration of the image to be segmented with the voxel template. The resulting transformation is then
applied to the dual wiremesh template, thus initializing them close to the respective final solutions in the image to be segmented. As a trade-off between complexity and robustness, an eight-parameter transformation model (three translation, three rotation and two scaling parameters along long and short axes) has been employed for registration.

4.3.3 Mesh refinement

As outlined in Figure 4.3, the intermediate solution obtained using the registration-assisted template initialization is further refined iteratively using energy minimization. Energy minimization step is an iterative procedure involving balancing of mesh-derived internal forces that maintain the overall LV shape and image-derived external (gradient vector flow-based) forces that drive the shape template (or the wiremesh) toward edges or image gradients. Edge detection followed by a gradient operator is used to produce the vector field that gives rise to the external forces. In the current work a 3D extension of the Sobel edge detector (Liou and Jain 1991) is used to clamp the edge intensities to lessen the amplitude of very strong edges and to remove very weak edges caused by noise. Next, the segmentation algorithm employs a 3D extension of the generalized gradient vector field (GGVF) algorithm developed by Xu and Prince (Xu and Prince 1998; Xu and Prince 1998) to iteratively grow the external force field based on the result of edge detection. See Appendix A for a brief summary of the GGVF algorithm. An extension of the Harvard Mesh Library (Gu) is used for creating and handling 3D triangular wiremeshes. The internal energy in a DM formulation generally comprises two kinds of forces: distance-preserving and curvature-preserving. The distance-preserving forces ensure that the spacing between neighboring vertices (nodes) of the wiremesh
remains within pre-defined limits. A spring-like model is employed to prevent excessive stretching and shrinking of edges. The curvature-preserving internal force uses a measure of local surface smoothness called “spike length”, and ensures overall smoothness of the mesh by preventing sharp spikes at mesh vertices/nodes. Once a frame in a sequence is segmented, the final shape is propagated to the next frame as the starting template and energy minimization step is performed (Figure 4.5).

4.3.4 Challenges in detecting epicardial surface

Theoretically, following initialization, mesh refinement can be implemented separately and identically for endocardium and epicardium templates. However, the DM refinement process for epicardium segmentation is more challenging than that for the endocardium. For refinement of epicardial DM after initialization, the mesh-derived forces can be derived without any problems; however, the reliability of the image intensity-based external forces calculated is questionable. Often the epicardial features are represented by lower intensity differences compared to the endocardial features due to the lower acoustic density differences at the tissue-tissue interfaces at the epicardial surface compared to the blood-tissue interface at the endocardial surface. Besides, if size of left ventricle is large, parts of LV myocardium do not fit within the field of view of the ultrasound imaging pyramid and hence are not imaged. Also, when the acquisition is from the apical view, the apical cap of the myocardium is often hidden in the high intensity artifact at the point of incidence of ultrasound pulses. This artifact predominantly affects the epicardial surface at the apex. Figure 4.6 illustrates the commonly described artifacts in images that are discussed above.
To summarize, the reasons for the lack of robustness of image intensity-derived forces for epicardium refinement include (1) frequent intensity dropouts near epicardium, (2) apical intensity artifacts, (3) incomplete image acquisition of LV wall, and (4) difficulty in correctly identifying epicardial border near opening of aorta. Examples of such artifacts are illustrated in Figure 4.6 (arrows point to regions of intensity artifacts). Due to these types of artifacts, the independent detection of epicardium is challenging. Due to the dominance of the endocardial features in the region of interest for segmentation, the DM template for epicardium has a tendency to attach itself to the endocardial surface if refined independently after initialization. Figure 4.7 shows an example of epicardial segmentation where mesh refinement was implemented separately for endo- and epicardial templates. As seen in the Figure 4.7, there is a disagreement between an expert’s estimation of epicardial border and the algorithm-determined border, especially in the apical region of the LV, if independent epicardium segmentation is attempted. As expected, this disagreement is more significant in regions of artifacts pointed to by the arrows in Figure 4.7.

4.3.5 Endo-epicardium mesh interaction force

To overcome the challenges in epicardium detection and make the segmentation more robust to intensity artifacts, the current algorithm utilizes a priori knowledge about the relative position of the endo- and epicardial wiremeshes to introduce another force called the mesh interaction force, $I_{x,y,z}$, that acts on each vertex at every iteration of the mesh refinement process, in addition to the internal mesh-derived forces and external image
intensity-derived forces. During the iterative mesh refinement procedure, the average separation between the endo- and epicardial wiremeshes is monitored at every iteration. At every vertex, the mesh separation is calculated as the perpendicular distance between the vertex and the endo-/epicardium. The average separation is then calculated by averaging over all the points of the dual wiremesh. If the mesh separation at any vertex falls beyond a predefined tolerance band about the average mesh separation calculated at every iteration, then a proportional interaction force acts on that vertex so as to oppose the motion of the vertex under the influence of other forces at that iteration.

Figure 4.8 shows a characteristic plot of the interaction force. From Figure 4.8 it is clear that as long as the mesh separation measured at any vertex stays within the predefined tolerance zone around ‘$Da$’, the magnitude of $I_{x,y,z}$ stays zero. The tolerance band is set conservatively at ±50% of average separation ($Da$) calculated between the two wiremeshes, but this band can be modified in further studies as LV wall thickness variation data becomes available from a larger sample of images. The value of the average separation ($Da$) between the two wiremeshes is not hardcoded to any specific value, but rather calculated at every iteration of the mesh refinement process. By constantly monitoring and updating the value of average separation ($Da$), the mesh interaction force is adaptively modulated according to the myocardial thickness as the dual wiremesh iteratively converges to the actual solution for every individual case (healthy/diseased).
The maximum possible magnitude of the mesh interaction force, $I_{\text{max}}$, at a vertex for a given iteration is obtained by normalizing to the magnitude of the external GGVF-derived force acting on the vertex at that iteration. By using this approach, it can be ensured that if the mesh separation at a particular vertex falls outside the tolerance band at that particular iteration, the effect of the external GGVF/image intensity-derived force at that vertex at particular iteration is proportionally nullified by the mesh interaction force. In such a scenario, the vertex moves only passively under the influence of the mesh-derived internal forces, which are affected by the movement of the other neighboring vertices, and without the influence of external image-derived forces, which are likely affected by intensity artifacts. In this sense, the mesh interaction force is more like a damping factor (and not a proactive force in itself) that modulates the external image intensity-derived force according to the relative mesh separation. The mesh interaction force thus ensures that the relative orientation of endo- and epicardial meshes is retained and the LV myocardial thickness is maintained within meaningful limits and helps in avoiding anatomically anomalous results similar to that illustrated in Figure 4.7.

4.3.6 Dual mesh refinement involving mesh interaction force

With the introduction of mesh interaction forces, the dual wiremesh is refined iteratively under the influence of the following forces: 1) the distance-preserving internal forces (summed up for each specific vertex from all the adjacent half-edges), (2) the GGVF-derived external force, (3) mesh interaction forces and (4) curvature-preserving force for smoothing the spikes at vertices. At each iteration, the resultant sum of forces is applied to each corresponding vertex, and the locations of all vertices are then simultaneously
refreshed. The curvature-preserving operation of spike smoothing follows the change of location of all vertices, thus completing the iteration. The part of the DM that lies along the base of the LV, i.e. the mitral valve region, is the ‘passive’ part, where no forces act on the DM. We have adopted this approach in order to prevent the position of the mitral valve leaflets from erroneously affecting mesh refinement. Similarly, due to the high intensity artifacts near the apical epicardial surface, the influence of external GGVF-defined forces for epicardial mesh is reduced in apical region. By propagating the results of each frame over each subsequent frame for initialization, followed by mesh refinement, the final endo-epicardial meshes for the entire cardiac cycle are obtained.

4.3.7 Validation of segmentation accuracy

Materials and methods

Accuracy of segmentation has been validated in a small study involving five RT-3DE image sequences acquired in clinical settings using the SONOS 7500 scanner manufactured by Philips Medical Systems (Andover, MA), with 10 to 22 frames per data set depending on the subject heart rate at time of imaging. All five data sets were acquired from the apical direction, i.e. the apex of the ultrasound pyramid was near the apex of the left ventricle. The images thus acquired included the left ventricle almost entirely and the right ventricle and left and right atria partially.

The segmentation algorithm was validated by comparing its results with a set of planar contours traced by a trained professional expert from the ‘Echo Core Lab’ in two frames (diastolic and systolic) selected from each of the five data sets. For each frame, manual
contours were drawn on a set of reformatted planar views. A predetermined set of six planes forming a fan with 30 degrees of angular separation between adjacent planes was used. The intersections of the segmented wiremesh with the six reformatted views produced the corresponding algorithm-generated contours, which were compared with expert-traced contours. The mismatch between the automatically determined myocardial contours and the corresponding six expert contours for a given frame was captured by root mean square (rms) distance, which averages the absolute radial differences between the automatic and manual contours

$$\text{diff}_{\text{rms}} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (a_i - b_i)^2}.$$ 

A comparison was also performed between the clinically significant LV parameters (volume and myocardial thickness) calculated using the algorithm-determined and expert-determined segmentation of the LV myocardium in the five test cases.

**Results**

Segmentation was successfully implemented for all image sets using the algorithm described above. Standard apical four-chamber and short-axis views with algorithm-generated endo- and epicardial borders superimposed for two separate phases of the cardiac cycle in a typical case are shown in Figure 4.9.

Table 4.1 reports segmentation accuracy for each of the five subjects in terms of rms distance between the automatic and expert-traced contours. The algorithm-expert variability presented in Table 4.1 is of the same order as the intra-expert variability of 2.6 mm (Zagrodsky, Walimbe et al. 2005) and inter-expert variability of 3.6 mm (calculated
based on manual endocardial border tracing by multiple experts) in endocardial contour tracing. Figure 4.10 shows a typical example for visual comparison of the algorithm-determined and expert-drawn endo- and epicardial contours. The screenshots show the expert-traced contour in dotted line and the cross-section of the algorithm-generated wiremesh in solid line. An overall agreement between the corresponding automatic and expert-traced contours is evident; any mismatch led to the variability presented in Table 4.2.

Table 4.2 provides a comparison between the clinical parameters calculated using the algorithm-determined and expert-determined segmentation of the LV myocardium. The average myocardial thickness was calculated from the planar views that were used for comparison between the algorithm-determined and expert-traced contours presented in Table 4.1. The expert-algorithm variability in myocardial thickness for each case in Table 4.2 is of the order of 10% of the corresponding value of expert-calculated myocardial thickness. Table 4.2 also provides the absolute difference between LV volumes calculated using our algorithm and by the expert using the TomTec software (TomTec Imaging Systems, Munich, Germany) for the end-diastolic and systolic frames, and also the absolute difference in ejection fraction. For RT-3DE, an 8.3% inter-observer variability and a 3.7% intra-observer variability has been reported in LV EF measurement (Angelini, Laine et al. 2001; Takuma, Ota et al. 2001). Comparison with the validation results summarized in Table 4.2 suggests the potential of the current segmentation algorithm to provide clinically acceptable accuracy for segmentation of LV myocardium and evaluation of clinical LV parameters.
To analyze the effectiveness of the mesh interaction forces for accurate myocardial segmentation, the mesh refinement step was repeated for all cases by disabling the mesh interaction force. Table 4.3 summarizes the differences between the automatic and expert-traced contours in the absence of mesh interaction forces. The t-test analysis indicates statistically significant difference between the two approaches for epicardium contours (4 of 5 cases), but no significant difference for the endocardium contours. The results suggest that the mesh interaction force is critical for epicardium segmentation, but not so much for endocardium segmentation, which is expected because intensity dropout artifacts are more common near the epicardial surface than the endocardial surface.

4.4 Global and regional LV quantitative analysis

Once the segmentation of LV myocardium is achieved, it is possible to divide the myocardial mesh for each frame into 16/17 segments for local measurement and regional analysis. The subdivision information is encoded in the wiremesh template used for segmentation. Using a priori information based on the standard American Society of Echocardiography (ASE)-recommended LV subdivision scheme (Cerqueira, Weissman et al. 2002), each vertex of the original wiremesh template was manually tagged with the LV wall subdivision it belongs to. As mentioned earlier, during segmentation of the cardiac sequence, wiremesh for each frame is initialized by propagation of the result of segmentation of the preceding frame. The vertices of the wiremesh retain their tag and accompanying information during the propagation of results over successive frames. The initialized wiremesh for each frame is then independently refined in 3D spatial
coordinates. Upon completion of refinement stage of the segmentation, vertices with the same tag are joined to recreate the LV subdivisions. By retaining segment tag information during propagation of results over successive frames, spatio-temporal continuity is retained for individual segments over the entire cardiac cycle. Further, since the individual tagged vertices of the wiremesh have freedom to move in the 3D spatial domain during refinement under spatial constraints imposed by forces ensuring mesh integrity, the changes in shape, size and orientation of individual segments due to scaling and gradual torsional motion of the left ventricle are inherently incorporated into sequence of wiremeshes representing the final segmentation over the cardiac cycle. An example of the endocardial surface subdivided into 16 segments over the complete cardiac cycle is shown in Figure 4.11.

Global LV functional quantitative measures, such as volume curves and ejection fraction can be evaluated directly from the meshes representing the segmented LV myocardium. Once the individual LV segments are identified in all rest and stress frames, regional quantification of LV parameters is also possible. The 3D segmental excursion is computed by measuring the net displacement of the center of the segment over the cardiac cycle. The per-segment wall thickness is computed by averaging distance between its endo- and epicardial surfaces. Percent wall thickening is then calculated as $100 \times \frac{(\text{thickness}_{\text{diasole}} - \text{thickness}_{\text{diastole}})}{\text{thickness}_{\text{diasole}}}$. Area of each segment is calculated by summing over the area of all triangular faces of the wiremesh belonging to that segment. Segmental fractional area change is then calculated as $100 \times \frac{(\text{area}_{\text{diasole}} - \text{area}_{\text{ystole}})}{\text{area}_{\text{diasole}}}$. Center of the left ventricle is identified in each frame as the center of the LV endocardial
mesh, and all parameters are calculated with reference to this point. Thus, successful myocardial segmentation allows accurate quantitative analysis of global and local structure and function of the left ventricle by calculation of parameters like wall thickness/thickening and fractional area change (for LV structure), and LV volume, ejection fraction and 3D wall-motion (for LV function).

4.5 Interactive, quantitative 3D-SE analysis software

After image acquisition, the pre- and post-stress image sequences can be registered and segmented, and the per-segment parameters can be calculated using the algorithms described above. With no manual steps, all these pre-processing tasks can be performed immediately after acquisition and before actual diagnosis through batch processing at a central workstation. It is also equally important to ensure that the images and results of quantitative analysis are made conveniently and readily available to the physician during diagnosis, so that the 3D-SE procedure remains efficient and streamlined for easy integration into clinical workflow. Accordingly, as part of the current work, standard PC-based interactive image analysis software has been developed that allows the physicians to efficiently and effectively analyze the images for diagnosis of wall motion abnormalities and underlying CAD. The interactive software allows comprehensive spatial interrogation of 3D image sequences in real-time through simultaneous dynamic, interactive visualization of aligned pre- and post-stress 3D image sequences (Figure 4.12). Because the pre- and post-stress images are temporally and spatially aligned, pre- and post-stress cross-sectional views at identical anatomical locations are available by navigating through either of the images when viewed simultaneously. The results of
automatic segmentation are displayed as contours superimposed over each cross-sectional view being visualized and as a dynamic 3D rendering of the LV endo-/epicardial mesh for both pre- and post-stress images. Individual segmental areas can be selectively highlighted and viewed simultaneously on the image and the LV endocardial mesh for more focused regional wall motion analysis (Figure 4.12). Results of the quantitative evaluation of regional (segmental thickening, 3D excursion and fractional area change) and global LV measures (volume curves, end systolic volume, end diastolic volume and ejection fraction) are made available interactively along with the images (Figure 4.13). The ‘normal’ ranges (i.e. range of values expected in healthy individuals) for segmental LV structural and wall motion parameters (segmental thickening, 3D excursion and fractional area change) are also displayed along with the respective values of each measure in a given case. Further, the values of these parameters for the current case are color-coded to indicate if they fall within the ‘normal’ range or above/below the range.

4.6 Study design for evaluation of novel interactive, quantitative 3D-SE

This section discusses a small-scale clinical study that was conducted with the main focus of demonstrating the feasibility of the novel interactive and quantitative 3D-SE procedure. A preliminary evaluation of the hypothesis regarding the reduced subjectivity and interobserver variability in diagnosing wall motion abnormalities using the novel 3D-SE procedure was also performed. Finally, preliminary results of a small-scale comparison between the diagnostic performance of the novel 3D-SE and conventional clinical 2D-SE procedures for detection of wall motion abnormalities are presented.
4.6.1 Patient recruitment and data acquisition

Fifteen consecutive patients with known/suspected CAD and referred for clinically indicated exercise SE were recruited after informed consent as part of a study approved by the Institutional Review Board of the Cleveland Clinic. Subjects were recruited without regard to sex and race, provided they were younger than 75 years of age and physically capable of exercise. The clinically indicated conventional 2D-SE followed the supine bicycle exercise stress protocol using modern ultrasound systems equipped with harmonic imaging (GE Vivid, Milwaukee, WI; Philips 5500, Andover, MA; or Siemens Sequoia, Mountview, CA). Endpoint for the study or early termination was determined according to standard clinical procedures for SE. 2DE images were collected before stress and at the endpoint of the test (85% of target heart rate or chest pain reported by subject) according to routine clinical standards for conventional 2D-SE and were saved for clinical diagnosis per standard institutional procedures. For 2DE images, the LV wall motion analysis followed conventional clinical practice.

Pre- and post-stress RT-3DE imaging was performed immediately (within few seconds) after the corresponding 2DE images were acquired. RT-3DE images were acquired using the Volumetrics Medical Imaging RT-3D scanner (Volumetrics Inc., Durham, NC), which was operated at 2.5 MHz and collected pyramid-shaped images at 25 frames/s. A typical pre-stress sequence contained 20–25 frames; a post-stress sequence typically contained 10–15 frames.
4.6.2 Image pre-processing – registration, segmentation, and quantitative analysis

After acquisition, RT-3DE images were transferred on a CD-ROM from the scanner to the PC for processing. Frames belonging to one cardiac cycle (end-diastolic frame as starting point) were marked from the sequence and used for further processing and subsequent diagnosis. The main image processing steps as described in previous sections, including pre- and post-stress image registration, segmentation for all frames of the cardiac sequence, and calculation of LV parameters, were performed. For this evaluation study, RT-3DE was performed using a first-generation Volumetrics scanner, which has inferior image quality compared to the latest-generation scanners. Due to the suboptimal image quality (lower spatial resolution, poor definition of epicardial surface), only endocardial segmentation was determined sufficiently robust for these images, and so the quantitative analysis presented to the experts during diagnosis did not include LV wall thickness information. All the other pre-processing steps were performed automatically with no manual intervention, before the experts reviewed each case.

4.6.3 Wall motion analysis using interactive, quantitative 3D-SE software

Two experts, blinded to the identities of the patients, independently evaluated pre- and post-stress regional LV wall motion in RT-3DE for all 15 cases using interactive, quantitative 3D-SE software. The diagnosis of regional wall motion was based on the experts’ assessment of the images; however, this assessment was aided by the availability of novel visualization tools and automatically evaluated quantitative information about the global and regional LV wall motion information, a novelty of the current approach. The ‘normal’ range for segmental 3D excursion and fractional area change was estimated
from healthy patients in the current patient pool (Table 4.4). Information for wall thickness/thickening was not included, because only endocardium segmentation was performed. For each case, each expert rated the overall confidence level about available information (image quality, usefulness of the display tools, and the quantitative analysis data) and diagnosis using the 3D-SE procedure on a scale of 1–5 (5: excellent, 4: very good, 3: good; 2: fair; 1: poor). The rating was not based on any specific factor, instead on the overall level of the expert’s confidence about the diagnosis made for a specific case and was used predominantly to assess the clinical utility of the overall 3D-SE procedure (image data and analysis tools).

For each normal segment at rest, unchanged or increased contractility at stress was considered normal. Development of new or worsening of existing resting wall motion abnormality at stress was considered an abnormal response, and the segment was classified as diseased. Using the various features of the software (interactive navigation through temporally and spatially aligned pre- and post-stress images and results of segmentation and quantitative analysis), experts analyzed wall motion for the 15 cases and assigned individual segmental wall motion scores for each of the 16 segments, according to the standard ASE-recommended scheme: 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurism. Based on the experts’ scores, a wall motion score index (WMSI) was calculated for each of the three main coronary artery territories – LAD, RCA, and LCx – for each case using the following formula:

\[ \text{WMSI} = \frac{\text{sum of segmental scores}}{\text{number of segments belonging to the respective coronary territory}}. \]
The distribution of segments to different coronary territories was determined according to the ASE scheme (Cerqueira, Weissman et al. 2002). WMSI \( \geq 1.1 \) was considered as a criterion for a positive finding of wall motion abnormality for that myocardial region (Yao, Qureshi et al. 2003).

4.6.4 Statistical analysis

The coefficient of variation (\( \kappa \)) was calculated to evaluate agreement between various test results (normal/abnormal wall motion, wall motion scores, healthy/diseased segment) obtained by the two experts using novel 3D-SE procedures (\( \kappa \) of 0.81–1.0 = excellent agreement; 0.61–0.8 = very good agreement; 0.41–0.6 = good agreement; 0.21–0.4 = fair agreement; 0.0–0.2 = poor agreement). Linear regression analysis was performed to evaluate correlation between WMSI values calculated from segmental scores assigned by the two experts using 3D-SE.

4.6.5 Comparison with clinical 2D-SE

In addition to demonstrating the technical and clinical feasibility of a novel quantitative 3D-SE procedure, a preliminary evaluation of the diagnostic performance of the novel techniques compared with conventional clinical stress echo procedures was also performed. Segment-wise regional wall motion scores were obtained for 2D-SE from the clinical records and were used to calculate regional WMSI values. A case-by-case comparison was performed between conventional clinical 2D-SE and experts’ 3D-SE-based diagnoses of each coronary vascular territory as healthy/diseased. WMSI \( \geq 1.1 \) was considered a criterion for a positive diagnosis (diseased region). Comparison between
2D-SE and 3D-SE was performed using reference clinical records based on angiography (≥50% stenosis considered as abnormal/diseased).

4.7 Results: Clinical evaluation of novel 3D-SE procedure

During the exercise protocol, all individuals included in the study reached or exceeded 85% of maximum predicted heart rate, considered necessary for inducing diagnosable myocardial ischemia in the setting of mild to significant CAD. Pre- and post-stress RT-3DE imaging and implementation of fully automatic pre-processing steps (registration, endocardium segmentation, and quantitative analysis) was successful in all 15 cases. No cases were excluded for reasons of suboptimal image quality and/or failure to implement pre-processing steps for RT-3DE images. The automatic image pre-processing steps for each dataset (pre- and post-stress image sequences) took an average of 40 min. After the pre-processing steps, all 15 cases were successfully analyzed by the two experts using the novel quantitative 3D-SE software, with average reading times of 16 min for expert 1 and 14 min for expert 2. Expert 1 had an average confidence rating of 3.4 for the 3D-SE procedure, whereas expert 2 had a rating of 3.5. The average rating for the cases was found above the threshold rating of 3 for clinical utility ($p < 0.05$). Only one case was rated as poor (rating of 1 by both experts), with unsatisfactory visualization of five of the 16 LV segments as the main reason cited. This case was retained as part of the study, and both experts performed diagnosis of wall motion for this case, based predominantly on the software-determined endocardial contours. It should be noted that all segments for this case were correctly identified by both experts as having normal wall motion. These
results indicate the clinical feasibility of the novel 3D-SE procedure and its applicability even with suboptimal image data.

Experts analyzed and scored wall motion for all 16 segments for each case \((15 \times 16 = 240 \text{ segments})\), regardless of quality of visualization of individual segments and using quantitative information as required. Based on segmental scores, interexpert agreement for classification of segmental wall motion as normal/abnormal was 94.2\% at pre-stress and 95\% at peak stress \((\kappa = 0.78 \text{ and } 0.85, \text{ respectively})\). Comparing segment-wise wall motion scores, interexpert agreement was 91.7\% pre-stress and 90\% at peak stress \((\kappa = 0.7 \text{ and } 0.73, \text{ respectively})\). Regarding classification of individual segments as healthy/diseased based on analysis of wall motion at pre- and peak-stress, interexpert agreement was 95\% \((\kappa = 0.85)\). Table 4.5 shows interexpert agreement based on a segment-wise comparison for the entire LV myocardium and also separately for the three coronary territories. All \(\kappa\) values indicate good-to-excellent interobserver agreement and a definite improvement over values reported for conventional 2D-SE methods \((\kappa = 0.45–0.55)\) (Hoffmann, Marwick et al. 2002). Results of linear regression analysis shown in Figure 4.14 indicate excellent correlation between WMSI values calculated using scores assigned independently by the two experts using 3D-SE procedures. There is 100\% agreement between the two experts regarding classification of coronary territories as healthy/diseased based on respective WMSI values \((\text{diseased if } \text{WMSI} \geq 1.1)\).

For 11 cases with reference diagnoses available, six were diagnosed as diseased \((\text{at least one coronary vascular territory diagnosed as abnormal; } \text{WMSI} \geq 1.1)\) by both experts.
using 3D-SE, whereas only four of these were diagnosed as diseased according to clinical 2D-SE records. Table 4.6 summarizes comparison between 2D-SE and 3D-SE for these 11 cases. 3D-SE had no false negatives and only 3 false positives, whereas 2D-SE had one false positive and nine false negatives. Four cases, for which no reference diagnoses were available, were diagnosed as healthy with both 2D-SE and 3D-SE.

4.8 Discussion

A significant limitation of previous 3D-SE studies was that wall motion analysis in RT-3DE was based on limited information made available during diagnosis, in the form of either limited numbers of pre-extracted cross-sectional 3D views (Ahmad, Xie et al. 2001) or cropped anatomic rendered views (Matsumura, Hozumi et al. 2005), and thus did not encompass the entire available 3D information and nor fully utilize the inherent imaging superiority of RT-3DE. Also, the diagnosis was quite subjective and based solely on visual interpretation of images and wall motion abnormalities, involving no quantitative analysis. The actual diagnosis of wall motion abnormalities in the 3D-SE approach proposed in this dissertation is also based on the experts’ analysis of images. However, unlike previous approaches, experts have access to novel tools for simultaneous interactive visualization of anatomically matched pre- and post-stress images along with quantitatively evaluated information about global and regional LV function. These novel methodologies for interactive and quantitative analysis are the distinctive features of the current work, and have the potential to reduce subjectivity and improve interobserver variability in diagnosis of wall motion abnormalities using
conventional 2DE-based methods and previously reported RT-3DE–based methods (Collins, Hsieh et al. 1999; Ahmad, Xie et al. 2001; Matsumura, Hozumi et al. 2005).

The results from the preliminary clinical trial indicate the feasibility of implementing the pre-processing steps for clinically acquired pre- and post-stress RT-3DE. Moreover, it is important to note that since these steps are fully automatic, all the pre-processing tasks are performed prior to actual diagnosis through batch processing at a central workstation. In a clinical setting, these image pre-processing steps can be implemented automatically at a central processing unit immediately after image acquisition, with results stored and readily available to the physician during diagnosis. The results further indicate that the final 3D-SE diagnosis by experts using the interactive software is at least as efficient as the conventional 2D-SE diagnosis procedure, with the advantage of much more information available for diagnosis. Thus, the technical feasibility of the proposed methods, coupled with the feasibility of pre- and post-stress RT-3DE imaging in clinical settings, indicate potential for successful integration of quantitative 3D-SE into routine clinical workflow.

The preliminary evaluation of the effectiveness of interactive, quantitative 3D-SE methods provides promising results. The results presented in Table 4.5 and Figure 4.14 indicate excellent interexpert agreement in evaluation of overall as well as regional wall motion (normal/abnormal classification, wall motion scores, healthy/diseased classification, WMSI), superior to that reported for conventional 2D-SE–based methods (Hoffmann, Marwick et al. 2002) and 3D-SE–based subjective methods (Ahmad, Xie et
al. 2001; Matsumura, Hozumi et al. 2005). In addition to more complete image information available from RT-3DE, the higher interexpert agreement for the proposed 3D-SE procedure can be attributed to (1) interactive dynamic visualization of matching side-by-side pre- and post-stress images, made possible by our image registration and interactive visualization tools; and (2) availability of quantitative information about the LV parameters during diagnosis, calculated using novel automatic segmentation and quantitative analysis tools. For each regional LV parameter, the software also has the capability to compare the quantitative information the case being evaluated with ‘normal’ range computed for this parameter from healthy patients. In the current study, ‘normal’ values are estimated from few healthy patients included in the study. This comparison will eventually be more clinically useful and robust, when the ‘normal’ values have been ascertained from a larger patient pool in a subsequent large-scale clinical study. With a larger sample size, it might also be possible to analyze the intra-patient variation of the quantitative information for different regions of the LV myocardium, which is also likely to yield a clinically useful indicator of overall myocardial health. A statistical global wall motion model and be created through such a study. Overall, in addition to reducing variability in diagnosis, all these features also help to make the diagnosis highly sensitive and specific by allowing accurate identification of developing, less severe, and localized wall motion abnormalities. Initial indications are evident from the results presented in Table 4.6 for a preliminary 3D-SE versus 2D-SE comparison. The higher number of false-negative diagnoses with 2D-SE can be attributed to the fact that wall motion abnormalities were too localized to be visualized unambiguously in the limited number of standard cross-sectional views in 2D-SE diagnosis and/or that the wall motion
abnormalities were not severe enough to be diagnosed accurately using the subjective analysis methods of conventional 2D-SE. These difficulties are overcome by the availability of true volumetric image information from RT-3DE and interactive quantitative analysis tools, thus leading to more accurate identification of even minor localized wall motion abnormalities using 3D-SE.

Overall, the technical and clinical feasibility of the proposed interactive, quantitative 3D-SE procedure was successfully demonstrated. Though epicardium segmentation was not included in the preliminary evaluation study due to suboptimal image quality of the images from the first-generation Volumetrics scanner, the feasibility and accuracy of the segmentation algorithm itself has been successfully demonstrated using RT-3DE images from the more recent generation scanners (results in section 4.3.7). Also, the sample size of this evaluation study is too small to derive statistically significant conclusions about the improved diagnostic accuracy of new interactive, quantitative 3D-SE approach. Nevertheless, the results of the preliminary evaluation are promising and encourage investigation in a large clinical trial. Such a trial, using latest-generation RT-3DE scanners (e.g. Philips’ iE33, GE’s Vivid7 Dimension) would lead to a more definitive evaluation of the research hypothesis of improved diagnostic performance using interactive, quantitative 3D-SE.

4.9 Summary
This chapter discussed an enhanced stress echo approach incorporating the advances in imaging technology (RT-3DE) and novel visualization and advanced image processing
(registration, segmentation and quantitative analysis). The proposed techniques are efficient and suitable for integration in the clinical workflow. The results of a small-scale clinical evaluation study indicate that this combination of “RT-3DE + interactive, quantitative analysis” has a very good potential for accurate detection of wall motion abnormalities and improved diagnosis of ischemia with underlying CAD.

Chapter 5 discusses the work related to the multimodality cardiac stress testing approach, that builds on the development of interactive, quantitative 3D-SE through utilization of a novel elastic registration algorithm for correlation of anatomic information from RT-3DE with perfusion information from myocardial gated SPECT.
### 4.10 Tables

#### Table 4.1 RMS distance metric comparing algorithm-generated and expert-traced contours for all five subjects. Results are presented separately for end-diastolic and end-systolic frames and also averaged over both frames for each case.

<table>
<thead>
<tr>
<th>Case</th>
<th>RMS error for end-diastolic frame (mm)</th>
<th>RMS error for end-systolic frame (mm)</th>
<th>RMS error averaged for end-diastolic and end-systolic frames (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endocardium</td>
<td>Epicardium</td>
<td>Endocardium</td>
</tr>
<tr>
<td>1</td>
<td>3.5</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>2</td>
<td>4.7</td>
<td>4.9</td>
<td>4.8</td>
</tr>
<tr>
<td>3</td>
<td>2.9</td>
<td>4.4</td>
<td>3.6</td>
</tr>
<tr>
<td>4</td>
<td>4.4</td>
<td>3.6</td>
<td>3.7</td>
</tr>
<tr>
<td>5</td>
<td>3.8</td>
<td>3.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Avg.</td>
<td>3.86 ± 0.72</td>
<td>4.0 ± 0.63</td>
<td>3.9 ± 0.51</td>
</tr>
</tbody>
</table>

#### Table 4.2 Comparison of clinical LV parameters derived from results of algorithm-determined and expert-determined LV myocardial segmentation.

<table>
<thead>
<tr>
<th>Case</th>
<th>Absolute difference in myocardial thickness</th>
<th>Absolute difference in LV volumetric parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apical (mm)</td>
<td>Mid (mm)</td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>1.9</td>
<td>1.1</td>
</tr>
<tr>
<td>4</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Avg.</td>
<td>1.64 ± 0.56</td>
<td>1.3 ± 0.58</td>
</tr>
</tbody>
</table>
Table 4.3 RMS distance metric comparing expert-traced contours with algorithm-determined contours, with (+) and without (-) mesh interaction force. * p < 0.05.

<table>
<thead>
<tr>
<th>Case</th>
<th>RMS error for endocardial contours (mm)</th>
<th>RMS error for epicardial contours (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
<td>5.1</td>
</tr>
<tr>
<td>3</td>
<td>3.3</td>
<td>3.4</td>
</tr>
<tr>
<td>4</td>
<td>4.1</td>
<td>3.8</td>
</tr>
<tr>
<td>5</td>
<td>3.8</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Table 4.4 Normal range for LV parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
<th>Apical segments</th>
<th>Mid-ventricular segments</th>
<th>Basal segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D excursion</td>
<td></td>
<td>Pre-stress</td>
<td>Post-stress</td>
<td>Pre-stress</td>
</tr>
<tr>
<td>mm</td>
<td>6.4-11.3</td>
<td>8.7-14.3</td>
<td>7.5-12.3</td>
<td>9.4-14.8</td>
</tr>
<tr>
<td>Fractional area change</td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>%</td>
<td>38.9-59.2</td>
<td>40.1-59.4</td>
<td>39.3-59.4</td>
<td>39.9-60.3</td>
</tr>
</tbody>
</table>
## Inter-observer agreement and Kappa-value

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overall</th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification of wall motion as normal/abnormal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-stress</td>
<td>94.2 % (0.78)</td>
<td>97.0 % (0.86)</td>
<td>90.0 % (0.94)</td>
<td>91.1 % (0.78)</td>
</tr>
<tr>
<td>Peak stress</td>
<td>95.0 % (0.85)</td>
<td>96.3 % (0.86)</td>
<td>90.0 % (0.74)</td>
<td>97.8 % (0.95)</td>
</tr>
<tr>
<td><strong>Wall motion score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-stress</td>
<td>91.7 % (0.70)</td>
<td>94.8 % (0.76)</td>
<td>88.3 % (0.69)</td>
<td>86.7 % (0.60)</td>
</tr>
<tr>
<td>Peak stress</td>
<td>90.0 % (0.73)</td>
<td>91.1 % (0.67)</td>
<td>85.0 % (0.87)</td>
<td>93.3 % (0.65)</td>
</tr>
<tr>
<td><strong>Classification as healthy/diseased based on assessment of pre- and post-stress wall motion</strong></td>
<td>95.0 % (0.85)</td>
<td>96.3 % (0.86)</td>
<td>90.0 % (0.74)</td>
<td>97.8 % (0.95)</td>
</tr>
</tbody>
</table>

Table 4.5 Interexpert agreement in segmental wall motion analysis using novel 3D-SE methods: Results for all segments grouped according to coronary territories.

<table>
<thead>
<tr>
<th>Reference</th>
<th>2D-SE</th>
<th>3D-SE (Expert 1)</th>
<th>3D-SE (Expert 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Reference</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>-</td>
<td>1</td>
<td>18</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4.6 Diagnosis of coronary territories as healthy/diseased according to 2D-SE and 3D-SE: comparison with clinical reference.
Figure 4.1 Flowchart of proposed interactive, quantitative 3D-SE procedure
Figure 4.2 Temporal and spatial registration scheme. (A) Pre-stress image sequence. (B) Post-stress image sequence. Temporal registration produces multiple phase-matched image pairs. (C) Single phase-matched pre- and post-stress image pair before spatial registration. (D) Phase-matched pre- and post-stress image pair after spatial registration. In C and D, left panel is pre-stress image and right panel is post-stress image. Solid and dotted arrows in C and D indicate spatial misalignment in phase-matched pre- and post-stress images and removal of misalignment after automatic spatial registration.
Figure 4.3 Flowchart of segmentation algorithm for single frame.
Figure 4.4 “Voxel + dual wiremesh” model for myocardial segmentation. Planar contours extracted from dual wiremesh are displayed here in long- and short-axis views.

Figure 4.5 Segmentation of entire cardiac cycle. Final solution of a given frame is used as initial solution of subsequent frame.
Figure 4.6 The arrows in the image point towards commonly observed intensity artifacts that affect epicardium segmentation.

Figure 4.7 Independent epicardium segmentation for image in figure 4.4, using basic segmentation algorithm. Solid line: algorithm-determined epicardial contour; dotted line: expert-estimated epicardial contour.
Figure 4.8 Mesh interaction force, I, applied to the mesh vertices as a function of the perpendicular distance between meshes at the vertex of interest (D). ‘Da’ is average distance between meshes over the entire LV.
Figure 4.9 Typical results of automatic segmentation. Standard apical four-chamber and short-axis views superimposed with algorithm-generated endo- and epicardial borders are shown in figure. Top and bottom rows show two separate phases of the cardiac cycle in a typical case.
Figure 4.10 Comparison of algorithm-derived contour (solid) and expert-drawn contour (dotted). Left panel shows endocardial contours. Right panel shows epicardial contours.
Figure 4.11 Automatic segmentation scheme. (A) Contour indicates position of endocardial mesh template before initialization. (B) Contour indicates endocardial template after registration-assisted initialization with LV image template. (C) Contour indicates final result of endocardial segmentation obtained by internal and external force-based refinement of initialized template. D, E, and F show 3D rendering of endocardial mesh corresponding to A, B, and C, respectively. (G) Automatically segmented volumetric shapes at different phases of the cardiac cycle, obtained by registration-assisted segmentation of each frame as illustrated in A–F. Different colors differentiate the automatically identified segments of the left ventricle.
Figure 4.12 Main display panel of the interactive 3D-SE software with side-by-side display of pre- and post-stress images for diagnosis of stress-induced wall motion abnormalities. White contour overlaid on the endocardial mesh tracks position/orientation of corresponding user-selected 2D cross-sectional view displayed at top.
Figure 4.13 Quantitative analysis of LV function. (A) Segmental analysis window. Pre-calculated values of segmental 3D excursion and fractional area change are displayed for any user-selected segment. Also, wall motion scores can be assigned/reviewed using this panel. (B) Results of LV volume quantification. This panel displays overall and segmental LV volume curves. The value corresponding to the current frame is displayed at the top left of each curve and highlighted in white on the volume. Values for end-diastolic volume, end-systolic volume, and ejection-fraction are displayed at the top right of each curve. Both quantitative analysis panels can be launched simultaneously from the main display panel to allow the physician to simultaneously view the images and the corresponding quantitative values.
Figure 4.14 Linear regression analysis. Correlation between regional WMSI for 3D-SE analysis conducted independently by two experts. Excellent correlation is seen for all three coronary territories, indicating very good interexpert agreement.
CHAPTER 5

MULTIMODALITY CARDIAC STRESS TESTING

As mentioned in section 2.4, of the two most commonly prescribed ‘first-step’ noninvasive diagnostic procedures for detection of CAD, stress echo (looking at wall motion deterioration with stress, as a marker of ischemia), is more specific but less sensitive, whereas stress SPECT (looking at myocardial perfusion using labeled isotope) is more sensitive but less specific. One of the main motivations for the current research is the hypothesis that simultaneous improvement in sensitivity and specificity for diagnosis of CAD can be achieved with diagnosis based on accurately registered (i.e. temporally and spatially correlated) and subsequently fused complementary anatomical and perfusion information available from echo and SPECT respectively. Accordingly, continuing on the development of novel interactive, quantitative 3DSE described in CHAPTER 4, this chapter discusses all necessary advanced imaging methodologies to enable clinical implementation of the quantitative multimodality stress testing procedure. Registration techniques to recover temporal and spatial misalignments in pre- and post-stress RT-3DE and SPECT sequences form the most critical requisite for the success of the proposed technique and a significant novel contribution of the current work and will
be the *main focus* of the discussion. Finally, the chapter discusses a small clinical study to evaluate feasibility and effectiveness of the proposed multimodality procedure.

5.1 Schematic of proposed multimodality stress testing approach

Figure 5.1 shows a flowchart of the proposed interactive, quantitative multimodality stress testing procedure. Similar to the 3D-SE procedure outlined in Figure 4.1, the clinical stress protocol, together with the RT-3DE and SPECT imaging protocols, produce pre- and post-stress echo and SPECT image sequences, depicting LV anatomy and perfusion, respectively. The current work contributes the development of new algorithms and compilation of these new and existing image processing algorithms to process the RT-3DE and SPECT image sequences before the physician performs diagnosis based on the interrogation of the fused images. Successful registration, which involves development of a new elastic registration algorithm, would allow side-by-side display of the fused images, thus enabling the physician to analyze the stress-induced effects on myocardial wall-motion, thickness and perfusion simultaneously. Automatically evaluated quantitative information about LV anatomy and perfusion from segmentation of the correlated multimodality images would further aid the physician in making a more objective diagnosis. The 3D-SE image analysis software described in CHAPTER 4 is extended here to allow simultaneous display of fused RT-3DE and SPECT images along with the desired quantitative analysis parameters.

The registration scheme for aligning pre- and post-stress echo and SPECT sequences, which is the most important aspect of the current multimodality work, is discussed next.
The other image processing algorithms and the validation study are summarized after that.

5.2 Overall registration scheme for multimodality cardiac stress testing

5.2.1 Significance of RT-3DE for multimodality cardiac image registration

Multimodality cardiac registration, in general, has been rarely attempted and the few attempts so far have been preliminary at best (brief overview in section 3.3). Specifically, multimodality cardiac image registration involving echo and SPECT (as is the case here) has been particularly difficult, mainly because of the technical difficulties in a 2D-to-3D registration – echo has traditionally been 2D while SPECT (as well as other cardiac imaging modalities like MR, CT, PET) has been predominantly 3D. Besides, even if 2D-3D registration is successfully achieved, the correlation of complementary information (the biggest payoff from multimodality registration) is possible only for the 2D cross-sectional locations where 2DE data is available. However, the emergence of RT-3DE has made cardiac image registration problem involving echo, both more tractable as well as beneficial. With the availability of true real-time volumetric information about the beating heart from RT-3DE, it has now become feasible to automatically and routinely perform 3D-to-3D multimodality spatial registration involving echo and SPECT, for all phases of the cardiac cycle. Also, following registration, the availability of volumetric information from RT-3DE allows quantitative correlation of complementary information for the entire LV myocardium, and not just few 2D anatomical cross-sections. Accordingly, this dissertation takes advantage of the emergence of RT-3DE and focuses on developing a multimodality cardiac stress testing approach based on accurate
temporal and spatial registration of pre- and post-stress RT-3DE and myocardial perfusion SPECT sequences.

### 5.2.2 Transformations between pairs of image sequences

The overall registration problem is broken down into three separate tasks: (1) registration of pre- and post-stress RT-3DE sequences, (2) registration of pre-stress RT-3DE and pre-stress SPECT sequences, and (3) registration of post-stress RT-3DE and post-stress SPECT sequences (Figure 5.2). The overall strategy involves initial implementation of pre- and post-stress RT-3DE registration, as described previously in section 4.2.2. Following the same procedure as with interactive, quantitative 3D-SE approach, this registration would allow simultaneous visualization of matching anatomical locations in the pre- and post-stress images. Using results of separate registration of pre-stress RT-3DE and SPECT sequences and post-stress RT-3DE and SPECT sequences, the perfusion information from SPECT can be superimposed over the appropriate echo images. Computing the transformation T1 will be the goal of the first task; second and third tasks will compute transformations T2 and T3, respectively.

Computation of the transformation between any particular pair of sequences (T1, T2 or T3) involves determination of initial temporal alignment, followed by spatial registration of phase-matched image pairs. Temporal alignment is necessary because heart rates generally differ during the different acquisitions, leading to sequences generally having unequal number of frames. Temporal alignment, thus, creates cardiac phase-matched image pairs, a necessity before meaningful spatial registration can be performed. Spatial
misalignment is present among sequences primarily due to coordinate system mismatch, repositioning of the patient during different scans and stress-induced changes. Spatial registration helps in determining the transformations between images to bring them into geometric alignment. The temporal and spatial registration techniques employed in the current work are described next.

5.3 Temporal registration

In order to appreciate the need and challenges in temporal registration, it is important to understand the sequence of image acquisition and the accompanying changes in patient heart rate. Figure 5.3 shows the timeline of image acquisition and the corresponding variation in heart rate during the multimodality stress testing approach discussed here. All image acquisitions, except post-stress RT-3DE, are performed at the resting heart rate. Thus, post-stress RT-3DE sequence has fewer frames spanning a cardiac cycle than the pre-stress echo image sequence, because the heart rate is elevated whereas scanner’s frame rate remains fixed. Typically, a rest RT-3DE image sequence has 20-25 frames, whereas the post-stress RT-3DE has 10-15 frames. In contrast, both SPECT sequences are always gated to have 8 volumetric frames per cardiac cycle. When performing temporal registration, it is important to account for these differences in heart rate and number of frames per cardiac cycle in the echo and SPECT image sequences.

5.3.1 Pre- and post-stress RT-3DE sequences (T1)

Pre- and post-stress RT-3DE registration follows steps identical to those described in section 4.2.2 describing registration procedure for interactive, quantitative 3D-SE. The
temporal alignment is carried out using a piecewise linear function, as shown in Figure 5.4 (Shekhar, Zagrodsky et al. 2004), that compensates for disproportionate shrinking of the durations of systole and diastole when heart rate increases from resting to peak-stress state. Through temporal alignment each post-stress echo frame is matched to a pre-stress frame belonging to the nearest matching cardiac phase. Since pre- and post-stress images are displayed side-by-side (i.e. not fused), it is not necessary to interpolate existing post-stress frames to equalize the number of frames in the two sequences. Thus, temporal alignment creates as many image pairs as the number of frames in the post-stress sequence, such that optimal registration can be determined for the two sequences using the median transformation for all the phase-matched image pairs.

5.3.2 Pre-stress RT-3DE and SPECT sequences (T2)

When performing temporal alignment for pre-stress RT-3DE and SPECT image sequences, it is important to note that the heart rate is roughly the same between the two serially acquired sequences. The temporal alignment, therefore, uses a single linear function over systole + diastole, and for each RT-3DE frame, a SPECT frame is generated by linear interpolation between existing SPECT frames. Figure 5.5 shows the schematic for this temporal interpolation scheme, using which echo-SPECT image pairs equal to number of original pre-stress RT-3DE frames are formed. By using RT-3DE sequence with the highest number of frames/cardiac cycle as the reference, it is ensured that the sequence of phase-matched image pairs has the highest possible temporal resolution. Since SPECT images are highly averaged and have inherently lower spatial
resolution, the interpolation does not severely hamper the spatial resolution of the images, while providing higher/improved temporal resolution in the final interpolated sequence.

5.3.3 Post-stress RT-3DE and SPECT sequences (T3)

Figure 5.3 shows that post-stress RT-3DE and SPECT image sequences are collected during drastically different heart rates (post-stress echo at elevated heart rate, while post-stress SPECT at resting heart rate). Thus, temporal interpolation is performed using a combination of methods used for T1 and T2. A piecewise linear approach, similar to that for T2, is adopted to compensate for disproportionate shrinking of the durations of systole and diastole between resting and peak-stress states. Next, for each of the two durations (systole and diastole), scheme similar to that shown in Figure 5.5 is implemented to generate a SPECT frame for each echo frame, by temporal linear interpolation between existing SPECT frames. Finally, post-stress echo-SPECT image pairs equal to number of original post-stress RT-3DE frames are formed.

5.4 Geometric transformation model for spatial registration

Following the generation of phase-matched image-pairs for each of the pair of sequences being registered, the next step is to perform spatial registration. The current section contains discussion about transformation models used for spatial registration between the pairs of sequences shown in Figure 5.2.
5.4.1 Pre- and post-stress RT-3DE sequences (T1)

Spatial registration of pre- and post-stress RT-3DE is challenging because it entails correcting for the undesired coordinate system mismatch (due to different ultrasound probe locations and orientations between the two imaging sessions), while retaining the clinically significant stress-induced anatomical and functional changes. The procedure mentioned earlier in section 4.2.2 (used for interactive, quantitative 3D-SE) is also employed here. The process consists of initially registering the image pair using a 7-parameter (rigid-body + global scaling) transformation model, followed by removal of the global scaling factor, treating the center of the image as the origin of the coordinate system. The rigid-body component recovers the coordinate system-related misalignment, whereas the global scaling models the stress-induced spatial change. This algorithm, including a validation study involving 10 subjects (healthy/diseased), has been reported previously (Shekhar, Zagrodsky et al. 2004).

5.4.2 Pre-stress RT-3DE and SPECT (T2) and post-stress RT-3DE and SPECT (T3)

Various factors are responsible for spatial misalignments between respective echo and SPECT images: (1) Each image sequence is reconstructed in its own coordinate system; (2) patient positions are different in echo and SPECT acquisitions – patient lies supine for SPECT acquisition, whereas echo is acquired with patient in left lateral decubitus position; (3) in case of post-stress echo-SPECT alignment, the stress levels in the myocardium are different during echo and SPECT acquisition. As seen in Figure 5.3, echo image acquisition occurs immediately at peak stress. On the other hand, though
radioactive tracer injection for stress SPECT occurs at peak stress, the image acquisition happens about 30-40 minutes after peak-stress. Thus, stress SPECT represents perfusion information locked in the myocardium at peak stress, with the underlying anatomy corresponding to resting state. The three main factors outlined above lead to complex non-rigid misalignments between corresponding echo and SPECT images. The objective of echo-SPECT registration in the current work is to accurately overlay the perfusion infusion from SPECT onto the anatomical information available in echo images. Thus, it is necessary to perfectly align the image features seen in the two images for accurate correlation of the multimodality information, regardless of the state of the myocardium (healthy/diseased, resting/stress). Accordingly, a nonrigid/elastic model is used for defining transformations T2 and T3 between phase-matched RT-3DE and SPECT images.

5.5 Elastic registration between RT-3DE and SPECT (T2/T3): Possible approaches

Section 5.4.2 explained the rationale behind adopting an elastic (nonrigid) transformation model for morphing the SPECT images to match the anatomical information in the echo images. The anatomy and complex motion of the heart and the necessity to ensure practicality/clinical viability of the procedure impose special constraints on the possible registration approaches that can be employed for registration between RT-3DE and SPECT. This section discusses the choice of registration approach for determining the elastic transformation fields T2 and T3 for echo-SPECT registration.
5.5.1 Registration methods: Prospective (Vs) Retrospective

Image registration methods can be broadly classified as (1) prospective, and (2) retrospective methods. Prospective methods that rely on the use of external markers that are implanted near the anatomy of interest have limited applicability in cardiac imaging, mainly because they assume no movement of the underlying anatomy with respect to the external markers. This condition is impossible to be met in cardiac imaging, because the heart is nonrigid and also moves significantly within the chest cavity, thus rendering such prospective methods inappropriate.

Retrospective methods, on the other hand, do not require alterations to the way images are acquired clinically, and present a viable alternative in the case of deformable organs such as the heart, making them more suitable for clinical implementation in the current scenario. Retrospective registration methods are either segmentation-based or voxel similarity-based. Segmentation-based methods rely on the identification of matching internal landmarks (anatomic locations, curves and surfaces) and are limited by the accuracy, reliability and speed of segmentation. Besides, it is difficult, if not impossible, to simultaneously, reliably and accurately identify landmarks (points, contours and/or surfaces) in RT-3DE and cardiac SPECT images that could be used for registration. Additionally, the landmark identification, and hence the registration process, can be semi-automatic at best.

Voxel similarity-based approaches utilizing the complete voxel intensity information provide the best theoretical framework for RT-3DE and cardiac SPECT image
registration. The flexibility of using voxel similarity for image registration and its superior accuracy compared to the surface segmentation-based approach for multimodality registration (West, Fitzpatrick et al. 1999) has been recognized in the literature. Also, there is no theoretical limit on the nature of transformation (rigid or nonrigid) involved. Besides, a voxel similarity-based technique has the potential for full automation, making the clinical application more feasible.

5.5.2 Mutual information-based registration

Of all the voxel-similarity-based approaches, MI/normalized mutual information (NMI)-based approach (Maes, Collignon et al. 1997; Studholme, Hill et al. 1997; Studholme, Hill et al. 1999), in principle, is the most robust, accurate and flexible approach for echo-SPECT registration. Since the registration is based on correlation between intensity histograms and not on anatomic structures directly, a satisfactory solution can be obtained despite disparate nature of intensity profiles of echo and SPECT images. In various multimodality image registration studies comparing measures of voxel similarity, the MI measure has emerged as the most accurate and robust measure (Maes, Collignon et al. 1997; Studholme, Hill et al. 1997; Studholme, Hill et al. 1999). Feasibility and suitability of using MI for registration involving ultrasound images has also previously been demonstrated (Shekhar and Zagrodsky 2002; Shekhar, Zagrodsky et al. 2003; Shekhar, Zagrodsky et al. 2004). Thus, MI/NMI-based registration appears to be a theoretically feasible approach for the echo-SPECT registration problem tackled here.
5.6 Feasibility study for MI-based RT-3DE-SPECT registration

5.6.1 Materials and methods

Following the initial choice of MI-based approach for echo-SPECT registration, a pilot study was performed to evaluate the feasibility of the approach for actual clinically acquired RT-3DE and SPECT images. The study involved four subjects, for which MI-based registration was performed between gated MIBI SPECT and RT-3DE images (first-generation Volumetrics scanner) acquired in the resting state. Temporal registration was initially performed, as outlined in section 5.3.2. MI-based spatial registration was then performed between each temporally registered pair. Though elastic transformation model has been proposed for the actual registration, for sake of simplicity of the feasibility study, the basic rigid-body transformation model was employed. MI was calculated using the individual and joint probability density functions estimated from the mutual (joint) histogram for the two images. The mutual histograms were computed using the partial volume interpolation scheme, which, compared to nearest neighbor and trilinear interpolations schemes, has been reported to produce the least interpolation error for MI/NMI-based registration (Maes, Collignon et al. 1997; Tsao 2003). Optimal global and individual subvolume transformations were determined by searching for the global maximum of the full-image MI. A modified multifunction downhill simplex method (Zagrodsky, Shekhar et al. 2001) was used for iterative optimization of the similarity measure.
5.6.2 Results

Registration was successfully implemented for all cases. Figure 5.6 shows long-axis and short-axis views of the heart in end-diastolic images selected from the registered sequences. Correspondence of the location of the partially visualized right ventricle in SPECT (left panel), echo (right panel) and fused (central panel) images visually confirms the accuracy of the registration. Five experts, with experience in reading echo as well as SPECT images, evaluated results of the registration on a scale of 1 to 5, with a rating of 1 meaning poor registration and a rating of 5 meaning near perfect temporal as well as spatial registration. See Table 5.1 for detailed description of evaluation ratings. The overall average rating for the four registrations was 2.85.

Repeatability tests were performed to determine the robustness of the registration procedure in arriving at the same correct result for variable starting orientations, estimating the relative independence of the initial manual seeding on the convergence of the automated MI-based registration algorithm to the correct solution. Initial random misalignment and subsequent registration was performed 50 times for each pair of spatially aligned RT-3DE and SPECT images. Figure 5.7 shows a plot of initial versus residual misalignment. The registration was said to have converged to the correct solution if the residual misalignment was < 8 mm (accuracy better than the 8-10 mm resolution of the SPECT image). A plot of the percentage convergence rate against initial misalignment for RT-3DE and SPECT registrations is shown in Figure 5.8. Note that the convergence rate is close to 100% for initial misalignments up to 15 mm. The scatter plot shows a steady pattern of good recovery for initial misalignments up to 20 mm, with a
large number of registrations converging very close to the correct solution (residual misalignment <5 mm). The initial misalignment was classified as lying within the capture range if the convergence rate was higher than 90%. Using this classifying factor, the capture range was determined to be 26 mm (Figure 5.8).

Overall, these results indicate feasibility of using a MI/NMI-based approach for spatial registration between RT-3DE and cardiac SPECT (Note: MI and NMI are fundamentally identical similarity measures). The lower expert-assigned ratings were primarily due to poor endocardial definition in RT-3DE images – attributed to the quality of RT-3DE image acquisition rather than the registration procedure itself. The image quality of RT-3DE has improved drastically with the latest-generation scanners (e.g., iE33 from Philips, Andover, MA, which is being used for the main clinical study) and will continue to improve in the future. Thus, the low clinical rating for this preliminary study was not considered particularly discouraging. Considering the expected misalignment due to stress-related changes, heart motion and patient-position differences between RT-3DE and SPECT in the current application, the technical robustness of the MI-based registration and capture range of 26 mm was determined sufficient for the current clinical application. The detailed elastic registration scheme for pre- and post-stress RT-3DE and SPECT registration, as implemented for the multimodality cardiac stress testing procedure, is discussed next.
5.7 Elastic registration algorithm for registration of RT-3DE and SPECT

Sections 5.4.2 discussed the rationale behind adopting an elastic registration approach for spatial alignment of phase-matched RT-3DE and SPECT image pairs, whereas section 5.6 discussed a small study that demonstrated the feasibility of using MI/NMI as a similarity measure for echo-SPECT registration. The current section provides an overview of the overall elastic registration algorithm that was used to perform the spatial registration. The elastic registration uses a course-to-fine volume subdivision-based approach. Figure 5.9 shows a basic flowchart of the registration algorithm. This generic hierarchical volume subdivision-based elastic registration algorithm, developed as part of the current dissertation work, has been described in detail in (Shekhar, Walimbe et al. 2005; Walimbe and Shekhar 2005).

Since the objective of registration is to superimpose matching perfusion information from SPECT over anatomic information from echo, the echo image is treated as reference image and the SPECT image as the floating image that is morphed to match the reference image. For a pair of phase-matched echo (reference) and SPECT (floating) images, the registration algorithm initially recovers the global mismatch, followed by hierarchical refinement of the localized matching between the globally registered images. Global registration uses the six-parameter rigid-body transformation model and is based on maximization of NMI between the two images. Next, a hierarchical octree-based subdivision scheme is implemented. At each subdivision level, the SPECT image is registered with the individual subvolumes of the reference echo image, considered one at
a time. Volume subdivision and subvolume registration continue until the voxel count for
an individual subvolume remains above a predefined limit (experimentally determined to
be $16^3$ for echo-SPECT registration). Subvolume registration also uses a six-parameter
rigid-body transformation model. Initial seeding of the undivided floating image with
respect to each subvolume is given by the transformation obtained from registration
involving the floating SPECT image and the corresponding parent subvolume at the
previous level of subdivision. Figure 5.10 shows a schematic of the volume subdivision
and subvolume registration for a single hierarchical level. Subvolume registration is
based on maximization of NMI, and uses the prior registration information for all
remaining parts of the image, available from the previous hierarchical level. Subvolume
registration is constrained by the maximum allowable deformation, in order to maintain
image integrity by preventing individual subvolumes from drifting far off from their
starting positions at each hierarchical level.

After registration at the last hierarchical level, the transformations are assigned to centers
of the respective subvolumes. A unique transformation is determined for every voxel in
the reference echo image by performing tri-cubic interpolation between the subvolume
centers surrounding the voxel. The 3D translational component of the transformation is
interpolated separately as three scalars using a cubic interpolation scheme. Interpolation
of 3D rotation is performed in the quaternion (Hamilton 1844) domain, by converting the
rotational matrices into quaternions. Appendix B provides a basic overview of quaternion
algebra and mathematical definition of the different quaternion interpolation schemes.
For the current algorithm a spherical cubic interpolation for quaternions called squad
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(spherical and quadrangle) (Shoemake 1985; Shoemake 1987) is implemented to generate a smooth continuous deformation field from results of subvolume registration at the last hierarchical level. The interpolated curve obtained using \textit{squad} interpolation scheme as proposed by (Shoemake 1985; Shoemake 1987) has $C^1$ or tangential continuity. Use of the six-parameter rigid-body transformation model for subvolume registration and direct interpolation of the subvolume transformations for generation of smooth transformation field are unique features of this elastic registration algorithm. Using the transformation field, each grid point from the reference image space is mapped to find the matching location in the floating image space. The intensity at this location in floating SPECT image space is determined using a trilinear interpolation scheme and assigned to the original grid point in the reference image space, resulting in a continuous elastically transformed floating SPECT image that closely matches the reference echo image.

Figure 5.11 (top row) shows a fused image generated after rigid-body registration between a phase-matched RT-3DE and SPECT image pair. Fused image after elastic registration between same pair of images is shown in the bottom row of Figure 5.11 for comparison. It is clear after comparing the images that elastic registration generates fused images with visually better alignment than rigid-body registration, especially in the basal/septal region of the left ventricle.
5.7.1 Validation of registration algorithm

Quantitative validation of accuracy of elastic registration algorithm is difficult to achieve in echo-SPECT images, due to the lack of a gold standard and difficulty in accurate identification of homologous anatomical landmarks in both images simultaneously. However, due to the generic nature of the above-described algorithm, it was also used successfully in a different clinical application involving registration of whole-body CT and PET images from either stand-alone or combined PET/CT scanners, wherein registration corrected for 1) patient movement and 2) misalignment caused by internal organ motion from differences in breathing protocols between two scans (Shekhar, Walimbe et al. 2005). The algorithm performance for this application was quantitatively evaluated based on thorough validation using expert-identified anatomical landmarks separately in 15 CT-PET image pairs from stand-alone scanners and five from combined scanners. The mean registration accuracy of 5.5 mm (for stand-alone scanners) and 5.9 mm (for combined scanners) was found comparable to the average accuracy of corresponding three expert-determined registrations (5.6 ± 2.4 mm and 6.6 ± 3.4 mm, respectively). These accuracy numbers give an idea of the overall performance of the generic registration algorithm. Validation for the specific echo-SPECT registration, which is the main interest here, was based primarily on visual analysis of images by a blinded clinical expert (similar to the pilot study reported before in section 5.6.2), and is presented later in section 5.11.1.
5.8 Segmentation and Quantitative Analysis

In addition to visually providing the physician with simultaneous complementary functional and perfusion about the LV myocardium in the form of fused images, the current work also focuses on providing quantitative information about the LV myocardium to aid the physician in making a more objective diagnosis of myocardial ischemia with underlying CAD. This section discusses techniques and features necessary to satisfy this objective.

5.8.1 Myocardial segmentation in RT-3DE and SPECT

Segmentation of the LV myocardium (endocardium + epicardium) is the pre-requisite for performing quantitative analysis of LV function and perfusion. Since the echo and SPECT images are spatially aligned following registration, segmenting one image segments the other image too. Since echo provides superior spatial resolution and definition of the myocardial borders, segmentation of the LV wall is performed in the echo images. The LV wall in the SPECT need not be directly segmented. Endo- and epicardial surfaces from an echo image are transferred to the corresponding temporally and spatially (elastic) registered SPECT image. LV myocardial segmentation in RT-3DE sequences is performed using the same algorithm as used for the interactive, quantitative 3D-SE approach. The development of this algorithm and validation of segmentation accuracy in clinically acquired RT-3DE sequences using new-generation scanners has been discussed in CHAPTER 4 (section 4.3). Figure 5.12 shows an example of segmentation in RT-3DE and transferring the segmentation to fused echo-SPECT image using spatial correlation information obtained from previously performed registration. It
is important to note that segmentation of LV myocardium in RT-3DE and subsequent transfer of segmentation results to corresponding SPECT/fused image sequence is fully automatic without any manual intervention steps.

### 5.8.2 Quantitative analysis of LV function and perfusion

Segmentation of the LV myocardium in all frames of the cardiac sequence allows quantification of global LV parameters such as ventricular cavity volume, stroke volume, and ejection fraction. For regional analysis, the LV wall is divided into 17 segments according to the standard ASE-defined scheme in both echo and SPECT images. This division of the LV wall is performed automatically, as described in 4.4. Figure 5.13 shows a 3D surface model of the LV obtained from segmentation, wherein 17 segments created using the technique just described are colored differently for visualization.

Once the LV segments are identified in all rest and stress frames, regional quantification of LV parameters is possible. Quantification of regional LV structural and functional parameters like wall thickening and 3D excursion is performed as described in section 4.4 for interactive, quantitative 3D-SE. Strength of the proposed multimodality procedure is the availability of the concurrent myocardial perfusion information from SPECT. Per-segment myocardial perfusion is computed as the average normalized SPECT image intensity within the segment, averaged over the cardiac cycle, because perfusion variation within a cardiac cycle is both undetectable and diagnostically unimportant. All the global and regional LV structure, function and perfusion parameters can be calculated.
automatically and made available to the physician along with the fused echo-SPECT images during diagnosis.

5.9 Interactive visualization of fused images and quantitative information

The interactive image analysis software for multimodality stress testing has been developed as an extension of the standard PC-based interactive software for quantitative 3D-SE procedure described in CHAPTER 4, the reason being that the overall requirements are similar for both the procedures.

Figure 5.14 displays a screen-shot of the user interface of the quantitative, multimodality image analysis software. The software utilizes the temporally and spatially registered RT-3DE and SPECT sequences and displays fused pre- and post-stress images side-by-side. Since the gated SPECT images are relatively small (4 MB), they do not overburden the utilization of texture memory of the 3D graphics card by the visualization program that was initially designed for handling only pre- and post-stress RT-3DE images. OpenGL, an open source graphics library, was used for developing various display features of the user interface, including the image fusion methods that used the “color blending” feature of the graphics library. Thus, SPECT image with its user-defined colormap can be overlaid on the grayscale echo image. Because the pre- and post-stress RT-3DE images are temporally and spatially aligned and the SPECT images are registered to the corresponding echo images prior to fusion, pre- and post-stress cross-sectional views of fused images at identical anatomical locations are available by navigating through either of the images when viewed simultaneously. The results of automatic segmentation are displayed as
contours superimposed over each cross-sectional view being visualized and as a dynamic 3D rendering of the LV endo-/epicardial mesh for both pre- and post-stress images. Using interactive controls, the physician can selectively highlight individual segments simultaneously on the cross-sectional image and the rendered wiremeshes, thus gaining a precise understanding of the regional wall motion for accurate and focused regional wall motion analysis (Figure 5.14). During analysis of any particular segment, results of the quantitative evaluation of corresponding regional LV parameters are made available interactively along with the images (Figure 5.14) in the form of numerical values as well as graphs/plots tracking the variation over the entire cardiac cycle. Similar to the 3D-SE software, the ‘normal’ ranges for regional LV structural and wall motion parameters are also displayed along with the respective values of each measure in a given case. Further, each segment being evaluated is color-coded to indicate if its LV parameters fall within the normal range or above/below the range.

5.10 Study design for evaluation of novel multimodality cardiac stress testing

This section discusses a clinical study that was conducted with focus on demonstrating the feasibility of the novel multimodality cardiac stress testing procedure. A preliminary evaluation of the hypothesis regarding the improved diagnosis of CAD from analysis of fused echo-SPECT images is presented through a comparison of diagnoses using echo, SPECT and fused images.
5.10.1 Patient recruitment and data acquisition

Twenty patients with known/suspected CAD and referred for clinically indicated stress SPECT studies were recruited after informed consent as part of a study approved by the Institutional Review Board of the Cleveland Clinic. Subjects were recruited without regard to sex and race, so long as they did not demonstrate atrial fibrillation. The clinically indicated conventional stress SPECT study followed the standard pharmacologic stress protocol.

SPECT images were acquired in the Nuclear Medicine division of the Cleveland Clinic using a Siemens scanner, following the standard institutional clinical protocol. Rest images were taken 10-15 minutes after the patient was given an intravenous injection of 2.0-2.5 mCi of Thalium-201. Pharmacologic stress protocol was used. An identical dose of MIBI was given four minutes after peak stress was achieved. The stress imaging was performed 30-40 minutes after MIBI was injected. ECG-gated reconstruction for 8 gates (cardiac phases) was performed using standard backprojection algorithm as part of the commercially available 4DM software.

The RT-3DE images were acquired simultaneously with stress SPECT scanning in the Nuclear Medicine division by a trained sonographer, using the Philips’ iE33 scanner (Philips, Andover, MA). Figure 5.3 shows the sequence of clinical image acquisition during this study. Pre- and post-stress image sequences were collected with the transducer/probe in the apical position so that the field of view covered the entire left ventricle and at least part of the right ventricle. Each RT-3DE sequence typically had
about 15-20 frames covering the cardiac cycle (acquisition triggered by R-wave of ECG),
the exact number depending on the heart rate of the patient.

5.10.2 Image pre-processing – registration, segmentation, and quantitative analysis
After acquisition, RT-3DE images were transferred on a CD-ROM from the scanner to
the PC for processing. Image data were stored on the scanner in native format (polar
coordinate system), and were first converted to a more standard Cartesian format using a
standard scan conversion routine. Reconstructed SPECT image data was directly
transferred to the PC over the local PACS system. The main image processing steps as
described in previous sections, including (1) pre- and post-stress image registration, (2)
segmentation for all frames of the cardiac sequence (initially performed on RT-3DE
images and transferred to corresponding SPECT/fused images), and (3) calculation of LV
parameters, were performed. All the pre-processing steps were performed automatically
with no manual intervention before the experts reviewed each case, following which all
images and results of quantitative analysis were stored before the experts reviewed each
case.

5.10.3 Evaluating feasibility and clinical utility of echo-SPECT registration
One of the goals of the current study was to evaluate the feasibility and clinical utility of
the multimodality registration algorithm for clinically acquired pre- and post-stress RT-
3DE and SPECT image sequences. This was evaluated in a sample of five subjects
selected randomly from the 20 cases included in the clinical study. In addition to the
elastic registration performed as part of the actual pre-processing steps, NMI-based rigid-
body registration was also performed for these pre- and post-stress echo-SPECT image sequences. In the absence of a gold standard, an expert cardiologist, blinded to the aims of the study, visually assessed the accuracy of registration on a scale of 1 (poor) – 5 (excellent) in fused images generated by elastic as well as rigid-body registration. A rating of 3 was predefined as a threshold for indicating clinical utility. See Table 5.1 for detailed description of evaluation ratings. During this comparison, the clinical expert was not aware of the specific objectives of the study, and evaluated the fused images as 10 registration cases independently. The expert evaluation of registration was used to assess the effectiveness of elastic transformation model to provide better registration results compared to the rigid-body transformation model and also to assess the overall clinical utility of the echo-SPECT registration process.

5.10.4 Image analysis by clinical experts

As part of the main clinical evaluation, for each case, an expert echocardiologist, an expert nuclear cardiologist and a third physician with expertise in reading both types of images reviewed the echo, SPECT and quantitatively analyzed fused images, respectively. All experts were blinded to the identities of the patients and reviewed the cases independently and in a randomized order. For each of the 20 cases and in each of the three methods, diagnostic rating was assigned by each reader on each of 17 LV segments, on a scale ranging from 1 (definitely normal) to 5 (definitely diseased). For diagnosis based on SPECT images alone, the nuclear cardiologist followed the standard clinical protocol using the commercially available 4D-MSPECT software (University of Michigan Medical Center). The echocardiologist reviewed the RT-3DE images in all 20
cases using the interactive 3D-SE software discussed in CHAPTER 3. For diagnosis based on the fused images, the clinical expert used the interactive and quantitative multimodality image analysis software described in the current chapter (section 5.9). During review of fused echo-SPECT images, the final diagnosis for each individual segment was based on the corresponding expert’s assessment of the images. However, this assessment was aided by the availability of novel visualization tools and automatically evaluated quantitative information about the global and regional LV structure, function and perfusion for fused image-based diagnosis. Table 5.3 summarizes these values for the ‘normal’ range for each regional LV structural parameter. ‘Normal’ range for 3D excursion and fractional area change was estimated from healthy patients pooled from the current study and the validation study for interactive, quantitative 3D-SE described in section 4.6. Normal range for wall thickness was compiled only from the patient pool in the current study, because epicardium segmentation (necessary for calculation of wall thickness) was not implemented in images collected for 3D-SE validation study described in section 4.6.

5.10.5 Comparison of diagnoses
In addition to demonstrating the technical and clinical feasibility of the novel quantitative multimodality procedure, the clinical validation also compared CAD diagnoses from echo alone, from SPECT alone, and from echo + SPECT combination. The diagnostic “truth” was determined using angiography. LV segmental ratings from each case were converted to per-vessel ratings using the standard ASE-determined scheme (Cerqueira, Weissman et al. 2002). For example, anterior, anteroseptal and apical LV segment ratings
lead to a unique rating for the LAD, basal-septal and inferior wall segment ratings lead to a single rating for the RCA and lateral wall segment ratings lead to a rating for the LCx. The relative comparison was performed between the three findings for each case, using reference clinical records from angiography.

5.11 Results

During the clinical stress protocol, all subjects recruited for the study reached or exceeded 85% of maximum predicted heart rate, considered necessary for inducing diagnosable myocardial ischemia in the setting of mild to significant CAD. Simultaneous pre- and post-stress RT-3DE and SPECT imaging was performed successfully in all 20 cases. After image acquisition, all fully automatic pre-processing steps – (1) all registration links (T1, T2, T3), (2) myocardium segmentation in RT-3DE and transferring results to corresponding SPECT, and (3) the quantitative analysis (all LV structural, functional and perfusion parameters) based on segmentation results – were implemented successfully in all 20 cases, without need for any manual intervention. No cases were excluded for reasons of suboptimal image quality and/or failure to implement any of the pre-processing steps for RT-3DE and/or SPECT images.

5.11.1 Feasibility and effectiveness of echo-SPECT elastic registration

Visual assessment of elastically registered and fused images by expert yielded an average rating of 4 for pre-stress and 3.8 for post-stress registration (Table 5.2), with mean rating greater than the predefined cut-off of 3 ($p < 0.05$). In addition to elastic registration, rigid-body registration was also successfully implemented without any manual intervention for
pre- and post-stress image pairs in all five sequences included as part of the preliminary study evaluating feasibility and effectiveness of echo-SPECT registration algorithm. As part of a blinded study, the ‘rigid-body’ and ‘nonrigid/elastic’ transformation models for the spatial alignment were also compared for these five cases. As mentioned earlier, during this comparison, the clinical expert was not aware of the objective of the study, and evaluated the images as 10 registration cases independently. In a pair wise comparison, elastically registered images received a higher accuracy rating compared to rigidly registered images for all five cases ($p < 0.05$), thus proving the hypothesis that nonrigid registration is essential and effective for spatially aligning RT-3DE and SPECT images. Overall, the results indicate feasibility of automatic registration of pre- and post-stress RT-3DE and SPECT image sequences acquired in clinical settings for healthy and diseased cases.

5.11.2 Clinical evaluation of multimodality approach

After the pre-processing steps, all 20 cases were successfully analyzed by the individual experts reading echo images, SPECT images and fused echo-SPECT images, respectively. Diagnosis based on SPECT images alone was successfully performed according to clinical conventions using the commercially available 4D-MSPECT software. The diagnosis based on echo images alone was successfully performed using the novel quantitative 3D-SE software described in section 5.9. The expert performing the diagnosis based on fused images used the novel multimodality image analysis software described earlier in this chapter (section 5.9). Each expert successfully analyzed and assigned diagnostic ratings for all 17 segments for each case ($20 \times 17 = 340$
segments), regardless of quality of visualization of individual segments and using quantitative information as required.

Table 5.4 summarizes the diagnoses for all 20 cases (60 coronary arteries) according to the different modalities. Reference data was available from angiography for 12 of the 20 cases (36 coronary artery territories). Table 5.5 summarizes the diagnoses for these 12 cases according to the different modalities. From a total of 36 coronary artery territories in these 12 cases, 13 were identified with mild (30-50%) or severe (> 50%) stenosis. Diagnosis based on fused images correctly identified 13/13 diseased coronary arteries, compared to 11/13 by clinical SPECT and 6/13 by echo-based analysis. Diagnoses based on fused images and echo images had zero false positives each, compared to three by clinical SPECT. In the eight cases (24 coronary territories), for which no reference diagnoses were available from angiography, all coronary territories were diagnosed as healthy by echo-based diagnoses, whereas clinical SPECT-based diagnosis identified three territories as diseased and fused image-based diagnosis identified two territories as diseased. Due to lack of reference data for these cases, the absolute truth could not be verified.

5.12 Discussion
To improve on the diagnostic accuracy of the individual stress echo and stress SPECT tests, this dissertation proposes correlation of the complementary functional and perfusion information available from RT-3DE and SPECT, respectively. Diagnosis of CAD using actual fused echo-SPECT images, obtained from accurate temporal and
spatial registration, is a significant novelty of the current work compared to prior attempts reported by Slavich et al. (Slavich, Guerra et al. 1996) and Senior et al. (Senior, Sridhara et al. 1994; Khattar, Senior et al. 1998). By relying on fused images for diagnosis, it is possible to truly correlate wall motion with underlying perfusion abnormalities, if any. Such ‘prospective’ correlation was absent in prior studies (Senior, Sridhara et al. 1994; Slavich, Guerra et al. 1996; Khattar, Senior et al. 1998), which was the main reason for their inability to simultaneously improve sensitivity and specificity of the diagnosis, as explained in section 3.3.2. The availability of correlated wall motion and perfusion information is particularly useful in (1) reducing false negatives in cases of mild disease where wall motion abnormalities may not be induced (in such cases the perfusion abnormalities are visible in fused images and can help in making the correct diagnosis), and (2) reducing false positives where the intensity artifacts in SPECT are mistaken for true perfusion abnormalities (in such cases the normal wall motion can be used to ascertain that the perfusion defect is in fact an image artifact).

The results in Table 5.5 provide initial indications of the improved diagnostic performance using the novel fused image approach. The higher false negatives from echo-based analysis are indicative of the fact that disease was not diagnosable at the early stage since stenosis was not significant enough to induce wall motion abnormalities. Similarly, the higher number of false positives from SPECT-based diagnosis indicates the effect of intensity artifacts in these images. Both these problems are mitigated by diagnosis based on fused images, leading to reduced false negatives and false positives compared to the individual modalities as summarized in Table 5.5.
A significant contribution of this dissertation is the development of a fully automatic procedure for temporal and spatial alignment of pre- and post-stress RT-3DE and SPECT, which is a necessary pre-requisite for meaningful fusion/correlation of the complementary information. Specifically important is the spatial registration algorithm, which is the first-reported attempt for a fully automatic alignment/correlation procedure for RT-3DE and myocardial SPECT images. The spatial registration algorithm utilizes MI/NMI, which is a voxel intensity-based image similarity measure. MI/NMI is especially suited for multimodality registration of echo and SPECT images since it does not depend on the absolute information content of the individual images, rather on the amount of information that can be obtained about one image given the other, and vice versa. Furthermore, MI-based registration is also a suitable approach for cardiac registration, because it does not require identification of any landmarks in the two images, making the automation of the process feasible. Section 5.6 describes results of the feasibility of performing MI/NMI-based echo-SPECT registration. The current work further argues the need for an elastic transformation model for accurate alignment of RT-3DE and SPECT images. Accordingly, a novel algorithm has been developed based on an image subdivision-based approach. Salient features of the novel registration algorithm include (1) six-parameter rigid-body transformation model for subvolume registration in place of the conventional 3D translations-only model, (ii) direct interpolation of the set of discrete six-parameter subvolume transformations for generation of a smooth deformation field, using a quaternion-based scheme. Effectiveness of registration was demonstrated by a study involving assessment by a blinded expert, which yielded an
average rating of 4 for pre-stress and 3.8 for post-stress registration, with mean rating greater than the predefined cut-off of 3 ($p < 0.05$; Table 5.2). The study also demonstrated the validity of the hypothesis that elastic registration is more suitable for cardiac echo-SPECT registration than simple rigid-body registration (results in section 5.11). The 3D spatial elastic registration algorithm developed as part of this study is generic and has been demonstrated (with rigorous quantitative validation) to have meaningful impact on other clinically relevant applications like registration of whole body PET-CT images (Walimbe, Zagrodsky et al. 2004; Shekhar, Walimbe et al. 2005), sequential respiratory-gated CT images of chest (Shekhar, Lei et al. 2005), and low dose and high dose CT images of thorax and abdomen (Dandekar, Siddiqui et al. 2006).

Enabling the availability of automatically and accurately quantified LV structural, functional and perfusion information in an interactive manner together with the fused images is also a novel contribution of the current work. CHAPTER 4 contained discussion about the uniqueness and effectiveness of the interactive visualization of images simultaneously with the quantitative information. Benefits of such an interactive, quantitative approach for analysis of fused echo-SPECT images are also obvious for the multimodality stress testing approach. For the physician, this means simultaneous knowledge of exact quantitative regional wall motion, wall thickening and perfusion information. The information, in conjunction with the ability to interactively view any cross-section simultaneously in fused pre- and post-stress images makes the diagnosis procedure more objective, leading to possibly less inter-observer variability.
As stated previously, the main objective of the current study was to demonstrate the feasibility of this approach in a clinical setting. This dissertation successfully demonstrates the feasibility of clinically acquiring images for actual patients referred for clinically indicated stress testing. RT-3DE imaging is non-invasive and totally safe, and with the use of latest-generation scanners adds no more than approximately 5 minutes to the clinical stress SPECT protocol. Thus, clinical integration of the extra imaging step to the clinical workflow is very convenient. Overall, the successful completion of the clinical study indicated the feasibility of the implementation of dual echo and SPECT imaging during the clinical cardiac stress protocol. Image data was collected using the latest generation echo and SPECT scanners. For these clinically acquired images, the implementation of the pre-processing steps (registration, segmentation and quantitative analysis) was demonstrated to be feasible. Furthermore, these tasks are fully automatic, and so do not add any significant effort on the part of the physician during diagnosis of the images. Thus, overall the multimodality stress echo procedure is clinically implementable.

The sample size of the current clinical study is small. Thus, it is difficult to derive a statistically significant conclusion regarding the improved diagnosis of CAD using the multimodality stress testing approach. The low sample size and the unavailability of the reference diagnosis for all patients preclude the calculation of sensitivity, specificity and accuracy for the proposed procedure. Despite these factors, however, the results in Table 5.5 provide an early indication of the improvement in diagnosis of CAD using the multimodality approach proposed in the current dissertation. A larger follow-up clinical
trial would be necessary to more rigorously evaluate the hypothesis of improved diagnosis of CAD using the proposed multimodality approach. Furthermore, with a larger sample size from such a clinical trial, a receiver operator characteristic (ROC) analysis would be possible to compare diagnostic accuracies of these tests and examine the confidence intervals of the sensitivity, specificity values, lending further credibility to the preliminary results presented here.

5.13 Summary

This chapter discussed a novel multimodality stress testing approach, involving RT-3DE and myocardial gated SPECT. The feasibility was successfully demonstrated for performing the dual imaging tasks in a clinical setting and implementing novel visualization and advanced image-processing (multimodality registration, segmentation and quantitative analysis) tasks integral to the proposed multimodality approach. The proposed techniques are efficient and suitable for integration in the clinical workflow. The results of a small-scale clinical evaluation study indicate that this combination of “(fused RT-3DE & SPECT) + interactive, quantitative analysis” has a very good potential for accurate detection of wall motion abnormalities and improved diagnosis of ischemia with underlying CAD.
## 5.14 Tables

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<tr>
<th>Rating</th>
<th>Description</th>
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<tbody>
<tr>
<td>5</td>
<td><strong>Excellent</strong>: There is nearly perfect registration of both images at all points in the cardiac cycle.</td>
</tr>
<tr>
<td>4</td>
<td><strong>Very Good</strong>: The two image sets are well registered, although there are minor spatial and temporal deviations. Even so, the results appear to be very useful clinically.</td>
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<tr>
<td>3</td>
<td><strong>Good</strong>: The two image sets are generally registered, although some regions and time points do not match up well. However, the results are still useful clinically.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Fair</strong>: Large areas of the heart are misregistered in the two image sets. The results have only minor clinical value.</td>
</tr>
<tr>
<td>1</td>
<td><strong>Poor</strong>: The two image sets do not match up at all. The results have absolutely no clinical value.</td>
</tr>
</tbody>
</table>

Table 5.1 Description of rating scheme for evaluation of echo-SPECT registration
### Table 5.2 Evaluation of echo-SPECT registration accuracy by clinical expert

<table>
<thead>
<tr>
<th>Case #</th>
<th>Pre-stress rating</th>
<th>Post-stress rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Average</td>
<td>4</td>
<td>3.8</td>
</tr>
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</table>

### Table 5.3 Normal range for LV wall motion parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
<th>Apical segments</th>
<th>Mid-ventricular segments</th>
<th>Basal segments</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-stress</td>
<td>Post-stress</td>
<td>Pre-stress</td>
</tr>
<tr>
<td>3D excursion</td>
<td></td>
<td>Pre-stress</td>
<td>Post-stress</td>
<td>Pre-stress</td>
</tr>
<tr>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>6.4-11.3</td>
<td>8.7-14.3</td>
<td>7.5-12.3</td>
<td>9.4-14.8</td>
<td>6.9-12.5</td>
</tr>
<tr>
<td>Fractional area change</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>38.9-59.2</td>
<td>40.1-59.4</td>
<td>39.3-59.4</td>
<td>39.9-60.3</td>
<td>40.1-60.2</td>
</tr>
<tr>
<td>Segmental thickening</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>0.1-29.1</td>
<td>0.2-30.4</td>
<td>0.5-30.8</td>
<td>0.9-31.1</td>
<td>0.7-30.3</td>
</tr>
</tbody>
</table>
Table 5.4 Diagnosis of coronary territories as healthy/diseased: Comparison between diagnoses based on echo, SPECT and fused images (N = 20 x 3 = 60 coronary arteries)

<table>
<thead>
<tr>
<th>Fused</th>
<th>Echo</th>
<th>SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>-</td>
<td>0</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 5.5 Diagnosis of coronary territories as healthy/diseased: Comparison between diagnoses based on echo, SPECT and fused images with reference to standard readings from angiography (N = 12 x 3 = 36 coronary arteries)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Echo</th>
<th>SPECT</th>
<th>Fused</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>6</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>-</td>
<td>0</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.4 Diagnosis of coronary territories as healthy/diseased: Comparison between diagnoses based on echo, SPECT and fused images (N = 20 x 3 = 60 coronary arteries)

Table 5.5 Diagnosis of coronary territories as healthy/diseased: Comparison between diagnoses based on echo, SPECT and fused images with reference to standard readings from angiography (N = 12 x 3 = 36 coronary arteries)
Figure 5.1 Flowchart of proposed interactive, quantitative multimodality stress testing procedure.
Figure 5.2 Transformations between pairs of RT-3DE and SPECT image sequences.
Figure 5.3 Timeline of clinical image acquisition, and corresponding variation of patient heart rate.

(1) Pre-stress SPECT; (2) Pre-stress echo;
(3) Post-stress echo; (4) Post-stress SPECT
Figure 5.4 Piecewise linear interpolation for temporal alignment
Figure 5.5 Scheme for temporal registration of RT-3DE and SPECT sequences
Figure 5.6 Long axis (top row) and short axis (bottom row) views of the heart with the SPECT image on the left, RT-3DE image on the right and the fused image in the center. The correspondence of the location of the (partially visible) RV in the bottom row further confirms the accuracy of registration.
Figure 5.7 Robustness of MI-based echo-SPECT registration. The horizontal axis shows the initial misalignment in mm. The vertical axis shows the residual misalignment after MI-based registration in mm.
Figure 5.8 Percent convergence plotted against initial misalignment. Horizontal axis shows initial misalignment in mm. The vertical axis shows the percentage convergence. The dotted line parallel to the horizontal axis indicates the threshold percent conversion (90%) for determination of capture range.
Figure 5.9 Flowchart of elastic registration algorithm. R: reference image, F: floating image, Rn: subvolume of reference image, and F': transformed floating image, after registration with reference image.
Figure 5.10 Schematic of volume subdivision and subvolume registration for single hierarchical level
Figure 5.11 Comparison of rigid-body (top row) versus elastic (bottom row) registration for RT-3DE and SPECT images. Regions marked by rectangular box show highlight differences between the two registrations. Note that elastic registration leads to better alignment of echo and SPECT image data.
Figure 5.12 LV segmentation in fused echo-SPECT images. Segmentation is performed in echo images, and meshes are transferred to fused and/or SPECT images using transformation field generated from corresponding spatial registration procedure.
Figure 5.13 3D surface model of the LV myocardium. Basal, mid, apical segments and apical cap are clearly distinguishable. The 17 segments created using the technique just described are colored differently for visualization.
Figure 5.14 Screen-shot of the user interface of the quantitative, multimodality image analysis software. User-defined matching pre- and post-stress fused images (echo+SPECT) are available following alignment of images using registration techniques. Corresponding LV meshes are obtained using the automatic segmentation technique. Results of quantitative analysis are displayed on the side.
CHAPTER 6

CONCLUSIONS

The current work focuses on development and application of advanced image processing algorithms for stress echo and stress SPECT, aimed towards improving diagnosis of CAD – the leading cause of death in the United States. The research takes advantage of RT-3DE, a recent innovation in ultrasound imaging that, for the first time, enables almost instantaneous volumetric imaging of the beating heart in 3D. In order to utilize these advances in echo imaging for improving diagnostic accuracy of stress echo and SPECT, this dissertation began with two main objectives:

1. To develop a novel interactive, quantitative stress echo procedure that combines, for the first time, fully automatic image analysis tools for accurate pre-/post-stress image alignment, LV myocardial segmentation and quantification of global and regional LV function for cardiac stress testing using RT-3DE images.

2. To develop necessary advanced image processing techniques to enable a novel quantitative multimodality cardiac stress testing approach involving fused RT-3DE and SPECT images.
To achieve the above-mentioned objectives, the current dissertation used previously reported algorithms for interactive ‘any-plane’ visualization and registration of pre- and post-stress RT-3DE. In addition following new algorithms/techniques were also developed as part of the current research effort:


2. Registration scheme for temporal and spatial alignment of all pre- and post-stress RT-3DE and SPECT sequences, for enabling a true multimodality cardiac stress testing technique (CHAPTER 5).

3. A 3D spatial registration algorithm for recovering nonlinear misalignment between echo and myocardial SPECT images (CHAPTER 5). Besides the current application discussed in this dissertation, the utility of the generic elastic registration algorithm has also been demonstrated for other clinical applications like registration of whole body PET-CT images, respiratory-gated chest CT images, among others (Walimbe, Zagrodsky et al. 2004; Shekhar, Lei et al. 2005; Shekhar, Walimbe et al. 2005; Walimbe and Shekhar 2005; Dandekar, Siddiqui et al. 2006).

CHAPTER 4 and CHAPTER 5 describe two versions of the interactive, quantitative image analysis software combining the various image processing techniques and specifically designed for (1) interactive, quantitative 3D-SE, and (2) interactive, quantitative multimodality stress testing, respectively. This novel image analysis software
was developed with continual clinical feedback and the resulting final version of the software was enthusiastically received by the clinicians, who specifically acknowledged the utility of the features enabling side-by-side interactive visualization of pre- and post-stress images together with the quantitative information about the LV parameters.

Two clinical studies are described in CHAPTER 4 and CHAPTER 5 for validation of the novel techniques proposed herein. The studies performed as part of this dissertation are preliminary in nature with the focus mainly on demonstrating the feasibility of the novel techniques and the potential for easy integration into the clinical workflow. Through comparison with current clinical procedures and diagnostic standards, the two studies also indicate the clinical diagnostic effectiveness of the novel procedures. Though the sample size for these studies was not large enough to draw statistically significant conclusions about improvement in diagnosis of CAD, the results definitely indicate promise for the proposed approach and encourage further investigation through larger clinical trials.

In the long run, the current work will potentially result in two new diagnostic techniques – quantitative 3D stress echo and a multimodality cardiac stress testing procedure – for all patients suspected of having CAD, irrespective of race, gender or socioeconomic stature. The proposed procedures are predominantly non-invasive, except introduction of stress-inducing drugs and radioisotopes, and require minimal deviation from existing clinical protocols, thus allowing easy introduction in the clinical workflow necessitating
minimal cost-increase. However, the cost-efficiency in terms of dollars saved and improvement in terms of quality-adjusted life-year (QALY) could be substantial.

In addition to early and accurate diagnosis, the methodologies developed in this research can also be used for validation of echo contrast agents, and can be naturally extended in the long term for identifying regions of viable myocardium that stand to benefit from specific treatment options like medical therapy or revascularization, thus saving many lives and dollars in healthcare.
APPENDIX A

GENERALIZED GRADIENT VECTOR FLOW (GGVF) FIELD
DM-based segmentation, as discussed in CHAPTER 4 (section 4.3) of this dissertation, is essentially a process of balancing the internal mesh-derived forces (which work to retain the mesh integrity) and the external image-derived forces (which work to drive the DM wiremesh to the image features of interest). The generalized gradient vector flow (GGVF) algorithm, introduced by Xu and Prince (Xu and Prince 1998; Xu and Prince 1998), is being used in the current work for generation of the image intensity-based vector field. The GGVF-based vector field is essentially a description of external forces providing a vector $v = (v_x, v_y, v_z)$ corresponding to every voxel location $(x,y,z)$ of the image and pointing to the nearest strongest edge. The following paragraphs provide a basic description of the GGVF algorithm.

An edge map $f(x,y,z)$ of the image represents the features of interest that should attract the DM. In the simplest of scenarios, a simple vector field with vectors ($v$) pointing toward the edges may be produced by calculating the simple gradient of an edge map ($\nabla f$) for an image. A major shortcoming of the gradient of an edge map is that the produced vectors have relatively large magnitudes only in the close vicinity of edges and have negligible magnitude away from the edges. As a result, such a vector field can successfully drive only the portions of the DM wiremesh that are initialized very close to the edges. This zone of influence is particularly small and non-robust for echo images, because of their inherent noisy nature. GGVF algorithm addresses this basic limitation of a simple image gradient-based vector field.
GGVF extends the vectors arising from a gradient edge map farther away from the edges into the homogeneous image regions using a diffusion-like process, thus extending the zone of influence of the vector field and making the segmentation process more robust. More formally, the GGVF is the vector field that minimizes the energy functional, and it can be found by solving the set of Euler equations of the form

\[
\begin{align*}
\mu \nabla^2 v_x - (v_x - f_x)(f_x^2 + f_y^2 + f_z^2) &= 0 \quad (A1) \\
\mu \nabla^2 v_y - (v_y - f_y)(f_x^2 + f_y^2 + f_z^2) &= 0 \quad (A2) \\
\mu \nabla^2 v_z - (v_z - f_z)(f_x^2 + f_y^2 + f_z^2) &= 0 \quad (A3)
\end{align*}
\]

where \( \nabla^2 \) is the Laplacian operator. These equations are solved in an iterative fashion by treating voxel intensity \( v \) as a function of time that converts them into partial differential equations known as generalized diffusion equations that are commonly employed in theoretical development for heat conduction and fluid flow. Figure A.1 illustrates a 3D echo image and the GGVF-based external vector field. Note that (1) the vector field is conserved in the areas densely populated with edges, and (2) it is smoothly spread through the homogeneous areas with vectors pointing to the nearest edge population. These two features make GGVF attractive for segmentation in noisy RT-3DE images.
Figure A.1 RT-3DE image and corresponding GGVF field. Top panel shows original image. Bottom left and right panels show x- and z- components of GGVF vector field. Vector field images are signed, so gray background level corresponds to ‘zero’ value for vector field, dark regions correspond to vectors pointing right for x-component and down for z-component, and bright regions mean vectors pointing left for x-component and up for z-component. Identical 2D cross-section is shown in all panels.
APPENDIX B

BASIC QUATERNION ALGEBRA
A quaternion is a simple extension of a complex number, and can be written as
\[ q = w + xi + yj + zk \]  
(B1)
where \( i^2 = j^2 = k^2 = -1 \), \( ij = k \), \( ji = -k \).

We can write a quaternion as a combination of a scalar and a vector in 3D space.
\[ q = [w, v] \in S^3; \quad w \in R, \quad v = [x, y, z] \in R^3 \]  
(B2)

A unit quaternion (magnitude unity) can be used to represent a 3D rotation \( \theta \) about an axis represented by a unit vector \( a = [a_x, a_y, a_z] \) as follows:
\[ q = \left[ \cos\left(\frac{\theta}{2}\right), a \sin\left(\frac{\theta}{2}\right) \right] \]  
(B3)

A 1:1 relationship exists between a \( 3 \times 3 \) real orthogonal rotation matrix \( \in SO(3) \) corresponding to a given Euler angle triplet and a unit quaternion representing a 3D rotation.
\[
M = \begin{bmatrix}
1 - 2y^2 - 2z^2 & 2xy + 2wz & 2xz - 2wy \\
2xy - 2wz & 1 - 2x^2 - 2z^2 & 2yz + 2wx \\
2xz + 2wy & 2yz - 2wx & 1 - 2x^2 - 2y^2
\end{bmatrix} \iff q = [w, (x, y, z)] \]  
(B4)

Quaternion interpolation is performed on the surface of a four-dimensional (4D) hypersphere and is in general called spherical interpolation. The equivalent of linear interpolation for quaternions on a 4D hypersphere is called spherical linear interpolation.
or **slerp**. For unit quaternions $q_0, q_1$ and interpolation fraction $t \in [0,1]$ the spherical linear interpolation curve is defined in (Shoemake 1985) as:

$$slerp(q_0, q_1, t) = \frac{\sin((1-t)\theta)}{\sin \theta} q_0 + \frac{\sin(t\theta)}{\sin \theta} q_1$$  \hspace{1cm} (B5)

where $\theta = \cos^{-1}(q_0 . q_1)$.

For unit quaternions $q_i, q_{i+1}$ and interpolation fraction $t \in [0,1]$, the spherical cubic interpolation or **squad** (spherical and quadrangle) is defined in (Shoemake 1987) as:

$$squad(q_i, a_i, a_{i+1}, q_{i+1}, t) = slerp(slerp(q_i . q_{i+1}, t), slerp(a_i . a_{i+1}, t), 2t(1-t)); t \in [0,1]$$

$$a_i = q_i \exp \left( - \left( \frac{\ln(q_i^{-1} \cdot q_{i+1}) + \ln(q_i^{-1} \cdot q_{i-1})}{4} \right) \right)$$  \hspace{1cm} (B6)
BIBLIOGRAPHY


