Myocardial Elastography: 
A Strain Imaging Technique for the Reliable 
Detection and Localization of Myocardial Ischemia 
in Vivo

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ABSTRACT

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According to the most recent report issued by the American Heart Association, cardiovascular disease remains the leading cause of death in the United States. Among cardiovascular diseases, coronary artery disease, which can cause, for instance, myocardial ischemia and myocardial infarction (or, a heart attack), accounts for 52% of the death toll. This underscores the urgent need and the critical role that a non-invasive, efficient and reliable imaging technique can play in the early diagnosis of coronary artery disease.

Echocardiography, namely cardiac ultrasound, has been extensively used in the clinic to evaluate both structural and functional changes of the heart due to its advantages of widespread availability, real-time capability, non-ionizing modality, low cost, portability and compatibility with pacemakers over other imaging modalities. The fact that abnormal myocardial motion and deformation (i.e., strain) is associated with coronary artery disease that leads to insufficient coronary blood and oxygen supply to the cardiac muscle (i.e., supply-type myocardial ischemia), has been well documented. Therefore, assessing myocardial motion and deformation may be the key to the detection of myocardial ischemia due to coronary artery disease.

Myocardial Elastography is such an ultrasound-based technique that utilizes cross-correlation on radio-frequency (RF) signals to estimate and image myocardial deformation.
in full echocardiographic views. Moreover, Myocardial Elastography aims at reliably identifying and localizing impaired myocardial segments attributable to coronary artery disease. Despite the fact that several ultrasound-based methods have been proposed to quantify 2D, or even 3D, myocardial motion and deformation, averaged temporal strain/strain-rate traces in a localized region are typically presented without simultaneously mapping motion and deformation images across the entire left-ventricle or the entire myocardial wall. In addition, a thorough fundamental performance assessment study of myocardial strain imaging has not been reported.

In this dissertation, Myocardial Elastography, a novel strain imaging technique, was evaluated in its full scope and firstly introduced, developed and evaluated using a theoretical framework based on a well-established, computational 3D model of the left ventricle and an ultrasonic image formation model. Full depiction of the nonuniformity of transmural (2D and angle-independent) myocardial deformation in short-axis views was shown. Not only were Myocardial Elastography strains obtained with good accuracy in comparison with the computational model solutions, but they were capable of differentiating the ischemic from the normal myocardial regions. In vivo validation of Myocardial Elastography deformation estimates in the canine left ventricle was thereafter performed against sonomicrometry under the conditions of progressive coronary blood flow reduction, which simulated the outcome of coronary stenosis and caused myocardial ischemia. Good correlation (r=0.84) and agreement (bias of 0.22% strain) of Myocardial Elastography with sonomicrometry were found. Most importantly, Myocardial Elastography was proven to detect the ischemic myocardial region at 40%, and possibly as early as 20%, flow reduction. Finally, a preliminary clinical validation study against MR
tagging was conducted. Qualitative side-by-side strain image comparison and quantitative measures showing good correlation ($r=0.75$) and agreement (bias of 5.59% strain) in six normal and three pathological human left ventricles between the two imaging modalities were provided. The pathological myocardial regions were identified and characterized by the angle-independent strain estimates. In conclusion, the aforementioned findings collectively demonstrated the strong promise of Myocardial Elastography to constitute an early diagnostic tool for the reliable detection, localization and characterization of myocardial ischemia as a result of coronary artery disease.
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Chapter 1

Introduction

1.1. Motivation

Cardiovascular disease (CVD) refers to all diseases that are associated with the heart or blood vessels. According to the most recent estimated mortality reported by the World Health Organization (WHO), cardiovascular disease is the No. 1 cause of death worldwide\(^1\), and cardiovascular disease is also the leading cause of death in the United States\(^2\). An estimated 80,000,000 American adults (one in three) present with one or more forms of cardiovascular disease\(^3\).

On the basis of the most recent mortality rate data, nearly 2400 Americans die of cardiovascular disease each day, namely, an average of 1 death every 37 seconds\(^3\). Cardiovascular disease encompasses coronary heart diseases (CHD), stroke, hypertension, and so on (Figure 1.1). Coronary heart disease, also called coronary artery disease (CAD), accounts for 52% of mortality among cardiovascular diseases (Figure 1.1). Coronary artery disease caused about 1 of every 5 deaths in the United States in 2005\(^5\). In 2009, an estimated 785,000 Americans will have a new coronary attack, and about 470,000 will have a recurrent attack\(^3\). It is estimated that an additional 195,000 first silent myocardial infarctions occur each year\(^3\). About every 25 seconds, an American will have a coronary event, from which approximately every minute someone will die\(^3\).
Coronary artery disease is a condition where coronary arteries, which supply blood and oxygen to cardiac tissue, are narrowed due to the formation of atherosclerotic plaques in the coronary arterial wall. As a result, the myocardium deprived of coronary blood supply due to the obstructed coronary arteries begins to lose its active contractile function. This regional mechanical impairment may further lead to global cardiac dysfunction. In the past two decades, imaging systems, including angiography, ultrasound, and magnetic resonance imaging, have been introduced to clinical cardiology for the detection of abnormal myocardial deformation.

Cardiac ultrasound (or, echocardiography) has been extensively used as an important tool to evaluate coronary artery disease because of its noninvasiveness, rapidity of
acquisitions, portability, inexpensiveness, and greater familiarity to cardiologists. Most current evaluations of the mechanical dysfunction based on echocardiograms rely on the wall motion score index (WMSI) performed by cardiologists. However, not only is WMSI a qualitative measure, there also exists variability from one cardiologist to another.

Despite the fact that many functional imaging techniques have been proposed and developed to provide diagnosis of a diseased heart, functional imaging methods at high precision and spatial resolution are still needed for the early assessment of cardiac function in CAD. Early diagnosis of CAD, such as myocardial ischemia caused by reduced coronary blood flow in stenosed coronary arteries, is critical for the avoidance of additional diagnostic procedures, such as stress echocardiography and ventriculography, and particularly for timely and appropriate treatment.

1.2. Overview and significance

The analysis of myocardial motion and deformation (or, strain) has been fast growing to assess cardiac function. Even though imaging methodologies used to analyze myocardial strains have been investigated in a huge number of studies, temporal strain curves with fewer examples of 2D motion/strain images have mainly been presented in the literature. Compared to the temporal strain profiles, 2D strain images in full standard echocardiographic views at high spatial and temporal resolution would facilitate both the detection and localization of dysfunctional myocardial segments. Most importantly, the capability of those strain imaging techniques to detect the early onset and stages of myocardial dysfunction remains to be investigated.
In this dissertation, Myocardial Elastography was evaluated and validated from the theoretical framework and *in vivo* animal experiments to clinical settings. As far as the Myocardial Elastography technique is concerned, several new aspects are incorporated and detailed in Chapter 4: 1) a 2D search is performed for cross-correlation; 2) the displacement estimation is extended from one- to two-dimension and the bi-plane configuration; 3) a recorrelation method is used to correct the axial displacement estimate for the lateral displacement; 4) cumulative 2D displacements are computed and images; 5) cumulative 2D strains are further calculated and images. In view of the *in vivo* assessment of Myocardial Elastography, its good performance is validated against the currently considered gold standards (sonomicrometry in animals and MR tagging in humans) in Chapters 5 and 6.

Different from other currently existing ultrasound-based techniques (see sections 3.2 and 3.3), Myocardial Elastography presented in this dissertation is a radio-frequency (RF)-based, functional imaging method that overcomes the difficulty of high precision 2D (i.e., lateral and axial) displacement estimation and provides angle-independent strain images in standard echocardiographic views. The primary objectives of Myocardial Elastography are 1) to identify and characterize impaired myocardial regions through the two-dimensional (2D) quantification and maps of transmural angle-independent strains; 2) to serve as a diagnostic tool of detecting cardiovascular disease, among which coronary artery disease that causes myocardial ischemia is particularly the focus here; and 3) to assess the performance of Myocardial Elastography in detecting myocardial ischemia at its early onset and quantifying progressive levels (from mild to severe) of myocardial ischemia.

This dissertation is structured as follows. Chapter 2 overviews basic cardiac physiology, cardiac mechanics, and the effect of myocardial ischemia on left-ventricular
dysfunction and myocardial impairment. Chapter 3 summarizes cardiac imaging modalities prevalent in the clinic and focuses on echocardiography and its associated cardiac motion analysis. Chapter 4 firstly presents the performance assessment of Myocardial Elastography in a theoretical framework based on an ultrasound image formation model and a previously established 3D finite-element model in both normal and ischemic cases. Chapter 5 details the in vivo assessment of Myocardial Elastography at progressive levels of myocardial ischemia, which simulates the outcome of coronary artery disease (or, coronary stenosis), in canine hearts. Findings with Myocardial Elastography were also validated against sonomicrometry, which was considered the ground truth. Chapter 6 describes the validation of Myocardial Elastography against Magnetic Resonance Imaging (MRI), specifically Magnetic Resonance (MR) tagging, in patients as well as normal human subjects in a clinical setting. Chapter 7 summarizes the findings shown in this dissertation and offers future directions. Appendix A illustrates the coordinate systems used in echocardiography and MR tagging. Appendix B demonstrates the strain calculation in the coordinate system in echocardiography.
Chapter 2

Cardiac Mechanics and Clinical Relevance to Myocardial Ischemia

2.1. Introduction

This chapter encompasses basic concepts of cardiac physiology at the organ level and basic cardiac mechanics. Previous findings in the literature that relate cardiac disease, particularly myocardial ischemia as a result of coronary artery disease, to cardiac mechanical behavior are summarized.

2.2. Basics of Cardiac Physiology/Cardiac Mechanics

2.2.1. Basics of Cardiac Physiology

A mammalian heart is composed of the left atrium, the left ventricle, the right atrium and the right ventricle and acts as a mechanical pump to deliver oxygenated blood to the entire human body and to deliver deoxygenated blood to the lung through the complex circulation system. The cardiac cycle describes the time-varying characteristic of pressure, volume and blood flow in the heart. The cardiac events begin with the electrical excitation and end with myocardial contraction through the excitation-contraction coupling.
mechanism. The electrical activation of the heart can be monitored by an
electrocardiogram (ECG), measured at the body surface (Figure 2.1(c)). The electrical
activation starts from the sinoatrial (SA) node, the primary pacemaker of the heart, reaches
the atrioventricular (AV) node, and then propagates throughout the ventricles via the His-
Purkinje system. The P-wave, QRS complex and T-wave of the ECG (Figure 2.1(c))
correspond to the depolarization of the atria, depolarization of the ventricles, and
repolarization of the ventricles, respectively. Each cardiac cycle consists of four phases:
isovolumic contraction, ejection, isovolumic relaxation and filling. The former two and the
latter two are customarily categorized as systole and diastole, respectively.

The left ventricle is the most critical heart chamber as it is responsible for supplying
oxygenated blood and nutrients to the entire human body. Consequently, the left heart and
left-ventricular mechanics constitute the focus of this dissertation. An example of the
temporal pressure (Figure 2.1(a)) and ventricular volume (Figure 2.1(b)) profiles in the
normal left ventricle over one cardiac cycle is shown. During the isovolumic phases, both
mitral and aortic valves are closed. The left ventricular pressure builds up and drops during
isovolumic contraction and relaxation, respectively. During filling, the aortic valve is
closed. Since the left-ventricular pressure is lower than the left-atrial pressure, the mitral
valve opens so that the oxygenated blood flows from the left atrium to the left ventricle.
The filling phase is rapid in the beginning due to the large pressure gradient between the
left atrium and the left ventricle. As this pressure gradient decreases, left-ventricular filling
slows down and reaches the state called diastasis. The late filling phase is rapid again
because of the atrial contraction caused by atrial depolarization. During ejection, the mitral
valve is closed. Since the left-ventricular pressure exceeds the aortic pressure, the aortic
valve opens so that the left ventricle contracts and pumps out oxygenated blood via the aorta to the main systemic circulation.

Figure 2.1 (The figure is adapted from Hurst’s the Heart and continued on the next page)
Figure 2.1: An illustration of chamber pressure curve, volume change and an electrocardiogram in one cardiac cycle. (a) shows how left-ventricular, left-atrial and aortic pressure varies with different cardiac phases in one cardiac cycle. (b) and (c) show the left-ventricular volume and electrocardiogram (ECG), respectively, in the same time sequence as (a). In (c), the P-wave, QRS complex and T-wave of the ECG correspond to the depolarization of the atrium, depolarization of the ventricle, and repolarization of the ventricle, respectively. Under the conventional definition, the R peak of the ECG corresponds to the end-diastolic phase, when the mitral valve closes and systole (or, contraction) begins; the end of the T-wave of the ECG corresponds to the end-systolic phase, when the aortic valve closes and ejection ends.
An alternative illustration of the cardiac events during one cardiac cycle is the pressure-volume (PV) relationship (Figure 2.2), and isovolumic, ejection and filling phases in the cardiac cycle are labeled accordingly. The instantaneous slope of the PV loop is defined as elastance, namely, chamber stiffness. Clearly, not only does this time-varying elastance increase during contraction and decrease with relaxation, but it also depicts the left-ventricular contractility. The PV relationship can be further used to evaluate the global left-ventricular function through the stroke volume (SV), ejection fraction (EF), and cardiac output (CO) as formulated in Eqs. (2.1)-(2.3).

\[
SV \text{ (mL)} = EDV \text{ (mL)} - ESV \text{ (mL)},
\]

\[
EF \text{ (%) } = \frac{SV \text{ (mL)}}{EDV \text{ (mL)}} \times 100\%
\]

\[
CO \text{ (mL/min)} = SV \text{ (mL/beat)} \times HR \text{ (beats/min)}
\]

where EDV, ESV, HR are end-diastolic volume, end-systolic volume, and heart rate, respectively. These measures respond to global changes in the oxygen consumption of the tissues.

This dissertation work focuses on evaluation of changes in active contraction of the heart consequent to myocardial ischemia caused by coronary artery disease, so the function during systole (i.e., between end diastole (ED) and end systole (ES)) is of the main interest. End diastole and end systole are identified by the R-wave and the end of the T-wave, respectively, in an ECG signal. Throughout the studies (Chapters 4-6) presented in this dissertation, end diastole (or, the R-wave of the ECG) is considered as the initial reference state.
Figure 2.2: An example of the pressure-volume relationship obtained from a normal in vivo canine left ventricle (see also Figure 5.3(a)). Filling, Isovolumic contraction, Ejection, and Isovolumic relaxation are indicated. The turning point between the end of filling and the beginning of isovolumic contraction is defined as end diastole (ED), whereas the one between the end of ejection and the beginning of isovolumic relaxation is end systole (ES).
2.2.2. Basics of Cardiac Mechanics

Global hemodynamic behavior of the heart, or more specifically the left ventricle, is described in section 2.2.1, but understanding both the detailed mechanical behavior and the material architecture of the heart is essential to assess regional cardiac function under normal and pathological conditions. Determination of the continuum mechanics for cardiac muscles requires 1) kinematics (e.g., displacements, strains), 2) the associated loads (e.g., stresses), 3) conservation laws (e.g., mass, energy), 4) constitutive relation formulation (e.g., material behavior), and 5) initial and boundary conditions\textsuperscript{7}.

2.2.2.1. Ventricular Structure

Before understanding cardiac mechanics, the structure of the ventricular wall needs to be introduced first. Numerous efforts have been made to investigate the characteristics of the myocardium, such as geometrical structure, fibrous architecture and material properties. The heart is surrounded by a collagenous membrane called pericardium, which is attached to ascending aorta, pulmonary veins\textsuperscript{5}. The pericardium limits rigid body motion of the heart, such as translation and rotation, constrains left-right ventricular overextension, contributes to ventricular interactions and increases the mechanical coupling between atria and ventricles\textsuperscript{7}. The wall of the heart is composed of the endocardium (i.e., inner surface), myocardium (i.e., middle layer) and the epicardium (i.e., outer layer) (Figure 2.3). The myocardium, which consists of subendocardium, midwall and subepicardium\textsuperscript{7}, is the major functional tissue layer to contract for the ejection action. Myocytes are comprised of the myocardium and arranged into muscle fibers (i.e., myofibers), which are embedded in an extracellular matrix.
Figure 2.3: Simplified schematics (adapted from Humphrey 2002) of (a) a canine heart, (b) excised left ventricular free wall, and (c) five layers of the free wall region, consisting of the endocardium, myocardium (including subendocardium, midwall and subepicardium), and the epicardium. Fiber orientation in the myocardium is shown in (c). Anti-diagonal, circumferential and diagonal myofiber orientations are found in the subendocardium, midwall, and subepicardium, respectively.
Muscle fibers are found to be generally oriented from -90 degrees at the epicardium to 90 degrees at the endocardium using the microscope\textsuperscript{8-10} or imaging techniques\textsuperscript{11-13}. Negative fiber angle represents the clockwise rotation from the local circumferential axis in the cardiac coordinates; positive denotes counterclockwise rotation. The transmural (from endocardium to epicardium) variation of the fiber angle can be observed from the simplified illustration shown in Figure 2.3(c). Myofibers are also arranged into laminar sheets with sheet orientation varying transmurally. This complex fibrous and laminar structure suggests that myocardium is considered to be transversely isotropic or orthotropic\textsuperscript{7}.

\subsection*{2.2.2.2. Cardiac Kinematics}

Understanding cardiac mechanics begins with cardiac kinematics, including motion, rotation, and deformation (i.e., strain). Cardiac kinematics can be depicted based on Lagrangian and Eulerian descriptions. The former describes kinematics over time with respect to the initial (or, reference) configuration, whereas the latter depicts kinematics with respect to each current (or, deformed) state. In other words, each material point is followed over time in the former case. Throughout this dissertation, the Lagrangian description is used.

Assume that there is a piece of myocardium, comprised of numerous material points, in the reference configuration, $A$, shown in Figure 2.4 and that the deformed state of the piece of the myocardium is represented by $B$ (Figure 2.4). Let the position of a material point, $P$, within the piece of the myocardium at an observation time point, $t$, be defined as

$$
\mathbf{x} = \mathbf{x}(\mathbf{X}, t) = \mathbf{x}(X_1, X_2, X_3, t) = (x_1, x_2, x_3),
$$

(2.4)
where \( \mathbf{X} = (X_1, X_2, X_3) \) is the position vector of \( P \) in the reference configuration, and \( \mathbf{x} \) is the position vector of \( P \) in the deformed configuration associated with time \( t \). The motion (i.e., displacement) vector of \( P \) can therefore be given by

\[
\mathbf{u} = \mathbf{x} - \mathbf{X} = \mathbf{x}(\mathbf{X}, t) - \mathbf{X}
\]  

(2.5)

**Figure 2.4**: The schematic of a material body in the reference (A) and deformed (B) configurations, both of which are defined in a three-dimensional orthonormal coordinate system, \( \mathbf{e} = (e_1, e_2, e_3) \), with an origin, \( \mathbf{O} = (0,0,0) \). The movement of a material point, \( P \), from \((X_1, X_2, X_3)\) to \((x_1, x_2, x_3)\) is represented by \( \mathbf{u} \).

Motion given by Eq. (2.5) provides both the magnitude and direction of the movement of each material point within the myocardium. In general, different material points within the myocardium undergo different amounts of motion. Questions that arise include how to interpret all these motion vectors and relate them to myocardial function, especially the
regional kinematics, and to what degree myocardium functions. The answer to these questions is to evaluate the difference in motion, i.e., deformation, between neighboring material points. The deformation depicts how myocardium stretches, shortens and changes its shape, can be quantified by *strain*, and is critical for the diagnosis of coronary artery disease (see section 2.3).

Since the Lagrangian description is used, how a material segment deforms from the reference to the deformed configurations is assessed. This Lagrangian deformation can be quantified using a transformation matrix, which is coined as a deformation gradient (\( F \)) and relates the position vector in the reference configuration (\( X \)) to that in the deformed configuration (\( x \)) as follows:

\[
\frac{dX}{dx} = F \cdot dX
\]

(2.6)

\[
F = \frac{dx}{dX} = \begin{bmatrix}
\frac{dx_1}{dX_1} & \frac{dx_1}{dX_2} & \frac{dx_1}{dX_3} \\
\frac{dx_2}{dX_1} & \frac{dx_2}{dX_2} & \frac{dx_2}{dX_3} \\
\frac{dx_3}{dX_1} & \frac{dx_3}{dX_2} & \frac{dx_3}{dX_3}
\end{bmatrix}
\]

(2.7)

The deformation gradient, \( F \), is not necessarily symmetric and may include rigid body motion component, so a right Cauchy-Green deformation tensor, \( C \), defined in the reference configuration, is used and formulated as

\[
C = F^T F
\]

(2.8)

The Green strain can therefore be defined as

\[
E = \frac{1}{2} (C - I) = \frac{1}{2} (F^T F - I)
\]

(2.9)

From Eq. (2.5), we can derive
\[
\frac{du}{dX} = \frac{dx}{dX} - \frac{dX}{dX} \tag{2.10}
\]
\[
\nabla u = F - I, \tag{2.11}
\]

where \( \nabla u \) denotes \( \frac{du}{dX} \) and is termed as a displacement gradient.

The Green strain tensor can also be written to describe cardiac deformation based on the displacement gradient, \( \nabla u \) in Eq. (2.11), as
\[
E = \frac{1}{2} \left( F^T F - I \right) = \frac{1}{2} \left( (\nabla u + I) (\nabla u + I) - I \right) = \frac{1}{2} \left( \nabla u^T \cdot \nabla u + \nabla u^T + \nabla u \right) \tag{2.12}
\]

The kinematics of the heart over cardiac cycles has been extensively studied. Originating from the seventies, studies involving the \textit{in vivo} measurement of myocardial deformation using markers, ultrasound crystals (or, sonomicrometers)\textsuperscript{14-16} were widely performed. Since the late eighties, imaging techniques which enable non-invasive depiction of the cardiac deformation (or, strain) have been proposed and implemented. They have recently emerged to be of the main interest in clinical cardiology. Such techniques include ultrasound-based methods, for instance, optical-flow-based methods\textsuperscript{17-20}, tissue Doppler Imaging\textsuperscript{21-23}, Strain or Strain Rate Imaging\textsuperscript{24-28}, B-mode and model-based methods\textsuperscript{29-31}, Myocardial Elastography\textsuperscript{4,32}, and magnetic resonance tissue tagging\textsuperscript{33,34}. The ultrasound-based techniques will be discussed in the next chapter.

The knowledge of left-ventricular kinematics together with stress facilitates the construction of the constitutive relations that govern myocardial mechanical behavior. However, stress cannot be measured in the intact heart \textit{in vivo}, so biaxial testing on excised myocardium is alternatively used to characterize the material properties, which can then be modeled by constitutive relations between stress and strain with adequate strain energy functions\textsuperscript{7}. The relation can further be solved according to conservation laws, including
mass, momentum and energy, subject to boundary conditions on pressure and displacement.

Computational models of the heart utilizing finite-element analysis have been well established\textsuperscript{9, 35-37} and permit the understanding of the mechanical behavior of the myocardium in pathological as well as normal cases. In brief, the overall framework is to model the heart using prolate spherical coordinates, and its computational complexity is reduced by the employment of Hermite shape functions\textsuperscript{36}. Continuity\textsuperscript{®}, developed by the Cardiac Mechanics Research Group at University of California, San Diego, is such a well-established computational platform for modeling the heart, and allows integration of mechanics into an imaging framework for the image analysis of myocardial deformation. This integrated framework serves as a first step for performance evaluation of Myocardial Elastography, developed by our group, and will be detailed and presented in Chapter 4.
2.3. Coronary Arteries and Myocardial Ischemia

Coronary circulation, the network of coronary arteries and their branches, is the key to the oxygen supply to cardiac muscles as a basis of normal myocardial contraction and left-ventricular function. The heart itself is perfused by the coronary arteries, which originate at the aortic sinuses. The three primary coronary arteries are left anterior descending (LAD), left circumflex (LCx) and right coronary artery (RCA) (Figure 2.5(a)). Regardless of variable patterns of coronary distribution from one to another individual, the LAD generally supplies 1) mid-ventricular and basal segments of the anterior, anterolateral and anteroseptal walls and 2) all apical segments; the LCx supplies mid-ventricular and basal inferolateral segments; and the RCA supplies the mid-ventricular and basal inferior wall and inferior septum (Figure 2.5(b))\textsuperscript{5}. Major coronary arteries run on the epicardial surface of the heart, with the branches diving into the muscular wall and running perpendicularly from the epicardial to endocardial regions. The epicardial region is closer to the source of supply, the subendocardial region further away\textsuperscript{38}. 
Figure 2.5: (a) A simplified schematic (adapted from *Hurst’s the Heart*) of the distribution of coronary circulation in a 16-segment model of the heart: LMA is the left main coronary artery. LAD and D indicate left anterior descending coronary artery and its diagonal branch, respectively. LCX and OM left circumflex coronary artery and its obtuse marginal branch, respectively. RCA is the right coronary artery. RM and PD represent right marginal branch and posterior descending coronary artery, respectively; (b) illustration of basal, mid and apical levels of short-axis views in the 16-segment model, where A, AL, PL, P, PS, AS, IL, I, IS, L, S and RV denote anterior, anterolateral, posterolateral, posterior, posterior ventricular septum, anterior ventricular septum, inferolateral, inferior ventricular septum, lateral, septum, and right ventricle, respectively.
The left ventricle receives the largest proportion of coronary blood flow, whose perfusion occurs mainly during diastole because of the decrease in intramyocardial pressure gradient generated by muscle contraction. Coronary blood flow is not only cardiac-phase dependent, but its distribution is also myocardial-region dependent. The subendocardial region receives more coronary flow than the subepicardium (1.25:1) in a normally perfused heart. Systolic compressive forces in the subendocardium are greater than in the subepicardium, so arteries and arterioles in the subendocardium are more vulnerable to the compression. Compared to the subepicardium, the subendocardium experiences more reduction of flow and is more susceptible to ischemia in the presence of coronary stenosis.

Ischemia, characterized as the imbalance between blood supply and demand, can be associated with coronary artery disease and can be categorized into supply ischemia and demand ischemia. The former is the focus of this dissertation. In other words, supply ischemia due to the reduced coronary blood supply caused by coronary stenosis is studied. Among the common causes of coronary stenosis, including coronary atherosclerosis, coronary thrombosis and coronary vasoconstriction, coronary atherosclerosis occurs most frequently. When the lumen of the coronary arteries is narrowed to a certain degree, mainly due to atherosclerosis (Figure 2.6), coronary autoregulation mechanisms cannot maintain a sufficient blood supply, so coronary blood flow will be reduced and thus result in deprivation of blood/oxygen in the cardiac muscle. Consequently, cardiac muscles weaken, lose their capability of generating active force and cannot contract normally.
Figure 2.6: Schematics (adapted from AHA Glossary Media Library\textsuperscript{40}) of (a) a normal coronary arterial segment and (b) a diseased coronary artery in the longitudinal (left) and cross-sectional (right) views. The plaque is formed in the intima layer due to atherosclerosis. The plaque may grow, further occlude the coronary artery lumen, and ultimately cause myocardial ischemia. When the plaque ruptures, thrombosis may be formed and further obstruct the artery.
Myocardial contractility can be indirectly assessed by quantifying myocardial deformation (or, strain). Strain is a quantity, describing how an object deforms in length and shape. As mentioned in section 2.2.2, strains have been well established to quantify myocardial deformation and characterize the ischemic region in an enormous amount of in vivo studies\textsuperscript{41-44}. Direct measurement of segmental or regional deformation was performed in normal and acute ischemia induced by ligating the coronary arteries. As the technology advanced, direct measurement was performed from the usage of radiopaque beads with X-ray to that of sonomicrometry. In short, previous studies\textsuperscript{44, 45} have shown that acutely ischemic myocardium loses its ability of active force generation and thus undergoes systolic lengthening and wall thinning; in contrast, normal myocardium experiences systolic shortening and wall thickening.

Figure 2.7, adapted from Villarreal et al.\textsuperscript{44}, shows temporal profiles of all normal and shear strain components within a region centered at the midwall over a full cardiac cycle in the control and 10-min ischemia cases in a canine left ventricle. The myocardial ischemia in their study was induced by complete LAD occlusion. Their findings have demonstrated that the ischemic myocardium experienced deformation opposite the normal myocardium. In other words, radial strains were positive (i.e., radial thickening) in the control condition and became negative (i.e., radial thinning) during acute ischemia; both circumferential and longitudinal strains were negative (i.e., circumferential and longitudinal shortening) in the control condition and became positive (i.e., circumferential and longitudinal stretching) during acute ischemia. The shear strains except for the circumferential-longitudinal component also exhibited opposite deformation occurred after LAD occlusion.
Figure 2.7: Temporal profiles (adapted from Figure 2 in Villarreal et al. 1991) of all normal (i.e., circumferential, longitudinal and radial) and shear strain components within a region centered at the midwall over a full cardiac cycle in the control (indicated by open circles) and 10-min ischemia caused by the complete LAD occlusion (denoted by closed circles) cases in a canine left ventricle. End diastole (0 ms) was used as the reference time point.
Consequently, imaging techniques that can estimate regional strains, such as Myocardial Elastography \(^4, 32\), as presented in this dissertation, have emerged and are steadily becoming a valuable tool to differentiate ischemic from normal myocardium. Moreover, the detection of myocardial ischemia at its earliest stages, namely the contrast between early ischemic and normal myocardium, is recognized as an essential step for early and effective treatment. The performance of Myocardial Elastography for the characterization of ischemic myocardium at the progressive stages of myocardial ischemia, which is simulated by progressively constricting coronary blood flow, will be assessed and presented in Chapter 5.
Chapter 3

Ultrasound Imaging and its Use for Cardiac Function Assessment

3.1. Cardiac Imaging

Primary existing cardiac imaging modalities \(^{46, 47}\) include X-ray ventriculography, computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET), and ultrasound. All of them can be used to study the anatomical or functional changes of the heart under pathological conditions. Global and regional cardiac, especially left-ventricular, function can therefore be evaluated. Their pros and cons render each modality complementary with one another in the reliable diagnosis of cardiac function. However, among those imaging modalities, ultrasound is the only imaging system that displays cyclic cardiac structural changes and movement in real-time while allowing instantaneous diagnosis of cardiac function, in and outside of the emergency room. In addition to its real-time feature, ultrasound has been extensively used for diagnosis in the clinic as it is non-ionizing, compatible with pacemakers, portable, relatively inexpensive, and not associated with claustrophobia.
3.1.1. Echocardiography

Medical ultrasound is normally operated at center frequencies ranging from 1 to 20 MHz. Imaging array transducers, which are composed of an array of piezoelectric crystals, transmit pulses and receive signals backscattered or reflected from the objects within the field of view. The three main types of ultrasound probes comprise linear, curved and phased array transducers. For superficial tissues, such as the breast and thyroid, linear array transducers are used. For abdominal organs, a curved array transducer is preferred as it offers a larger and deeper field of view. As for the heart, a phased array transducer is typically utilized given that its size (or aperture dimension; 24 mm for a 1D phased array) is suitable for intercostal imaging while achieving large imaging depth and field of view.

Cardiac ultrasound, referred to more commonly as ‘echocardiography’, relies on the same principles of ultrasound physics to image the heart. Nowadays, 1D and 2D phased array transducers are available to depict 2D and 3D cardiac structures and function, respectively. However, 3D images of the heart are not commonly acquired in real time and require multiple breath-holds and electrocardiogram (ECG)-gating or –triggering. Although 3D imaging provides the overall 3D structure of the heart, smoothing is often performed so that detailed structural information is usually lost. Therefore, in comparison with 3D, 2D echocardiograms exhibit higher spatial and temporal resolution, both of which are critical for cardiologists to perform more accurate and detailed diagnosis. Consequently, 2D echocardiography is primarily utilized throughout this dissertation.

In a clinical setting, standard 2D echocardiographic views of the heart include parasternal long-axis, parasternal short-axis, apical four-chamber, and apical two-chamber views (Figure 3.1). These four views provide structural and functional information of
different wall regions of the heart and are therefore always examined together to properly evaluate the overall cardiac function.

Figure 3.1: Examples of four standard 2D echocardiographic views of normal human heart in vivo (female, 28 y.o.): (a) parasternal long-axis; (b) parasternal short-axis; (c) apical four-chamber; and (d) apical two-chamber. ANT, Ao, AoV, INF, LA, LV, MV, PM, POST, RA, RV, SEP, and TV denote the anterior wall, aorta, aortic valve, inferior wall, left atrium, left ventricle, mitral valve, papillary muscle, posterior wall, right atrium, right ventricle, septal, and tricuspid valve, respectively.
Echocardiography has been widely used for the diagnosis of coronary artery disease, which usually accompanies impaired myocardial deformation as explained in the previous chapter. A conventional way of evaluating myocardial motion is through the wall motion score index, semi-quantitatively graded by cardiologists. However, there may involve diagnosis variations among cardiologists or even among different observation times by the same cardiologist. Therefore, automated quantitative cardiac motion analyses have emerged as more objective diagnostic methods.

### 3.2. Ultrasound-Based Cardiac Motion Analysis

The first question to arise is how we can obtain motion information from the echocardiograms. An intrinsic characteristic of all ultrasonic images is speckle, defined as a coherence pattern. Even though speckle is regarded as noise in terms of image quality, speckle is in fact a natural marker, which encodes the motion information of the imaged heart. Estimation of tissue motion, which is related to the underlying change in tissue elasticity, was first reported by Dickinson and Hill[^48^], who used the correlation coefficient between two successive A-scans (i.e., one-dimensional envelope-detected ultrasound signals) as a measure. Tissue motion and its associated change in the speckle patterns of the myocardium were also reported later by Meunier et al.[^19^, ^20^]. In other words, tracking speckle allows us to perform motion analysis.

Cardiac motion analysis on ultrasound can be categorized into two groups. In one group, the displacements are estimated using B-mode images, while in the other, motion is estimated using RF signals. Gray level values (brightness), which represent the acoustic intensity after envelope detection of the unprocessed ultrasonic RF signals, are tracked in
the first group. Although B-mode images do not contain phase information, they provide a fair and efficient method for displacement estimation, compared to the estimation based on RF signals. However, the B-mode-based motion estimation is less accurate\textsuperscript{49,50} due to the lack of complete information (i.e., phase) on the signals tracked. Further details and discussion are given in this section.

### 3.2.1. B-Mode-Based Speckle Tracking

Speckle tracking using B-mode images relies on the measurement of the amount of similarity between the reference and comparative images. Since only the magnitude (or, brightness) is preserved on the B-mode images, block-matching\textsuperscript{49-53} and optical flow\textsuperscript{17,18,20,54} methods are commonly employed to obtain tissue kinematics.

In B-mode-based speckle tracking algorithms, the motion of each pixel from a reference frame to a deformed frame is of interest. Take the 2D configuration (i.e., a sequence of 2D B-mode images) as an example. In the block-matching method (Figure 3.2.), the size of the region of interest, or, the matching windowed block, on the reference image should be appropriately chosen first and centered at the pixel of interest (indicated by the cyan dot in Figure 3.2). The matching block is usually a 2D kernel that should be large enough to meet the requirement of speckle statistics. Thereafter, a search region on the comparison image (gray shaded region in Figure 3.2) is defined and centered at the location of the pixel of interest. Several candidate blocks, of the same (or, similar) size as the matching block, on the comparison image are then chosen within the pre-defined search region (Figure 3.2). The similarity between the matching block and each candidate block
within the search region is calculated using the sum-of-squared differences (SSD), sum-of-
absolute differences (SAD), cross-correlation, etc. The candidate window which results in
the greatest similarity (e.g., smallest SSD or SAD value, largest correlation coefficient) is
considered the best match with the matching block. Take the SAD measure as an example:

$$SAD(i, j) = \sum_{k=-m/2}^{m/2} \sum_{l=-n/2}^{n/2} \left| I_1(i+k, j+l) - I_0(x_0 + k, y_0 + l) \right|,$$

(3.1)

where $I_0$ and $I_1$ are the reference and comparison images, respectively; $x_0$ and $y_0$ represent
the location of pixel of interest in the reference image; $i$ and $j$ indicate the location of each
pixel within the search region; the size of the matching/candidate block is $(n+1)$-by-$(m+1)$;
SAD$(i, j)$ is the SAD value at the pixel location $(i, j)$.

$$\arg \min_{i \in [x_0 - M, x_0 + M], j \in [y_0 - N, y_0 + N]} (SAD(i, j)),$$

(3.2)

where $M$ and $N$ define the size of the search region centered at $(x_0, y_0)$ on the comparison
image (represented by the cyan dot on the right panel of Figure 3.2). The pixel location $(i, j)$
which results in the minimum SAD value (or, the highest similarity to the matching
block centered at $(x_0, y_0)$) can be obtained using Eq. (3.2). Consequently, the spatial shift
between the matching block centered at $(x_0, y_0)$ and its best match centered at $(i, j)$
represents the incurred motion, indicated by the motion vector, $\mathbf{u}$, in Figure 3.2. The same
method is repeated for each image pixel in the reference image. The full
motion/displacement field can therefore be estimated on B-mode images, such as in the
cardiac motion study by Li et al.\textsuperscript{52,53}. 
Figure 3.2: A schematic of the block-matching-based speckle tracking strategy: a matching block on the reference image is defined and centered at \((x_0, y_0)\), i.e., pixel of interest (indicated by the cyan dot). A search region on the comparison image is represented by the gray shaded area. The candidate block which is the best match with the matching block is indicated and centered at the image pixel labeled in magenta color. \(\mathbf{u}\) is the estimated motion vector for the pixel of interest, \((x_0, y_0)\).

In the conventional optical flow method\(^{18, 20}\), the motion is estimated through the observation of the changes in brightness in space and in time. The principal assumptions of this algorithm are that the brightness of the reference point is conserved in space and time and that the velocity is continuous in space. The application of this technique to myocardial motion and deformation was first reported by Mailloux et al. and Meunier et al.\(^{18, 20}\). Since then, tracking cardiac motion using optical flow and its variations on echocardiograms has been extensively investigated in 2D or 3D\(^{17, 55-58}\). Several different techniques for cardiac
motion analysis on B-mode images have also been reported in the literature\textsuperscript{29-31, 59, 60}. Even though B-mode based techniques have shown promising results for quantifying myocardial motion and strains and can be implemented in real time, lack of the phase information in B-mode images results in less accurate and precise motion estimation compared to RF-based methods, thus less accurate strain, and less reliable diagnosis of left-ventricular dysfunction.

### 3.2.2. Radio-Frequency-Based Speckle Tracking

In contrast to B-mode images, where only the magnitude is preserved (see section 3.2.1.), radio-frequency (RF) signals inherently represent both magnitude and phase information. Common RF tracking techniques can be categorized into frequency domain and time domain analyses. In the frequency domain, the RF signals are in fact the complex RF signals, while in the time domain the RF signals are the unprocessed RF signals. In both, the similarity measure between signals is usually determined by the normalized cross-correlation coefficient. A representation of the normalized cross-correlation on real-valued signals, or RF signals, is as follows:

\[
\rho_{k,l} = \frac{\sum_{i=1}^{m} \sum_{j=1}^{n} (A_{i,j} - \overline{A})(B_{i+k,j+l} - \overline{B})}{\sqrt{\sum_{i=1}^{m} \sum_{j=1}^{n} (A_{i,j} - \overline{A})^2 \sum_{i=1}^{m} \sum_{j=1}^{n} (B_{i+k,j+l} - \overline{B})^2}},
\]  

(3.3)

where \(A\) and \(B\) are the reference and candidate frames, respectively; \(i\) and \(j\) indicate the local coordinates of each sample point within a window kernel of size \(m \times n\); \(k\) and \(l\) define the locations where similarity is to be measured; \(\overline{A}\) and \(\overline{B}\) are average values of the \(A\) and \(B\) within the defined window kernel.
The normalized cross-correlation coefficient shown in Eq. (3.3) is calculated for each target sample point \((k, l)\) within a pre-defined search region. The location in the candidate frame which produces the maximal cross-correlation coefficient is considered the best match with the reference location. The shift between the two locations indicates the incurred motion.

In the frequency domain, complex, or analytical, RF signals are utilized\(^{24, 26, 61-64}\). The normalized complex cross-correlation coefficient is therefore computed using an equation similar to Eq. (3.3) but on complex RF data to obtain the phase shift presenting with maximum complex cross-correlation coefficient. Motion can be further derived from the estimated phase shift.

On the other hand, in the time domain, the unprocessed RF signals are used as previously defined. The normalized cross-correlation coefficient\(^{4, 28, 65-70}\) or SAD\(^{25}\) has been reported to be the best estimator of the time shift, which can be easily converted to motion/displacement with an assumed sound speed (1540 m/s, similar for all soft tissues). Because of the complete information contained in RF signals, RF-based techniques estimate motion with higher accuracy and precision than B-mode-based methods. As a result, RF signals are employed in our proposed technique, Myocardial Elastography (Chapter 4).

Motion/displacement, estimated using either B-mode- or RF-based speckle tracking methods, is essential in deriving strains so as to quantify myocardial deformation. Accurate motion estimation leads to reliable strain estimation and may enhance the contrast between pathological and normal myocardium. In this regard, estimation of cardiac strains using ultrasound speckle tracking techniques becomes worth noting in the detection of abnormal
myocardial function associated with coronary artery disease, especially given the strong clinical interest\textsuperscript{71, 72}. The main cardiac strain imaging techniques in echocardiography are introduced in the next section.

### 3.3. Cardiac Strain Imaging Techniques

A substantial number of ultrasound-based techniques for strain or strain-rate estimation can be found throughout the recent literature\textsuperscript{4, 22, 24, 25, 28, 32, 52, 63, 64, 70, 73-78}, and ultrasound-based cardiac strain imaging techniques have been booming and arisen the clinical interest. Below is the summary of several well recognized research reports in the strain or strain rate imaging field.

#### 3.3.1. Tissue Doppler Imaging (TDI)

In ultrasound, the Doppler method is typically used to estimate blood velocity. The feasibility of a Doppler-based method for tracking tissue velocity, specifically myocardial motion, was firstly reported by McDicken et al.\textsuperscript{22}. Thereafter, Miyatake et al. developed a tissue Doppler imaging (TDI) technique based on a modified color Doppler method, where low frequency Doppler signals are unfiltered for tissue motion/velocity estimation\textsuperscript{23}. Detailed algorithms were described, and \textit{in vivo} data of both normal and pathological (infarcted or dilated cardiomyopathy) myocardium were analyzed and presented to show the potential of TDI in the clinical setting\textsuperscript{23}. Edvardsen et al. further proposed Strain Doppler Echocardiography (SDE) to calculate strains from tissue velocity\textsuperscript{21}. Their results have demonstrated that strains are a more precise quantity than velocity in the evaluation of
myocardial deformation since strains can in fact separate myocardial (active) contraction from (passive) relaxation\textsuperscript{21}.

Despite the proven clinical significance of these Doppler-based techniques in the assessment of myocardial function, they suffer from the Doppler-associated angle-dependence on the orientation of the ultrasound probe with respect to the tissue motion direction. Doppler-based methods primarily estimate the velocity component parallel to the ultrasound beams (i.e., axial direction). Therefore, if there is an angle between the velocity direction and the ultrasound beams, this angle needs to be corrected in order to obtain accurate velocities. In the clinical setting, this angle is unknown and can be difficult to measure throughout the cardiac cycle. Moreover, in the standard short-axis echocardiogram, the lateral and septal walls of the left ventricle mainly exhibit lateral motion, which can be perpendicular to the ultrasound beams. This perpendicularity limits the velocity estimation using Doppler-based methods. When echocardiograms in the apical views are considered, the longitudinal motion is estimated. When echocardiograms in the short-axis view are considered, only the radial motion estimation in the anterior and inferior wall regions is reliable. These findings show that the Doppler-based techniques complicate the quantification and diagnosis of the myocardial function owing to their angle dependence.
3.3.2. Strain Rate Imaging (SRI)

Strain Rate Imaging (SRI) was initially a TDI-based strain imaging method\textsuperscript{75}. The strain rate is calculated as the spatial derivative of the tissue velocity, which is estimated from TDI. Same as the conventional strain definition (see section 2.2.2.2), negative and positive strain rates denote tissue compression/shortening and stretching/elongation, respectively, along the observation axis. Although strain can be more informative than velocity in myocardium, this first generation SRI is TDI-based and thus limited by the associated angle dependence, explained in the previous section.

The angle-dependence issue was later overcome by employing two-dimensional cross-correlation-based speckle tracking techniques on either complex RF\textsuperscript{26} or unprocessed RF\textsuperscript{25}, signals to estimate tissue motion and deformation. Strain or Strain Rate Imaging has become a general term for myocardial strain rate estimation regardless of which estimation method is employed\textsuperscript{17, 28, 30, 52, 69, 70, 79, 80}.

3.4. Elastography/Myocardial Elastography

Myocardial Elastography, first proposed by Konofagou et al.\textsuperscript{4, 65}, is an ultrasound-based strain imaging technique for the assessment of myocardial function that aims at imaging reliable myocardial displacement and deformation (or, strain) in early stages of ischemia as well as in the normal case. It was inspired and rooted in the Elastography method, originally proposed by Ophir et al.\textsuperscript{81} for breast cancer detection. Elastography is a technique that estimates tissue deformation (or, strain) through an applied external compression of tissues along the axial direction and/or to further obtain tissue elasticity.
based on the known compression force. This technique has been extensively investigated for depiction of one- to three-dimensional deformation of soft tissues\textsuperscript{82-84} such as in the breast and liver. Both strain and modulus images have been provided\textsuperscript{81}.

In conventional elastography, an external compression is applied to deform tissues for the assessment of their tissue properties and distinction between normal and pathological tissues. Different from breast and abdominal soft tissues, the heart undergoes intrinsic deformation, which serves as the foundation of Myocardial Elastography\textsuperscript{4}. In its first feasibility study, incremental axial displacements and strains of the septal wall in the four chamber view and of the posterior wall in the parasternal long-axis view of a normal human left ventricle were shown\textsuperscript{4}.

In the following chapters, Myocardial Elastography with some novel amendments\textsuperscript{32} will be presented and further investigated as a diagnostic tool for assessment of the mechanical function of myocardium. Although a great deal of strain imaging techniques have been reported (section 3.3.), displacement and strain images are presented in the literature without associated justification and accuracy assessment of the strain estimation. Hence, the primary objective of Myocardial Elastography is to provide reliable displacement and strain images as well as their validation in a full, 2D configuration. In addition, the comparison of Myocardial Elastography with other RF-based techniques highlighted in section 3.3 is summarized in Table 4.1 in Chapter 4 in order to help identify its potential advantages over others.

As far as the Myocardial Elastography technique is concerned, several new aspects are incorporated and detailed in Chapter 4: 1) a 2D search is performed for cross-correlation; 2)
the displacement estimation is extended from one-dimension to two-dimension and the bi-plane configuration; 3) a recorrelation method is used to correct the axial displacement estimate for the lateral displacement; 4) cumulative 2D displacements are computed and imaged; 5) cumulative 2D strains are further calculated and imaged. In view of the in vivo assessment of Myocardial Elastography, its performance is validated against the currently considered gold standards (sonomicrometry in animals and MR tagging in humans) in Chapters 5 and 6.
Chapter 4

Myocardial Elastography-

Theoretical Quality Assessment

4.1. Background

As mentioned in section 2.3., abnormal patterns of regional myocardial deformation are often an important indicator of cardiac disease. Even though the non-invasive assessment of myocardial deformation using tagged magnetic resonance imaging (tMRI)\(^{85}\) is regarded as a gold standard, echocardiography has important advantages owing to its higher temporal resolution, low cost, portability, familiarity to cardiologists and widespread availability in hospitals and offices. Thus, echocardiography has been widely used for the detection of abnormal myocardial function, due to ischemia or infarction, through the estimation of the motion and strain of the cardiac muscle.

Several groups have recently applied elasticity imaging techniques to echocardiography; these are mainly time-shift-based techniques for Strain Rate Imaging (SRI), which have been successful in temporal imaging of the strain or strain rate\(^{25, 75}\) in several applications ranging from theoretical elasticity reconstruction models\(^{86}\) and phantoms\(^{26, 70}\) to monitoring of cardiac resynchronization\(^{87}\) and stress echocardiography\(^{88}\). These techniques encompass imaging of various mechanical parameters that reflect
myocardial deformation, such as displacement, strain, strain rate, velocity, shear strain, rotation angle, etc. In Myocardial Elastography, a recorrelation method, in addition to cross-correlation, is used to estimate tissue displacements from the radio-frequency (RF) signals, and strain is computed from these displacements. The image that depicts the strain is called an ‘elastogram’. Therefore, since assessment of myocardial deformation has proven to be a crucial step in the detection of cardiac abnormalities, Myocardial Elastography can help make a significant impact in this field by measuring the mechanical response of the cardiac muscle at various phases of the cardiac cycle. Myocardial Elastography further benefits from high precision, time-shift-based strain estimation techniques, and from the high frame rate currently available in ultrasound systems that enables a detailed map of the transmural strain in normal and pathological cases over different phases and over several cardiac cycles. Similar to the time-domain, RF-based strain estimation and SRI techniques, Myocardial Elastography estimates the strain at high precision. In contrast to these techniques, which typically use M-mode or averaged temporal strain/strain-rate traces in a localized region or use specific phantoms and in vivo cases without a theoretical performance assessment, Myocardial Elastography estimates and compiles all orthogonal strain components through a recorrelation method in order to obtain fully angle-independent estimates for the reliable depiction of disease. It then images the total systolic transmural deformation fields associated with contraction between end-diastole (ED) and end-systole (ES) in standard echocardiographic view, in both theory and a clinical setting.
Therefore, in this chapter, a theoretical deformation model of the left ventricle is used in order to evaluate the performance of the Myocardial Elastography technique. Previously, Rabben et al.\textsuperscript{92} proposed a kinematic model, which utilized physiologic left-ventricular deformation patterns based on measurements, including wall thickness and dimensions of the long and short axes from 15 healthy volunteers. Two groups further utilized this kinematic model to validate their proposed strain and SRI techniques\textsuperscript{24, 93}. Nevertheless, the measures used in the kinematic model were individually averaged to form a general normal deformation pattern in a cardiac cycle. The left ventricle (LV) was approximated as a thick-walled ellipsoid and deformed according to the averaged measures. Torsion of the LV was also considered by assuming that the rotation varied linearly from base to apex. Although the model-calculated displacements and strains were in good qualitative agreement with \textit{in vivo} observations, the simplified kinematic model did not include a realistic geometry, tissue structure, material properties and other features required to faithfully reproduce regional variations in deformation during normal as well as abnormal contraction. It is widely accepted that finite-element (FE) analysis provides the most comprehensive approach to model mechanical function of the left ventricle (LV) with the incorporation of a mathematical representation of three-dimensional (3D) ventricular anatomy, orthotropic material properties and fiber orientation\textsuperscript{35, 36, 94}. 
4.2. Methodology

4.2.1. A Three-Dimensional (3D) Finite-Element (FE) Model

Three-dimensional (3D) FE models of a normal (Control) and left circumflex ischemic (LCx) left ventricle (LV) of an open-chest mongrel dog were employed for quality assessment of Myocardial Elastography (Figure 4.1). The models were developed by the Cardiac Mechanics Research Group, led by Andrew D. McCulloch, at the University of California, San Diego (http://cmrg.ucsd.edu/) and were reported previously\textsuperscript{37, 95}.

![Figure 4.1](image-url): Anterior views of three-dimensional FE left-ventricular meshes at end-systole: (a) normal (Control) and (b) left-circumflex ischemic (LCx) models shown in the Cartesian coordinates ($x, y, z$), where positive $x$, $y$ and $z$ point toward lateral wall, anterior wall and apex. The endocardium and epicardium are represented by red shading and wire frame, respectively. The blue shaded surface depicts the ischemic region on the endocardium. The base, apex, anterior (ANT), lateral (LAT) and septal (SEP) regions are indicated.
Figures 4.1(a) and (b) show anterior views of the normal (Control) and ischemic (LCx) models, respectively, at ES. The LCx model has been designed to simulate an ischemic region two minutes after constriction of the left circumflex coronary artery. Abnormal contractile function is a result of inhibited activation in the posterior-lateral region, which is perfused by the LCx coronary artery. The ischemic myocardium behaves as a passive tissue and lacks the ability to contract during the entire cardiac cycle. The ischemic muscle occupies approximately 40% of the left-ventricular wall (Figure 4.1(b)). The employed model uses the so-called ‘time-varying elastance’ scheme to simulate the end-systolic configuration of the left ventricle. Briefly, this method calculates active stress as a function of intracellular calcium concentration. There is no explicit dependence on pressure load. Starting from an unloaded reference configuration, systolic ejection is therefore modeled by simultaneously gradually increasing the pressure and intracellular calcium concentration until the desired end-systolic configuration is reached. This path in fact simulates the gradual increase in stiffness (elastance) experienced by the left ventricle during systole, but does not correspond to the isovolumic contraction and ejection phases represented in pressure-volume curves. The time-varying elastance has been shown to adequately describe end-systolic mechanics. For this study, an end-diastolic pressure (EDP) of 11 mmHg and an end-systolic pressure (ESP) of 129 mmHg are assumed in both the control and LCx models. The two models contain ten passive filling and 15 time-varying elastance steps with respect to the unloaded state, with each maximum strain between two consecutive configurations being approximately 2.5%, which is within the optimal range of strain estimation in elastography. Compared to passive filling, the added complexity of the length-dependent activation equations used during systole requires smaller load
increments to ensure convergence, resulting in a greater number of intermediate load configurations.

The 3D Control and LCx ischemic models were initially described with 48 nodes and 24 bicubic elements\textsuperscript{95}. The LV wall was two-elements thick, with endocardial, midwall and epicardial surfaces defined in Cartesian coordinates \((x, y, z)\). Both the normal and ischemic canine models had wall thicknesses of 10.92 mm and 17.8 mm at the end-diastolic phase in the septal and lateral regions, respectively. In the 2D ultrasound simulation, a 2D short-axis slice at the model equator (i.e., \(z = 0\)), which intersected the ischemic region of the LCx model, was considered to represent the 2D ultrasound image plane (Figure 4.1). Using cubic Hermite polynomials, which allowed continuity of both the displacements and strains across all element boundaries and ensured continuous representation of myocardial deformation, any arbitrary number of locations could be extracted within each element, throughout the entire model. For this study, 840 evenly distributed material points (21 radially \(\times\) 40 circumferentially) were used to track the regional deformation of the equatorial model slice. Considering a 2D short-axis slice in a 2D ultrasound image formation model, only the in-plane displacement components, i.e., the \(x\)- and \(y\)-components in this case, were taken into account. The out-of-plane motion was ignored in order to examine the performance of the Myocardial Elastography under optimal conditions, i.e., in a simplified scheme with pure 2D motion. To represent the 2D displacement field throughout the short-axis slice of the myocardium, bicubic interpolation of the extracted material points was used.

A simulated echocardiogram in the equatorial short-axis slice with overlayed 2D motion vectors of the inner (endocardium) and outer (epicardium) walls for the first
incremental step during passive filling is shown in Figure 4.2(g), where the endocardium experiences larger motion than the epicardium. A 2D motion vector can be obtained by the vector sum of its horizontal \((x)\) and vertical \((y)\) components. The horizontal and vertical displacement fields are shown in Figures 4.2(a) and (d), respectively. The 3D finite-element model used is validated in open-chest canine left ventricles. Therefore, a linear array configuration is suitable for the experiment simulated. Since a linear array image formation model is employed (see below), horizontal \((x)\) and vertical \((y)\) axes coincide with the lateral and axial ultrasound axes, respectively.

In the 3D ultrasound simulation model, five short-axis slices obtained at the sub-basal to the sub-apical levels were considered. The purpose of the 3D ultrasound simulation was to study the effect of the out-of-plane motion on the in-plane deformation estimation based on the fact that out-of-plane motion varied at elevational (or, longitudinal in cardiac coordinates) levels of the left ventricle. Unlike the previous 2D simulation scheme with 840 material points used, only the solutions (3D motion and nodal coordinates) at the endo- and epicardium were extracted from the finite-element model and considered so that the transmural strain variation was constant in the 3D simulation scheme. The entire in-plane (lateral and axial) displacement fields in the myocardium between two consecutive configurations were calculated using bilinear interpolation with the known in-plane motion of each node at the element boundaries, while the out-of-plane (elevational) displacement field at each short-axis level within a certain slice thickness was considered as rigid motion. Unlike the physiologic case \textit{in vivo}, the apex of the left ventricle moved towards the base, which was constrained not to move in the finite-element model during systole. The out-of-plane motion thus decreased from the apex to the base.
Figure 4.2: An example of the effect of the recorrelation method for the first incremental step from the unloaded state to ED at the short-axis slice at the equator of the left ventricle: (a) and (d) are FE results; (b) and (e) are the first estimation (without recorrelation); (c) and (f) are the second estimation (with recorrelation); (g) shows a simulated short-axis echocardiogram at the unloaded state with overlayed motion vectors of the inner (endocardium) and outer (epicardium) walls, and anterior (ANT), lateral (LAT), septal (SEP) and posterior (POST) regions are indicated; (h) and (i) are cross-correlation coefficient (CC) maps for the first estimation (without recorrelation) and the second estimation (with recorrelation), respectively. The ME stands for the Myocardial Elastography technique.
4.2.2. Ultrasonic Image Formation Model

4.2.2.1. Two-dimensional simulation

In the simulated 2D ultrasound image corresponding to the selected equatorial short-axis slice, scatterers were assumed to be two-dimensionally distributed at 96 scatterers per square wavelength in order to simulate fully-developed speckle. Note that the background was assumed to have null scattering. According to the displacement field shown in Figures 4.2(a) and (d), the corresponding scatterer distribution could be used to generate two successive RF images. Similarly, the 2D, in-plane FE displacement field could also be employed to generate RF signals at each loading configuration during passive filling and time-varying elastance steps, explained in section 4.2.1. Radio-frequency (RF) signals (128 in total) with an aperture size of 80 mm were generated by convolving the 2D Gaussian-distributed scatterer function with a 2D simulated ultrasound point-spread function (PSF):

\[
I(x, y) = PSF(x, y) \otimes T(x, y)
\]

\[
PSF(x, y) = \exp\left(-\frac{1}{2}\left(\frac{x^2}{\sigma_x^2} + \frac{y^2}{\sigma_y^2}\right)\right) \cos\left(2\pi\frac{y}{\lambda_w}\right)
\]

where \(I(x, y)\) was a 2D RF echographic function, \(T(x, y)\) was the tissue scatter function, \(x\) and \(y\) were the lateral and axial coordinates, respectively, \(\lambda_w\) was half the wavelength (taking into account the round-trip of the wave in pulse-echo), and \(\sigma_x\) and \(\sigma_y\) were the standard deviations of the Gaussian function in the \(x\)- and \(y\)-directions at Full Width Half Maximum (FWHM), respectively. The 2D PSF had a center frequency of 2 MHz and 60% fractional bandwidth, representative of clinically used ultrasound systems, where the beamwidth was 2 mm and the pitch 0.625 mm (128 beams with a lateral dimension of 80...
mm). The sonographic signal-to-noise ratio (SNRs) was equal to 60 dB, similar to what was previously considered in prior literature on tissue strain estimation100. Despite the fact that this SNRs might be higher than what was typically measured in vivo, our preliminary studies in Myocardial Elastography dependence on SNRs showed that the quality (i.e., elastographic SNR, SNRe) of the technique remained identical when the SNRs was higher than 20 dB. These parameters were within a reasonable range. Each simulated 2D B-mode image was 80 mm-by-80 mm in size.

4.2.2.2. Three-dimensional simulation

Similarly, a 3D ultrasonic image was generated by convolving a 3D scatterer distribution with a 3D point spread function, formulated as Eq. (4.3)99. The scatterers were assumed to be three-dimensionally distributed at 96 scatterers per cubic wavelength in order to simulate fully developed speckle. The 3D FE displacement field was employed to generate RF signals at each loading configuration during passive filling and time-varying elastance steps. The defined 2D linear array consisted of 128 and 6 elements in the lateral and elevational directions, respectively, with a center frequency of 2 MHz and 60% fractional bandwidth.

\[
PSF(x, y, z) = \exp\left(\frac{-1}{2} \left(\frac{x^2}{\sigma_x^2} + \frac{y^2}{\sigma_y^2} + \frac{z^2}{\sigma_z^2}\right)\right) \cos\left(2\pi \frac{y}{\lambda_w}\right)
\] (4.3)

where \(z\) was the elevational coordinate and \(\sigma_z\) was the standard deviation of the Gaussian function in the \(z\)-direction at FWHM. Each simulated 3D B-mode image had an 80x80x6 mm\(^3\) field of view. The lateral beamwidth was 2 mm, the elevational beamwidth 2 mm, the lateral pitch 0.625 mm, and the elevational pitch 1 mm. The SNRs was equal to 60 dB.
4.2.3. Myocardial Elastography

4.2.3.1. Radio-Frequency (RF)-Based Displacement Estimation

Only the 2D, in-plane (i.e., lateral and axial) motion and deformation were estimated using the proposed Myocardial Elastography in both 2D and 3D simulations. The corresponding RF signals for each load increment could be generated using the image formation model described in section 4.2.2. Typically, myocardial function is evaluated during systole, i.e., from ED to ES. In our finite-element analysis, active contraction and passive filling were modeled separately as described in section 4.2.1. Finite strains from ED to ES could be computed directly from the two end-point configurations, taking advantage of the history-independent assumption of the time-varying elastance model of activation. Since Myocardial Elastography aimed at assessing the total systolic deformation, which was associated with contraction and independent of frame rate, by first accumulating incremental displacements, we estimated and compiled incremental displacements along the path from ED to ES to obtain cumulative displacements. These estimates were then compared to the solution of the model with ED as the reference and ES as the deformed state.

Several sets of consecutive RF frames from ED to ES were thus used to estimate the incremental 2D displacements. The reference and comparison frames respectively contained the RF signals before and after the displacements occurred. The comparison frame from the previous RF frame set thus became the reference frame in the next RF frame set. Alternatively, the incremental 2D displacements were accumulated to obtain the cumulative 2D displacement that occurred from ED to ES. Note that appropriate registration for each pixel on two consecutive displacement images needed to be performed.
in order to guarantee that the cumulative displacement represented the motion of material points; thus, the displacement information was used both for correction and accumulation.

In order to estimate the 2D displacement, cross-correlation and recorrelation techniques similar to those described in the literature\textsuperscript{82, 83} were employed, i.e., the cross-correlation technique employed a 1D matching kernel of 3 mm and an 80\% overlap, and performed a search in 2D. A 1D, instead of a 2D matching kernel, was used since the lateral motion stayed within one pitch (0.625 mm) for each incremental step, in which case a larger kernel size in the lateral direction would decrease the lateral resolution of the estimation\textsuperscript{51}.

The two displacement components could thus be estimated simultaneously (Figure 4.3). The steps of estimating 2D displacement are described as follows. First, a 16:1 linear interpolation scheme between two adjacent original RF signal segments of the comparison frame within the 1D kernel was employed (Figure 4.3 (b)) to improve the lateral resolution\textsuperscript{83}. Note that higher linear interpolation, i.e., 32:1 or higher, did not improve the estimation further and that the performance of linear interpolation has been shown to be close to that of a bandlimited (or sinc) interpolation using a 16:1 interpolation scheme\textsuperscript{101}. Second, the cross-correlation between the reference RF signal segment and the candidate RF signal segments of the comparison frame was performed. Third, the RF signal segment in the comparison frame that yielded the highest 2D correlation coefficient was considered the best match with the RF signal segment in the reference frame (Figure 4.3(a)). One-dimensional cosine interpolation along each direction was then applied around the initial maximal value of the cross-correlation function in order to increase the precision of the peak detection\textsuperscript{83}. Thus, the lateral displacement, i.e., $\Delta l$ in Figure 4.3(c), denoted the estimated motion occurring between the reference RF signal segment and its best
comparison frame match. The axial displacement, $\Delta a$ in Figure 4.3(c), was the estimated axial time-shift, or displacement, along the matched RF signal segment. So, a kernel in a 2D search yielded the two orthogonal, in-plane components of the displacement simultaneously, i.e., $(\Delta l, \Delta a)$.

The lateral decorrelation due to axial motion reduces the accuracy of the lateral displacement estimation\textsuperscript{102}. Therefore, the correction in axial displacement estimation, or recorrelation, had to be performed to reduce this decorrelation noise. Konofagou and Ophir showed that correction for axial strain by global stretching reduced the lateral decorrelation in breast and prostate elastography, i.e., where an external compression was used\textsuperscript{83}. However, global axial stretching could not be used to correct for axial decorrelation in the myocardium due to the unknown a priori information in the cardiac case and higher complexity (e.g., nonlinear transmural variation) inherent to the myocardial function. In Myocardial Elastography, an axial displacement correction method was instead implemented by shifting RF signal segments according to the estimated axial displacement in the comparison frame, prior to the second lateral displacement estimation (Figure 4.3(d)). In order to precisely correct for the axial displacement of the RF signals, i.e., to correct for sub-precision displacements, an interpolation factor of ten was used to interpolate the RF signals of the comparison frame and then correct for axial decorrelation by re-arranging interpolated RF signal segments based on the estimated axial displacement. The second lateral displacement estimation was thus performed after correction of the previously estimated axial displacement. Similarly, the lateral displacement correction prior to axial displacement estimation was also performed by shifting RF signal segments in the lateral direction by the amount previously estimated. Note that 2D displacement
components could not be corrected simultaneously because only 2D residual (or, minute) displacements would be left to estimate. Thus, the lateral and axial displacements were obtained following correction for axial and lateral displacements, respectively. Although four iterative steps of the correction and estimation were performed in order to improve the accuracy of the 2D estimation, three iterative steps were considered sufficient for reliable lateral estimation (Figure 4.2(c)) according to the SNR_e of the elastograms. In this three-iteration estimation scheme, both 2D displacement components were obtained in the first iteration step, while the second and the third iteration steps provided lateral and axial displacements, respectively.
Figure 4.3: Cross-correlation and axial recorrelation with 1D kernel (window) in a 2D search on RF signals: (a) RF signals in reference frame A. Spacing between two RF signals is denoted by $d$. The rectangle represents the 1D kernel used; (b) RF signals in comparison frame B, where solid and dotted lines are original and interpolated RF signals, respectively. Cross-correlation values between the 1D kernel in frame A and those 1D kernels in frame B are calculated; (c) The solid RF signal segment is the one in frame A, while the dotted line is the interpolated RF signal segment in frame B. $\Delta l$ and $\Delta a$ are the lateral and axial shifts, which yield the maximum cross-correlation value between the two signal segments; (d) Axial displacement is corrected based on $\Delta a$. 
An example of the recorrelation results is shown in Figure 4.2. Figures 4.2(a) and (d) show the FE calculated lateral and axial displacements within the plane at \( z = 0 \) (i.e., equatorial model slice). Positive displacements indicate motion rightwards in the lateral direction or upwards in the axial direction. Figures 4.2(b) and (e) respectively show the first-iteration, lateral and axial displacement images (without correction), and 4.2(c) and (f) respectively show the second-iteration lateral and the third-iteration axial displacement images (with correction).

The cross-correlation coefficient maps shown in Figures 4.2(h) and (i) indicate that the recorrelation method improves the displacement estimation. The mean values and standard deviations of the cross-correlation coefficients within the myocardium, namely in the spatial distribution, for the first (Figure 4.2(h)) and the second (Figure 4.2(i)) estimation are 0.90±0.06 and 0.98±0.01, respectively. The cross-correlation coefficient is, on average, improved by 9% through the use of the proposed recorrelation technique.
4.2.3.2. Two-Dimensional Strain Calculation

Strain can be defined in terms of the gradient of the displacement. The 2D, in-plane displacement can be written as \( \mathbf{u} = u_x \mathbf{e}_x + u_y \mathbf{e}_y \), where \( u_x \) and \( u_y \) are lateral and axial displacements, respectively. The \( \mathbf{e}_x \) and \( \mathbf{e}_y \) are unit coordinate base vectors in lateral and axial directions, respectively. The 2D displacement gradient tensor, \( \nabla \mathbf{u} \), is defined as\(^{103}\)

\[
\nabla \mathbf{u} = \begin{bmatrix}
\frac{\partial u_x}{\partial x} & \frac{\partial u_x}{\partial y} \\
\frac{\partial u_y}{\partial x} & \frac{\partial u_y}{\partial y}
\end{bmatrix}
\]

(4.4)

The 2D Lagrangian finite strain tensor, \( \mathbf{E} \), is defined as\(^{103}\)

\[
\mathbf{E} = \frac{1}{2} \left( \nabla \mathbf{u} + (\nabla \mathbf{u})^T + (\nabla \mathbf{u})^T \nabla \mathbf{u} \right),
\]

(4.5)

where \( (\nabla \mathbf{u})^T \) is the transpose of \( \nabla \mathbf{u} \). Lateral and axial strains are the diagonal components of \( \mathbf{E} \), i.e., \( E_{xx} \) and \( E_{yy} \), respectively. In order to improve the SNR\(_e\), a least-squares strain estimator (LSQSE)\(^{104}\) with a kernel of 7.5 mm in the lateral direction and a kernel of 4 mm in the axial direction on an 80mm-by-80mm field of view was used. The LSQSE reduces the noise from the gradient operation through a piecewise linear curve fit to the displacement. A larger lateral kernel, together with the recorrelation method (II-C2), improves the quality of the estimated lateral strain and renders it comparable to the estimated axial strain.

Due to the finite size of the window used, at the boundaries between the background and the myocardium, the myocardium on the interpolated displacement images and elastograms appeared thicker on the motion images than on the original RF images\(^{104}\). Therefore, a binary mask with the known myocardial boundaries from the FE model was
applied on the estimated displacement images and elastograms to display the displacements and strains only within the myocardium, i.e., only in the regions where motion occurred. The cavity and background had null displacement and strain.

4.2.3.3. Angle-Independent Strain Calculation

The 2D strain tensor (i.e., \( \mathbf{E} \) in the previous section), including normal and shear strain components, was highly dependent on the orientation of the imaging beam relative to the ventricular wall. This might complicate the interpretation of the direction of in-plane myocardial deformation. Thus, radial and circumferential strains were considered. A rotation matrix, \( \mathbf{R} \), for each material point within the myocardium in a 2D short-axis view was written as

\[
\mathbf{R} = \begin{bmatrix}
\cos \theta & \sin \theta \\
-\sin \theta & \cos \theta 
\end{bmatrix}
\]  

(4.6)

where \( \theta \) was the angle relative to the origin of the Cartesian coordinates in the FE models. Strains in cardiac coordinates were therefore obtained by

\[
\hat{\mathbf{E}} = \mathbf{RER}^T
\]

(4.7)

where \( \hat{\mathbf{E}} \) was the 2D radial-circumferential strain tensor. The diagonal components of \( \hat{\mathbf{E}} \) were radial (\( E_{rr} \)) and circumferential (\( E_{cc} \)) strains. Positive and negative radial strains indicated myocardial thickening and thinning, respectively, while myocardial stretching and shortening were represented by positive and negative circumferential strains.

The estimation errors for 2D displacement and strain are calculated using a mean absolute error (\( MAE_{AB} \)), which is defined as
where \( A \) and \( B \) are selected regions in FE computed and 2D estimated displacement images or elastograms, respectively. The two subscripts, \( m \) and \( n \), respectively indicate the dimension of \( A \) and \( B \) in the axial and lateral directions. Note that MAEs in this study were obtained within the myocardium across the entire image but excluding the artifacts at the endocardial and epicardial borders in order to avoid bias errors around the boundaries.

In summary, Myocardial Elastography is an RF-cross-correlation-based strain imaging technique. As introduced in section 3.3, there are several other RF-based strain imaging techniques. Therefore, the differences among these techniques should be noted and are summarized in Table 4.1 in order to help identify the relative differences, progress, and advantages of Myocardial Elastography over other methods.
Table 4.1. The main RF-based strain imaging techniques

<table>
<thead>
<tr>
<th>Method</th>
<th>Strain Rate Imaging (RF cross-correlation)\textsuperscript{25}</th>
<th>Strain Rate Imaging (phase-sensitive)\textsuperscript{24, 26, 63}</th>
<th>3D Cardiac Strain Imaging\textsuperscript{28}</th>
<th>Myocardial Elastography\textsuperscript{32, 76}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signal used</strong></td>
<td>Radio-frequency (2D)</td>
<td>Complex baseband (2D/3D)</td>
<td>BiPlane mode (RF in axial, demodulated in lateral/elevation)</td>
<td>Radio-frequency (2D/3D)</td>
</tr>
<tr>
<td><strong>Similarity measure</strong></td>
<td>Sum of absolute differences (SAD)</td>
<td>Complex cross-correlation</td>
<td>Cross-correlation</td>
<td>Cross-correlation</td>
</tr>
<tr>
<td><strong>Tracking kernel</strong></td>
<td>1D in a 2D search</td>
<td>2D</td>
<td>2D</td>
<td>1D in a 2D search</td>
</tr>
<tr>
<td><strong>Correction</strong></td>
<td>Temporal stretching</td>
<td>N/A</td>
<td>Spatial registration and local stretching</td>
<td>2D recorrelation (shifting signals instead of stretching them)</td>
</tr>
<tr>
<td><strong>Strain estimation</strong></td>
<td>Linear strain</td>
<td>Displacement gradient</td>
<td>2D least-squares strain estimator (LSQSE)</td>
<td>2D Lagrangian strain using LSQSE</td>
</tr>
<tr>
<td><strong>Parameter</strong></td>
<td>Strain rate (M-mode images)</td>
<td>2D displacement and strain images</td>
<td>2D/3D displacement and strain images; temporal strain curves</td>
<td>2D/3D displacement and strain images; temporal strain curves</td>
</tr>
<tr>
<td><strong>Theoretical assessment</strong></td>
<td>×</td>
<td>√ (kinetic cylindrical model)</td>
<td>√ (static compression by finite-element analysis)</td>
<td>√ (3D finite-element model)</td>
</tr>
<tr>
<td><strong>Phantom study</strong></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√ (section 4.4)</td>
</tr>
<tr>
<td><strong>In vivo animal study</strong></td>
<td>√</td>
<td>√</td>
<td>×</td>
<td>√ (Chapter 5)</td>
</tr>
<tr>
<td><strong>Clinical study</strong></td>
<td>√</td>
<td>×</td>
<td>√ (only averaged strain curves)</td>
<td>√ (Chapter 6)</td>
</tr>
</tbody>
</table>
4.3. Results

The 2D (i.e., lateral and axial) displacement images and elastograms of the first incremental step during passive filling from the unloaded state to ED for the normal model are shown respectively in Figures 4.2(c), 4.2(f) and 4.4. Note that these displacement and strain images are mapped onto the unloaded geometry. The incremental displacements (Figures 4.2(c) and (f)) and strains (Figure 4.4) are on the average within ±0.5 mm and ±2.50%, respectively. Positive and negative strains represent tensile (lengthening) and compressive (shortening) strains, respectively. The estimated incremental 2D displacements and axial strains are in excellent agreement with the FE results qualitatively (Figures 4.2(a), (c), (d) and (f); Figures 4.4(d) and (e)), while the lateral strain (Figure 4.4(b)) is the noisiest (the MAEs for the incremental lateral and axial strains are 0.26±0.21% and 0.18±0.19%) and presents larger boundary effects due to the larger least-squares kernel (7.5 mm in lateral direction) used in the strain estimation\textsuperscript{104}. Despite the higher noise, the incremental lateral elastographic estimate (Figure 4.4(b)) is also found in good agreement with the FE lateral strain quantitatively (Figure 4.4(c)).

The cumulative 2D displacements between ED and ES can be obtained by accumulating incremental 2D displacements estimated from ED to ES. The cumulative systolic 2D strains can thus be calculated from the cumulative 2D displacements. Note that the cumulative 2D displacements and strains are mapped onto an end-systolic LV geometry. Figures 4.5(i) and (ii) show the cumulative 2D systolic displacements and strains for the normal model, respectively. Figures 4.6(i) and (ii) show the cumulative 2D systolic displacements and strains for the ischemic model, respectively. Despite the fact that both qualitative (displacement images and elastograms) and quantitative (MAE, Table 4.2)
results demonstrate the high performance of Myocardial Elastography, the use of the radial and circumferential strains, which are computed from 2D strains, can provide more accurate and direct characterization of myocardial abnormalities.

**Figure 4.4**: Two-dimensional strains at the first incremental step from the unloaded state to ED: (a) and (d) respectively show finite-element (FE) lateral and axial strains; (b) and (e) are the estimated lateral and axial strains using Myocardial Elastography (ME), respectively; (c) and (f) are the difference images between the first and the second columns. Positive and negative strains respectively indicate lengthening and shortening.
Figure 4.5: Cumulative systolic 2D (i) displacements and (ii) strains for the normal (Control) model between ED and ES: (a) and (d) respectively show finite-element (FE) lateral and axial displacements/strains; (b) and (e) are the estimated lateral and axial displacements/strains using Myocardial Elastography (ME), respectively; (c) and (f) are the difference images between the first and the second columns.
Figure 4.6: Cumulative systolic 2D (i) displacements and (ii) strains for the LCx (ischemic) model between ED and ES: (a) and (d) respectively show finite-element (FE) lateral and axial displacements/strains; (b) and (e) are the estimated lateral and axial displacements/strains using Myocardial Elastography (ME), respectively; (c) and (f) are the difference images between the first and the second columns.
Figure 4.7: Cumulative radial and circumferential strains for (i) the normal (Control) model and (ii) the LCx (ischemic) model between ED and ES: (a) and (d) respectively show finite-element (FE) radial and circumferential strains; (b) and (e) are the estimated radial and circumferential strains using Myocardial Elastography (ME), respectively; (c) and (f) are the difference images between the first and the second columns.
As mentioned in section 4.2.2.3., positive or negative radial strains represent myocardial thickening or thinning, while myocardial stretching or shortening is indicated by positive or negative circumferential strain. Figure 4.7(i) shows radial thickening ((a) and (b)) as well as circumferential shortening ((d) and (e)) of the contracting normal myocardium from ED to ES. The differences between FE and estimated radial and circumferential strains are shown in Figures 4.7(i): (c) and (f), respectively. In contrast, the LCx model shows radial thinning (Figures 4.7(ii): (a) and (b)) and circumferential stretching (Figures 4.7(ii): (d) and (e)), instead of radial thickening and circumferential shortening, in the posterior-lateral (lower right), i.e., the ischemic region, during contraction. This is consistent with the fact that the ischemic muscle behaves as a passively tethered region undergoing inflation during systole (Figure 4.1(b))\(^9\). Figure 4.7 also demonstrates that the elastographic radial and circumferential strains are in good agreement with the FE solutions, both qualitatively and quantitatively (see Table 4.2.).

Table 4.2. The mean absolute errors (MAEs) for lateral \(u_x\) and axial \(u_y\) displacements, lateral \(E_{xx}\) and axial \(E_{yy}\) strains, and radial \(E_{rr}\) and circumferential \(E_{cc}\) strains in both Control and ischemic cases under 2D/3D simulation schemes.

<table>
<thead>
<tr>
<th>MAEs</th>
<th>2D simulation</th>
<th>3D simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>LCx ischemia</td>
</tr>
<tr>
<td>(u_x) (mm)</td>
<td>0.10±0.06</td>
<td>0.16±0.11</td>
</tr>
<tr>
<td>(u_y) (mm)</td>
<td>0.07±0.05</td>
<td>0.07±0.06</td>
</tr>
<tr>
<td>(E_{xx}) (% strain)</td>
<td>2.63±2.72</td>
<td>3.49±4.02</td>
</tr>
<tr>
<td>(E_{yy}) (% strain)</td>
<td>1.57±1.65</td>
<td>2.00±2.94</td>
</tr>
<tr>
<td>(E_{rr}) (% strain)</td>
<td>3.14±2.68</td>
<td>4.05±4.43</td>
</tr>
<tr>
<td>(E_{cc}) (% strain)</td>
<td>1.37±1.31</td>
<td>1.72±2.02</td>
</tr>
</tbody>
</table>
The FE and estimated Cartesian (i.e., lateral and axial) and polar (i.e., radial and circumferential) strains for the Control model at multiple slices in the 3D simulation scheme are shown in Figure 4.8(i). The elevational displacement increases, while the in-plane motion and strains are smaller, near the apical level. The larger the elevational motion is, the larger the in-plane strain estimation errors become.

Furthermore, Figure 4.8(i) shows radial thickening ((c) and (g)) and circumferential shortening ((d) and (h)) throughout the normal left ventricle (i.e., Control model). The FE and estimated Cartesian and polar strains for the LCx model at multiple slices in the 3D simulation scheme are shown in Figure 4.8(ii). Unlike in the normal case, the polar strains show radial thinning (Figure 4.8(ii): (c) and (g)) and circumferential stretching (Figure 4.8(ii): (d) and (h)) in the ischemic region (i.e., posterior-lateral wall) and confirm the smaller size of the ischemic region toward the apical level (Figure 4.1(b)). Note that all images shown in Figure 4.8 are mapped onto the geometry at the end-systolic phase, and their orientation is the same as in Figure 4.1. The MAEs in the 3D simulation scheme are summarized in Table 4.2 and show that the myocardial elastographic estimates remain in good agreement with FE solutions in the presence of out-of-plane (i.e., elevational) motion.
Figure 4.8: Anterior view of cumulative strains for the (i) the normal (Control) model and (ii) the LCx (ischemic) model at multiple slices in 3D simulation; (a)-(d) are finite-element (FE) lateral, axial, radial and circumferential strains, respectively; (e)-(h) are estimated lateral, axial, radial and circumferential strains using Myocardial Elastography (ME), respectively. The images are mapped on the end-systolic geometry. Note that the orientation is the same as Figure 4.1.
The model previously presented did not reliably simulate myocardial deformation in a physiologic cardiac cycle, so the frame-rate issue in the ultrasound simulation could not be studied. Thereafter, a 3D, canine biventricular FE model (Continuity 6.3®) also developed by Andrew D. McCulloch’s group at UCSD became available to simulate myocardial deformation in a physiologic cardiac cycle. The model was coupled to a circulation model in both normal (Control) and ischemic (left-anterior descending, LAD) cases; encompassing hemodynamics and biomechanics in agreement with experimental measures, where the end-diastolic and end-systolic pressures were respectively equal to 13 mmHg and 84 mmHg in the normal case and 18 mmHg and 76 mmHg in the LAD ischemic case. A time step of 1 ms was utilized to simulate the biventricular deformation for the entire cardiac cycle. A 3D linear convolution model (see section 4.2.2.) was then used to simulate (RF) echocardiograms at a frame rate of 1000 fps. Variable frame rates, starting from 50 fps to 1000 fps, were achieved by progressively decimating the number of RF frames in the estimation procedure of 2D transmural displacements and angle-independent strains using Myocardial Elastography.

Figure 4.9 shows that the normalized cross-correlation coefficient increased exponentially with the frame rate in both normal (Figure 4.9(i)) and ischemic (Figure 4.9(ii)) cases, in the anterior (a) and septal (b) regions at peak systole. In brief, at the frame rate of 50 fps, the normalized cross-correlation coefficient was as low as 0.64, whereas at 1000 fps, a normalized cross-correlation coefficient of 0.98 was found. The higher the frame is, the higher the correlation between two successive RF frames and the more reliable the estimates become. In theory, this should lead to higher accuracy in motion estimation using RF signals and thus higher strain quality.
Figure 4.9: The relationship between the normalized cross-correlation coefficient ($\rho$) and variable frame rates in the normal (i) and LAD ischemic (ii) cases in the (a) anterior and (b) septal regions estimated from 7 different frame rates at the peak systolic phase.
Nevertheless, the SNR<sub>e</sub>, the elastographic SNR, which determined the strain quality, initially increased in the case of the axial strain and then decreased, with the frame rate (Figure 4.10) with the maximum occurring at 250 fps or 500 fps except in the anterior wall region in the ischemic case (Figure 4.10(ii)(a)). The lateral SNR<sub>e</sub> did not exhibit the same behavior as the axial SNR<sub>e</sub>. On the contrary, the lateral SNR<sub>e</sub> reached the peak at 125 fps or 200 fps, depending on the deformation in the myocardial wall region of interest.

**Figure 4.10**: The relationship between SNR<sub>e</sub> and frame rate in the normal (i) and LAD ischemic (ii) cases in the radial (Err), circumferential (Ecc), lateral (Exx), and axial (Eyy) strain estimation in the (a) anterior and (b) septal regions estimated from 7 different frame rates at the peak systolic phase.
4.4. Phantom experiments

Phantom experiments were performed as a separate study\textsuperscript{105, 106} for the controlled, experimental quality assessment of Myocardial Elastography, which was validated under both rotation and torsion. In brief, two polyacrylamide phantoms in a cylindrical shape were made to mimic the normal and ischemic left ventricles. The inner cavity and outer wall of the normal-tissue-mimicking phantom were manufactured using 25% and 30% polyacrylamide, respectively. The ischemic-tissue-mimicking phantom was designed as shown in Figure 4.11, and the regional impairment was designed to have higher stiffness than the simulated normal region. The stiffness of the phantom at different concentrations of polyacrylamide was measured through mechanical testing\textsuperscript{107}, showing that 25%, 30%, and 40% polyacrylamide produced a phantom with the average stiffness of 13.4 kPa, 25.5 kPa, and 50.3 kPa, respectively.

![Diagram of phantom with different polyacrylamide concentrations](image)

**Figure 4.11**: The schematic of the ischemic-tissue-mimicking polyacrylamide phantom, where the simulated normal region was made of 30% polyacrylamide, while the stiffer region (shaded gray color) was made using 40% polyacrylamide. Slices 2-4 shown in Figures 4.13-15 are indicated by the solid blue lines.
**Figure 4.12**: The experimental setup for the phantom study, where a phased array transducer, a polyacrylamide phantom, and a customized motor are indicated.

A Terason (Teratech Corp, Burlington MA, USA) portable ultrasound system equipped with a 3 MHz, 64-element phased array transducer (4V2) was used to acquire the RF signals under rotation and torsion, driven by a customized motor, indicated in the actual experimental setup (Figure 4.12). Both lateral and axial displacement components were first estimated using Myocardial Elastography. The circumferential displacement (in mm) was further calculated through the rotation matrix (4.6). Finally, the angular displacement (in radians) was obtained by dividing the circumferential displacement by the radius to quantify the total rotation experienced by the phantom.
Figures 4.13 and 4.14 show the cumulative angular displacement images for the normal-tissue-mimicking phantom under pure rotation and torsion. In the pure rotation case (Figure 4.13), the angular displacement was estimated accurately compared to the theoretical value of -0.314 radians, where the negative sign denotes clockwise rotation. In the torsion case (Figure 4.14), the angular displacement decreased from slice 1 to slice 5, which was close to the constrained side of the phantom as expected.

![Figure 4.13](image)

**Figure 4.13:** Cumulative angular displacement images in the normal-tissue-mimicking phantom during pure rotation. (a)-(e) are angular displacements across five depth-varying cross-sectional slices, and (f) shows the average angular displacement for each slice. The red line indicates the theoretical angular displacement of -0.314 radians, where the negative sign denotes clockwise direction.
Figure 4.14: Cumulative angular displacement images for the normal-tissue-mimicking phantom under torsion. (a)-(e) are angular displacements across five depth-varying cross-sectional slices. (f) shows the average angular displacement for each slice.

Figure 4.15: Difference images of the angular displacement between two sets of two adjacent slices of the (a) and (b): normal-tissue-mimicking and (c) and (d) ischemic-tissue-mimicking phantoms under torsion. The schematic for the location of slices 2, 3 and 4 is shown in Figure 4.11.
Figure 4.15 shows the difference images of the angular displacement between two pairs of two adjacent slices (slices 2 and 3; slices 3 and 4) in order to help evaluate the torsional effect in the ischemic tissue region. In the ischemic-tissue-mimicking phantom, slices 3 and 4 were both within the stiffer region, whereas slices 2 and 3 were acquired through the softer and stiffer regions, respectively. Undergoing torsion, slice 4 exhibited smaller angular displacement than slice 3 as shown in Figures 4.14(c) and (d). Therefore, the uniformity of the difference with the positive value in the angular displacements between slice 3 and 4 was observed in both normal- and ischemic-tissue-mimicking phantoms in Figures 4.15 (b) and (d) as expected. This difference was also noted in the normal-tissue-mimicking phantom (Figure 4.15(a)). In contrast, the difference between the regions with different stiffnesses in the ischemic-tissue-mimicking phantom (Figure 4.15(c)) was overall smaller compared to other regions. This finding may further support that the estimated torsion effect could be an indicator of the presence of the ischemic-tissue-region.

### 4.5. Discussion and Conclusion

In this theoretical framework, a normal (Control) and an ischemic (LCx) FE left-ventricular model were used to assess the performance of Myocardial Elastography in both 2D and 3D ultrasound simulation schemes. Qualitatively and quantitatively (Table 4.2), 2D, in-plane estimated displacement and strain showed good agreement with the 2D, in-plane FE displacement and strain, in both the lateral and axial directions and in the presence of out-of-plane motion. The results thus demonstrated the high performance of Myocardial Elastography.
The accuracy of the current Myocardial Elastography was previously limited by the lateral displacement estimation. The precision of lateral displacement is typically lower than that of axial displacement\textsuperscript{108}. In addition, without correction, the amount of axial displacement exacerbated the lateral decorrelation and then further lowered the accuracy of the lateral displacement estimation (Figure 4.2). In previously reported work\textsuperscript{83}, axial stretching was performed before lateral displacement estimation. In this study, correction of axial (lateral) displacement for lateral (axial) decorrelation was performed by shifting the RF signals based on the estimated displacement. According to the increased mean and decreased standard deviation of the correlation coefficient map in Figure 4.2(i) compared with those in Figure 4.2(h), the recorrelation method for 2D estimation reduced the decorrelation of RF signals between two consecutive frames and therefore improved the accuracy of the estimation. Moreover, the greatest benefit of the recorrelation method was in the lateral estimation since the decorrelation due to the lateral displacement was too small (i.e., within one beamwidth) to corrupt the axial displacement estimation.

The MAEs of 2D displacements and strains for the LCx model were larger than those for the Control model as summarized in Table 4.2. This was mainly due to the complex motion pattern around the borders between normal and ischemic myocardium and larger 2D motion between two successive activation configurations in the LCx model compared with the Control model. The estimation errors would be accumulated when obtaining the cumulative 2D displacements. Moreover, the strain MAEs were larger than those of displacements since the gradient operation amplified the errors in strain calculation.

Two-dimensional Myocardial Elastography was performed using cross-correlation with a 1D kernel. The displacement within a window was assumed to be uniform, and the center
of a window represented the displacement in the entire window. There were two kinds of boundary effects on the motion and deformation images. First, because of the finite window size used, the myocardial region on the elastogram appeared thicker than the actual myocardium. Therefore, a binary mask, obtained from the 2D ultrasound simulation model, was superimposed onto the 2D estimated displacement image and elastogram in order to obtain the same geometrical dimensions. Second, the boundaries on the elastograms increased in thickness with the kernel size used for the least-squares method\textsuperscript{104}. The estimation samples (i.e., displacements) outside the myocardial region (i.e., in the background) were used for curve fitting and resulted in subsequent erroneous strain estimates. As Figure 4.4 shows, outer boundaries are indicated by high (noisy) strain values. This second boundary effect on elastograms could be reduced by applying curve fitting with the same kernel size over the reduced domain. In clinical applications, the actual myocardial region could be obtained using the contour obtained from segmentation techniques\textsuperscript{109,110}.

Myocardial Elastography has thus been demonstrated to be a reliable technique for the estimation of the lateral and axial components of 2D displacement and strain at each load step in the 2D/3D simulation scheme. However, it is difficult to clearly detect the ischemic region according to the 2D Cartesian elastograms (axial or lateral) as shown in Figure 4.6(ii) and Figure 4.8(ii): (a)-(b) and (c)-(f). Radial and circumferential strains, which are angle-independent and can be obtained from a 2D strain tensor through coordinate transformation, have been demonstrated to be a more conspicuous indicator of normal and abnormal myocardial deformation. Figures 4.7(i) and (ii) respectively show cumulative radial and circumferential strains for the normal and the ischemic models in the 2D
simulation scheme. Not only are elastographic estimates and FE solutions in good agreement, but the radial and circumferential strains also offer the capability of clearly indicating the extent of an ischemic region. Nevertheless, only if a precise centroid is chosen can radial and circumferential strains be obtained accurately. In other words, radial and circumferential strains are highly dependent on the selection of a centroid. An angle-independent and less centroid-independent measure, the principal strain, is computed from 2D finite strains and has been shown to be also capable of differentiating ischemic from normal myocardium. In chapter 6, it is shown that the polar strains are equivalent to principal strains in terms of estimation accuracy.

The 3D simulation framework further assessed the performance of 2D elastography with a reccorrelation technique at various short-axis slices of the 3D canine left-ventricular model as shown in Figure 4.8. Despite the fact that the estimation errors increase with out-of-plane motion, the elastographic estimates (Figure 4.8) remain in good agreement with the FE solutions. In addition, the cumulative polar strains (Figures 4.8(ii): (c), (d), (g) and (h)) depict and confirm the reduced ischemic region from the base to the apex in the lateral-posterior region.

The effect of frame rate was thereafter evaluated when the 3D finite-model in Continuity 6.3® became available to reliably simulate left ventricular deformation in a physiologic cardiac cycle. The results showed that, for good quality axial strain estimates, a two-fold higher frame rate than for lateral strain (250-500 fps vs. 125-200 fps) was required. Thus, this finding indicated the lateral strain to be estimated at lower frame rates and the axial strain at higher frame rates. The implementation of cardiac-phase-varying frame rate may further improve the strain estimation.
Through a separate polyacrylamide phantom study, the estimation accuracy of Myocardial Elastography was validated with the known rotation and torsion controlled by a customized motor. The results (Figures 4.13-4.14) demonstrated good displacement estimation accuracy of Myocardial Elastography under both pure rotation and torsion. The findings (Figure 4.15) further supported that accurate torsion estimation could be used to identify a tissue region with different stiffness. Strains were not further computed as the phantom study was conducted mainly for the assessment of displacement estimation accuracy using Myocardial Elastography. Accurate displacement estimates would lead to reliable strain estimates. In addition, pure rotation occurred in the cross-sectional image planes acquired, so in-plane strains were not expected to occur. However, in the torsion case, strains may facilitate the quantification of torsion in the longitudinal image planes. This can be considered as part of future phantom studies.

A theoretical framework was described that could assess the performance of Myocardial Elastography using normal and ischemic FE left-ventricular models in both 2D and 3D ultrasound simulation schemes. The Myocardial Elastography technique that utilized a 1D kernel in a 2D search, together with iterative recorrelation and estimation, was used to simultaneously estimate lateral and axial displacements and to image the transmural displacement and strain fields in a full view. Using the correction for one displacement component, the precision of the estimation of its orthogonal displacement component was significantly improved in the absence of stretching techniques. It was also shown that the displacement images as well as elastograms estimated by the 2D three-iterative-step elastographic techniques were in good agreement with those calculated from the FE model, clearly demonstrating the high quality and high reliability of the Myocardial Elastography
estimates, even in the presence of the out-of-plane motion. Furthermore, based on the high quality of the 2D elastographic estimates, radial and circumferential strains, which conspicuously indicated the abnormality of the ischemic myocardium in a full echocardiographic view, were also imaged.

The findings from this theoretical framework allow us to investigate Myocardial Elastography in an *in vivo* animal study (Chapter 5) and a clinical setting (Chapter 6). The need for high frame rate ultrasonic RF data acquisition (at least 200 fps for both lateral and axial displacement estimation) has been proven, so standard echocardiography systems were controlled and programmed to operate at the required frame rate (see sections 5.2.5. and 6.2.3.) in both animal and clinical studies. Through the knowledge gained from the theoretical framework that the ischemic myocardial region exhibits opposite, angle-independent (i.e., radial and circumferential) strains compared to the normal myocardial region, the detection and localization of the ischemic myocardium reliably performed in an *in vivo* animal study will firstly be shown in Chapter 5.
Chapter 5

In Vivo Assessment and Validation of Myocardial Elastography in the Detection and Characterization of Ischemia

5.1. Background

The relationship between reduced coronary blood flow and impaired left-ventricular deformation has previously been investigated in vivo in anesthetized and conscious animals. Decrease in percent shortening of myocardial segments at risk measured by piezoelectric crystals has been shown to be correlated with percent reduction in coronary blood flow measured by a flowmeter or with percent decrease in regional myocardial perfusion measured with microspheres. As a result, techniques that can be employed to quantify regional myocardial deformation shed light on the detection of myocardial ischemia resulting from stenosed coronary arteries. Noninvasive imaging techniques, such as echocardiography and magnetic resonance imaging (MRI), have emerged to quantify myocardial deformation (or, strain). Compared to MRI,
echocardiography typically enjoys higher temporal resolution, lower cost, portability, and compatibility with pacemakers.

Several previous studies have validated their echocardiography-based strain analysis techniques against sonomicrometry in animal models in vivo, where myocardial ischemia was induced by completely occluding the coronary arteries. Urheim et al.78 validated the longitudinal strain estimated by Doppler echocardiography against estimates obtained by sonomicrometry in apical views of canine left ventricles during both control and ischemic conditions, the latter induced by completely occluding the left anterior descending (LAD) coronary artery. The longitudinal strains of the Doppler method were found to closely approximate those of sonomicrometry. Langeland et al.117, 118 validated their echocardiographic radial and longitudinal strain estimates against sonomicrometry strain measures in the inferolateral wall in a parasternal long-axis view of the ovine left ventricles, under normal and ischemic conditions in vivo. The ischemia was induced by ligating the distal left circumflex (LCx) coronary artery. Their echocardiographic strain estimates and the sonomicrometry measures were proven to be in good agreement in both normal and ischemic cases. Sengupta et al.119 compared the longitudinal strain rates obtained by Tissue Doppler Imaging (TDI) to sonomicrometry measurements in the basal-anterior and mid-anterior segments of the porcine left ventricle. The strain-rate measures using the two methods were correlated and depicted the asynchronous deformation of subendocardial and subepicardial layers during the isovolumic phases. Amundsen et al.79 validated their speckle tracking echocardiography technique against sonomicrometry in dogs in both normal and ischemic (5- to 15-minute ligation of the LAD coronary artery) states. The results indicated good correlation (r=0.90) between the echocardiography and
sonomicrometry longitudinal strain measures and short-axis shortening ($r=0.79$). In their study, short-axis shortening referred to the diameter change of the left-ventricular cavity instead of transmural radial strain. Papademetris et al.\textsuperscript{30} validated their shape-tracking algorithm in three-dimensional (3D) echocardiograms against sonomicrometry before and after LAD ligation. High correlation in 3D strains between the shape-tracking algorithm and sonomicrometry ($r^2=0.8$) was found. Segmental dyskinesia in the region at risk after coronary constriction was also observed. Even though the aforementioned studies have demonstrated the \textit{in vivo} validation of their techniques in the normal and complete coronary constriction cases, at what extent and to what degree of myocardial ischemia that their techniques can detect remains unknown. In addition, temporal strain profiles without 2D strain imaging have mainly been presented in the literature due to the known additional challenge posed in high quality strain imaging. Compared to the temporal strain profiles, strain images in full echocardiographic views at high spatial and temporal resolution facilitate the instantaneous detection and identification of dysfunctional myocardial segments.

Myocardial Elastography\textsuperscript{4, 32, 76, 77, 120-123}, a radio-frequency (RF)-based, angle-independent strain imaging technique previously reported by our group, aims at mapping 2D displacement and 2D angle-independent strains in full left-ventricular echocardiographic views at high spatial and temporal resolution. Its good performance in imaging myocardial deformation has been demonstrated in both a theoretical framework\textsuperscript{32} and clinical setting\textsuperscript{67}, in normal and pathological cases. In this chapter, different from previously reported studies, quality performance of Myocardial Elastography for early ischemia detection with \textit{in vivo} validation against sonomicrometry was studied in dogs at
graded ischemia levels as induced by progressive LAD restriction. The primary objective of this study was to assess the performance of Myocardial Elastography in detecting the early onset, extent and severity of myocardial ischemia. In addition, conducting a series of validation studies using graded ischemia and sonomicrometry in large animals was deemed essential for reliable performance evaluation of Myocardial Elastography.

5.2. Methodology

5.2.1. Animal Preparation

Ten dogs of either sex, weighing 27.8±2.5 kg, were anesthetized with an intravenous injection of thiopental (10-17 mg/kg) and morphine (0.15mg/kg), intubated, and maintained with isoflurane (0.5-5%). Lidocaine was infused at a constant rate of 50 μg/kg/hr. The respiration of the animal was controlled by a ventilator. The electrocardiogram (ECG), arterial blood pressure and oxygen saturation were monitored throughout the entire experiment. A heating pad was used to maintain the body temperature. Lateral thoracotomy was performed in the fifth intercostal space to access the heart. Pericardium was removed for further constrictor placement and crystal implantation. The removal of the pericardium did not influence the results of this study, since the latter dealt with changes in the myocardium as a result of progressive coronary flow reduction with respect to the baseline.
5.2.2. Instrumentation

A pressure catheter (SPR-360, Millar Instruments, Inc., Houston, TX, USA) was inserted into the left ventricle via the right carotid artery to monitor the left ventricular pressure. A flow probe (Figure 5.1)(2.5SB, Transonic Systems, Inc., Ithaca, NY, USA) connected to a Transonic® flowmeter (T206) was placed around the LAD to measure the coronary flow.

A customized constrictor (Figure 5.1) was placed around the LAD, distal to the first diagonal branch, and was externally adjusted to gradually restrict the coronary flow in LAD, from 0% to 100% at 20% increments.

A total of 12 crystals were implanted into the canine left-ventricular myocardium (Figure 5.1). Two separate sets of four piezoelectric crystals (2 on the epicardium; 1 in the sub-epicardium; 1 in the sub-endocardium) (Sonometrics Corp., London, Ontario, Canada) in a tetrahedral configuration were placed in the expected ischemic (i.e., anterior) and remote (i.e., posterior) regions to compute regional strains in cardiac coordinates (radial, circumferential, and longitudinal). The average separation of the tetrahedral crystals were 13.5 mm. Sub-epicardial crystals were implanted immediately beneath the epicardium, while the sub-endocardial crystal was inserted using an introducer, ensuring implantation depth. Even though the extent of the ischemic region could be estimated by temporarily ligating the LAD, the affected myocardial region at lower flow reduction levels could not be as easily predicted. The difference in the coronary architecture between animals posed additional challenges in the implantation of the crystals. Four additional crystals, placed in the lateral, septal, basal and apical walls, together with the sub-epicardial anterior and posterior crystals, which formed the tetrahedrons, were used to calculate the left-ventricular
volume. The distance between each pair of crystals was recorded over multiple cardiac cycles using the sonomicrometry system in real time at a sampling rate of 379 Hz. Sonomicrometry data of 1-min duration each time was separately acquired immediately before each echocardiographic data acquisition to avoid ultrasonic signal interference and any functional changes between sonomicrometry and echocardiography data acquisitions.

All animal study methods were approved prior to use by the Institutional Animal Care and Use Committee of Columbia University.
Figure 5.1: Left anterior and posterior views of a schematic heart. The location of a tetrahedron of crystals implanted is shown. One crystal (represented by a green dot) was sutured in the sub-endocardium, one in the sub-epicardium and two crystals on the epicardium. A constrictor and a flow probe were placed after the first diagonal of the left anterior descending (LAD) coronary artery. The shaded region in yellow shows the ischemic region. The plane in gray shows the short-axis echocardiographic plane. Anterior (ANT), lateral (LAT), posterior (POST), septal (SEP), basal (BASE) and apical (APEX) regions are indicated.
5.2.3. Graded Myocardial Ischemia

Regional myocardial ischemia was therefore progressively induced. The constriction percentage throughout this study refers to the percentage of coronary flow reduction. Each constriction level was continuously monitored to ensure that the desired coronary blood flow was attained and stabilized prior to data acquisition. This stabilization duration was dependent on each animal's coronary autoregulation response to each constriction level and ranged from 15 to 40 minutes. The 100% (i.e., complete) constriction level was sustained for 30 minutes. In two canine experiments, reperfusion (i.e., full release of the constrictor) was also performed and lasted for 15 minutes prior to euthanizing the animals with pentobarbital (100 mg/Kg) as a preliminary study in the investigation of the left ventricular function after reperfusion.

5.2.4. Sonomicrometry

5.2.4.1. Data Acquisition

The distance between each pair of crystals was recorded at multiple cardiac cycles using the sonomicrometry system in real time at a sampling rate of 379 Hz.

5.2.4.2. Data Denoising

The acquired sonomicrometry data were denoised using the built-in functions in the software, SonoSOFT® (Sonometrics Corp., London, Ontario, Canada).

5.2.4.3. Strain Calculation

In sonomicrometry, the regional strain in cardiac coordinates was calculated based on the distance change of the tetrahedron of crystals. In order to calculate the in-plane
transmural strains in a short-axis view, the four crystals, which form a tetrahedron in the anterior or posterior region, were used. An illustration of the tetrahedron in the undeformed and deformed configurations is shown in Figure 5.2, where capital and lower-case letters indicate the vertices of the tetrahedron before and after deformation, respectively.

Figure 5.2: An illustration of a tetrahedron composed of four crystals in (a) an undeformed and (b) a deformed configuration. A, B, C, and D indicate the vertices of the tetrahedron in the undeformed case, while a, b, c, and d in the deformed case.

The normal and shear components of a 3D strain tensor were computed from the changes in squared vector lengths defined by these four crystals using the following equation\textsuperscript{103, 124, 125}:

\[
\begin{bmatrix}
\frac{d}{ds_{ab}} - \frac{d}{ds_{AB}} \\
\frac{d}{ds_{ac}} - \frac{d}{ds_{AC}} \\
\frac{d}{ds_{ad}} - \frac{d}{ds_{AD}} \\
\frac{d}{ds_{bc}} - \frac{d}{ds_{BC}} \\
\frac{d}{ds_{bd}} - \frac{d}{ds_{BD}} \\
\frac{d}{ds_{cd}} - \frac{d}{ds_{CD}}
\end{bmatrix}
= 2 [E_{11} \ E_{22} \ E_{33} \ E_{12} \ E_{13} \ E_{23}]
\begin{bmatrix}
X_{1,ab} & X_{1,ac} & X_{1,ad} & X_{2,bc} & X_{2,bd} & X_{2,cd} \\
X_{2,ab} & X_{2,ac} & X_{2,ad} & X_{3,bc} & X_{3,bd} & X_{3,cd} \\
X_{3,ab} & X_{3,ac} & X_{3,ad} & X_{2,bc} & X_{2,bd} & X_{2,cd} \\
2X_{1,ab}X_{1,ac} & 2X_{1,ab}X_{1,ad} & 2X_{2,bd}X_{2,bc} & 2X_{1,ab}X_{1,ad} & 2X_{2,bd}X_{2,bc} & 2X_{1,ab}X_{1,ad} \\
2X_{2,ab}X_{2,ac} & 2X_{2,ab}X_{2,ad} & 2X_{3,bd}X_{3,bc} & 2X_{2,ab}X_{2,ad} & 2X_{3,bd}X_{3,bc} & 2X_{2,ab}X_{2,ad} \\
2X_{3,ab}X_{3,ac} & 2X_{3,ab}X_{3,ad} & 2X_{2,bd}X_{2,bc} & 2X_{3,ab}X_{3,ad} & 2X_{2,bd}X_{2,bc} & 2X_{3,ab}X_{3,ad}
\end{bmatrix}
\]

(5.1)

where \(ds^2\) and \(dS^2\) denote the squared vector lengths in the deformed and undeformed configurations, respectively; the alphabetical subscripts in upper and lower cases represent
the six edges in the undeformed and deformed configurations, respectively; \( X_1, X_2, \) and \( X_3 \) denotes the three orthogonal components of the vector defined by each edge of the tetrahedron; the numerical subscripts 1-3 indicate the three orthogonal axes in the Cartesian coordinates; and \( E \) is the strain tensor.

The strain tensor was computed in Cartesian coordinates, which were computed in the SonoSoft® software. The computed sonomicrometry strains needed to be further transformed from Cartesian to polar coordinates, in which the myocardial deformation could be depicted more adequately and the two different modalities could be appropriately compared. A coordinate transformation matrix was thus obtained by defining the centroid of the left ventricle and then determining the left-ventricular polar coordinates.

### 5.2.4.4. Pressure-Volume (PV) Relationship

The 3D coordinates of each crystal and the pressure-volume relationship were also obtained using SonoSoft® with user-defined axes and a reference crystal. The anterior-posterior, lateral-septal and apex-base axes were used to compute the left-ventricular volume. The position of the crystal at the apex was selected as the reference.
5.2.5. High Frame-Rate RF Echocardiographic Data

Acquisition/Analysis

A Sonix RP system (Ultrasonix Medical Corp., Richmond, BC, Canada) with a 3.3 MHz phased array (beam density of 128) was used to acquire RF frames in a 2D short-axis view at the frame rate of 211 fps using an automatic composite technique previously reported by our group\textsuperscript{126}. Please note that the frame rate of 211 fps was deemed essential for reliable displacement and strain calculation as demonstrated in Figures 4.9 and 4.10 (Chapter 4). Degassed ultrasound gel was considered essential in improving the image quality. Additionally, it was critical that the sonomicrometry and ultrasound RF data were acquired separately in order to avoid signal interference between the two systems. The 100\% constriction data shown in this chapter were acquired approximately eight minutes immediately after the onset of complete constriction, and the reperfusion data were acquired 15 minutes after the onset of reperfusion.

In Myocardial Elastography, the two in-plane orthogonal displacement components (lateral and axial) were iteratively estimated on RF signals using one-dimensional (1D) cross-correlation and recorrelation in a 2D search\textsuperscript{127}. The cross-correlation technique employed a 1D matching kernel of 3.5 mm and 80\% overlap.

The incremental lateral and axial displacements were integrated to obtain the cumulative displacements that occurred from end-diastole (ED) to end-systole (ES). Lagrangian lateral and axial strains were computed from the cumulative displacements using a least-squares strain estimator (LSQSE)\textsuperscript{104} with a lateral kernel of 8.5 mm and an axial kernel of 3.4 mm. Since the phased-array configuration is used in echocardiography
(see Appendix A), strains were calculated in polar coordinates (see Appendix B). Radial and circumferential strains, which are inherently angle-independent, were further obtained from Lagrangian lateral and axial strains through coordinate transformation in order to depict the myocardial deformation in cardiac coordinates and facilitate the detection of the ischemic region\textsuperscript{91,127}.

Myocardial Elastography provided higher resolution in transmural strain than sonomicrometry as the latter measures strains in an average fashion and outputs a single radial strain value within each crystal tetrahedron. In order to compare the two methods, the regional ME radial strains were obtained by averaging the estimated strain values within a region-of-interest (ROI) of 3×3 mm\textsuperscript{2} to match the resolution of sonomicrometry (see section A.2).

5.2.6. Pathology

At the termination of the procedure, the heart was excised, stored in the refrigerator at 4°C overnight and then sliced with a thickness of 10 mm. The sliced heart sections were immersed in 1% Triphenyltetrazolium chloride (TTC) solution and incubated at 37°C for 1.5 hours. The sections were then fixed in a 10% formalin solution for 30 minutes. The region unstained by TTC appears pale in color, indicating the location of infarct formed, while the region stained by TTC appears red in color, indicating the normal cardiac muscle\textsuperscript{128}. 
5.3. Results

Experiments on ten (n=10) dogs were performed. Among the ten dogs studied, three pilot experiments were performed to improve and finalize the experimental procedure and design. In addition to the three dogs, one dog had frequent premature ventricular contraction starting at 40% constriction, and therefore its RF data acquisition relying on ECG gating could not be properly performed. Another dog had ventricular fibrillation immediately after the onset of 100% constriction and thus did not survive and sustain the 100% constriction level. Only the experiments that completed the graded constriction levels from 0% to 100% were considered; hence, data from the remaining five canine experiments are reported in this section.

Figure 5.3: The pressure-volume (PV) relationships of two canine left ventricles measured by sonomicrometry from 0% to 100% constriction levels at a 20% increment and after reperfusion.
Examples of the pressure-volume (PV) loop in two canine left ventricles at six different levels of LAD constriction and reperfusion are shown in Figure 5.3. In general, the observed rightward shift at increased constriction levels, except for the 80% constriction level in Figure 5.3(a), indicated that regional myocardial ischemia due to reduced blood supply was successfully induced in good agreement with existing literature\textsuperscript{129}.

Cumulative systolic radial strains in a canine left ventricle with the PV relationship shown in Figure 5.3(a) in all six different constriction levels (0%, 20%, 40%, 60%, 80%, 100%) and after reperfusion are shown in Figure 5.4. The initial flow rate of the LAD was 52 mL/min. Overall, systolic radial thickening was observed. Reduced radial thickening and radial thinning in the anterior and anterior-lateral regions were noted at constriction levels beyond 20%. Radial thinning was also noted in the lateral wall region at 80% and 100% constriction levels. The septal wall region experienced augmented radial thickening at 80% and 100% constriction levels.

Figure 5.4(h) shows the basal side of the canine basal slice of the left ventricle (right ventricle removed), which was stained using the TTC technique and oriented in correspondence to the short-axis echocardiogram shown in Figure 5.4(g). The finding that the negative radial strain, or radial thinning, in the anterior wall region exhibited after reperfusion (Figure 5.4(g)) was confirmed by the pale color (i.e., unstained by TTC) in the anterior wall region in the pathology slice (Figure 5.4(h)). Positive radial strain, or radial thickening, in the posterior wall region after reperfusion was noted and confirmed by the brick-red color in Figure 5.4(h).
Figure 5.4 (Continued on the next page)
**Figure 5.4:** Cumulative systolic radial strain images of a canine left ventricle with a PV loop shown in Figure 5.3(a) at (a) 0%, (b) 20%, (c) 40%, (d) 60%, (e) 80% and (f) 100% constriction levels and (g) after reperfusion. Below each image shows the electrocardiograms (ECGs), and the red dot indicates at which cardiac phase each radial strain image is displayed. Anterior (ANT), lateral (LAT), posterior (POST) and septal (SEP) regions are also indicated. (h) the basal side of the approximately corresponding canine basal slice (right ventricle removed) stained using 1% triphenyltetrazolium chloride (TTC) solution with pale (unstained by TTC) and red (stained by TTC) colors indicating infarcted and normal tissues, respectively. This pathology image was oriented to align with the echocardiogram. The white squares in the anterior wall region indicate where the strain curves shown in Figure 5.5 were obtained.
Figure 5.5: Temporal radial strain curves of the same canine heart shown in Figure 5.4 in an anterior-lateral wall region of 3 mm by 3 mm indicated by the white square in Figures 5.4(a)-(g) at (a) 0%, 20%, 40%, and (b) 60%, 80%, and 100% constriction levels and after reperfusion. Below the figure shows the ECG at the 0% constriction level. ME and SM denote Myocardial Elastography and sonomicrometry, respectively.
Temporal cumulative radial strain profiles, from both sonomicrometry and Myocardial Elastography, over the entire cardiac cycle are shown in Figure 5.5. In Myocardial Elastography, the temporal radial strain profiles were obtained by averaging strains within a region-of-interest (ROI) of 3x3 mm$^2$ in the anterior wall region indicated by the white squares in Figure 5.4. Prior knowledge of the crystal location relative to the imaging transducer and the visible crystals shown in the acquired images were considered to select the ROIs for the temporal strain profiles. Not only is the radial strain of Myocardial Elastography in good agreement with sonomicrometry (root mean square error of 3.97% strain), but it also reliably depicts the progression of ischemia across and along the myocardial wall. This progression is detected by myocardial thinning during systole in the expected ischemic region, i.e., the anterior-lateral wall (Figure 5.5).

In addition, cumulative systolic radial strain images of another canine left ventricle with the PV relationship shown in Figure 5.3(b), in a short-axis view mapped at the end-systolic phase, over all six different constriction levels (0%, 20%, 40%, 60%, 80%, 100%) and reperfusion are shown in Figure 5.6. The baseline flow rate of the LAD was 21 mL/min. Again, positive radial strain indicates radial thickening, while negative values indicate radial thinning. At baseline (i.e., 0% constriction), radial thickening throughout the entire myocardium was observed (Figure 5.6(a)). At 20% constriction (Figure 5.6(b)), reduced radial thickening and radial thinning were observed in the sub-epicardium and sub-endocardium in the anterior region, respectively. At 40% (Figure 5.6(c)), 80% (Figure 5.6(e)) and 100% (Figure 5.6(f)) constriction, the ischemic (anterior) wall regions underwent radial thinning, while the remaining myocardium still exhibited radial thickening. The reduced radial thickening or radial thinning indicated impaired myocardial
function due to ischemia in the anterior region, which was perfused by the occluded LAD coronary artery in this canine left ventricle. This finding was in agreement with the literature. However, at 60% coronary flow obstruction, no reduced radial thickening in the anterior wall region was noted as suspected due to the fact that the echocardiographic images were erroneously acquired at a different short-axis plane. Thus, 60% coronary flow obstruction was considered as an outlier in this case.

Reperfusion, namely the complete release of the constrictor on the LAD, was also performed in order to assess the restoration level of myocardial deformation and examine the performance of Myocardial Elastography on depicting this myocardial viability. Figures 5.4(g) and 5.6(g) show systolic radial strain images of the reperfused left ventricles. The ischemic segment (i.e., anterior-lateral wall region) of the first canine left ventricle shown in Figure 5.4(g) remained dyskinetic after reperfusion. On the contrary, the ischemic segment (i.e., anterior wall region) of the second canine left ventricle shown in Figure 5.6(g) presented systolic radial thickening after reperfusion. In other words, the mechanical function of the region that previously experienced an episode of ischemia recovered after reperfusion.

Figure 5.6(h) shows both sides of the canine mid-ventricular slice which was stained using the TTC technique and corresponded to the short-axis echocardiogram shown in Figure 5.6(g). The left and right pathology images are the apical and basal sides of the same heart slice, respectively. The pathology image viewed from the apical side was oriented in accordance with the echocardiogram. The finding that the mechanical function of the ischemic region recovered after reperfusion based on the radial strain (Figure 5.6(g)) was confirmed by the red color (stained by TTC) in the anterior wall region in the pathology
image of a canine heart slice (Figure 5.6(h)) that corresponded to the short-axis echocardiogram shown in Figure 5.6(g).

Figure 5.6 (Continued on the next page)
Figure 5.6: Cumulative systolic radial strain images of a canine left ventricle with a PV loop shown in Figure 5.3(b) at (a) 0%, (b) 20%, (c) 40%, (d) 60%, (e) 80% and (f) 100% constriction levels and (g) after reperfusion. Below each image shows the ECGs, and the red dot indicates at which cardiac phase each radial strain image is displayed. The arrows and the white lines on the anterior wall region signify the ischemic region. Anterior (ANT), lateral (LAT), posterior (POST) and septal (SEP) regions are indicated. (h) both sides of one canine mid-ventricular slice stained using 1% triphenyltetrazolium chloride (TTC) solution with pale (unstained by TTC) and red (stained by TTC) colors indicating infarcted and normal tissues, respectively. The left and right pathology images are the apical and basal sides of the same heart slice, respectively. The pathology image viewed from the apical side was oriented in accordance with the echocardiogram. Note that the echocardiographic image shown in (d) was erroneously acquired at a different short-axis plane.
Temporal cumulative radial strain profiles of the same canine left ventricle (Figure 5.6) over the entire cardiac cycle are shown in Figure 5.7. The overall decreasing radial strain magnitude showed that regional myocardial deformation steadily decreased with progressive coronary flow reduction. Anterior radial thinning during systole was first identified at 20% flow reduction (Figure 5.7(a)) and was increasingly pronounced at higher constriction levels up to 100% (Figure 5.7(b)). However, radial thickening in the same region was detected upon reperfusion, indicating that the function had been reinstated.
Figure 5.7: Temporal radial strain curves of the same canine heart shown in Fig. 5.6 in an anterior wall region of 3×3 mm² at (a) 0%, 20%, 40%, and (b) 60%, 80%, and 100% LAD flow reduction levels and after reperfusion (Reper). Below the figures show the ECG at baseline. ME denotes Myocardial Elastography. Note that the standard deviation represented the spatial variation of the radial strains within the ROI and that the temporal resolution was downsampled by a factor of 15 only for the purposes of the plot shown.
Figure 5.8: A scatter plot of the end-systolic radial strain ($E_{rr}$) in the anterior wall region between Myocardial Elastography (ME) and sonomicrometry at six different constriction levels and reperfusion (Reper) in five dogs. A correlation coefficient of 0.84 was found.
Figure 5.9: A Bland-Altman plot of the end-systolic radial strains of five dog left ventricles in an anterior wall region of 3 mm by 3 mm at six different constriction levels and reperfusion (Reper). $E_{rr}$ denotes the radial strain, and ME stands for Myocardial Elastography. SD denotes standard deviation. The bias and 95% limits of agreement were found to be 0.22% strain and -13.9% to 14.3% strain, respectively.
Good correlation \((r=0.84)\) in the end-systolic radial strain of the ischemic region between sonomicrometry and Myocardial Elastography at all graded constriction levels in all five dogs was found by a scatter plot (Figure 5.8). Agreement between the two methods was also evaluated by the Bland-Altman analysis\(^{130}\), which estimates the bias and errors by graphing the difference between the two methods against the average between the two methods. A Bland-Altman plot based on five dogs in all constriction and reperfusion cases (Figure 5.9) shows good agreement in the end-systolic radial strain between sonomicrometry and Myocardial Elastography with a bias of 0.22\% strain and 95\% limits of agreement (-13.9\% to 14.3\% strain). Compared to the range of the average radial strain measured (between -20\% and 30\% strain), the bias reported was deemed insignificant.

Table 5.1 summarizes the end-systolic ME radial strain \( (r_{rr}) \), wall motion score index, ejection fraction, and end-diastolic left-ventricular pressure in five dogs at six graded LAD flow reduction levels and after reperfusion. Overall, \( r_{rr} \) and wall motion score indices consistently decreased with increasing levels of LAD flow reduction.
Table 5.1. Wall motion score index (WMSI), $E_{rr}$, Ejection Fraction (EF) and End-Diastolic Left-Ventricular Pressure (EDLVP) in five dogs under graded myocardial ischemia. WMSI was assessed with 5: Normal; 4: Mild hypokinetic; 3: Hypokinetic; 2: Severe hypokinetic; 1: Akinetic; 0: Dyskinetic. $E_{rr}$ denotes the ME end-systolic radial strain.

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5.4. Discussion and Conclusion

Noninvasive real-time imaging techniques that can quantify myocardial deformation play an important role in the early detection and diagnosis of myocardial ischemia. Myocardial Elastography, an ultrasound RF-based strain imaging technique, has previously been proven (see Chapter 4) to be capable of depicting transmural deformation and of differentiating pathological from normal myocardium.

In this study, Myocardial Elastography was further employed in order to investigate at which degree of myocardial ischemia (i.e., graded levels of the coronary blood flow reduction) the abnormal regional deformation can first be depicted. To our knowledge, for the first time, Myocardial Elastography was shown feasible in imaging 2D transmural angle-independent strain of the canine left ventricle in vivo at distinct levels of LAD constriction. Qualitatively, initially reduced systolic radial thickening, leading to systolic radial thinning at larger constrictions, was observed in the region at risk (Figures 5.4 and 5.6) during myocardial ischemia. In both cases, the ischemic region (i.e., anterior wall) was imaged and identified in a full short-axis view starting at 40% constriction and compared to radial thickening at the baseline, i.e., 0% constriction (Figures 5.4(a) and 5.6(a)). Dyskinesia of the anterior wall region at the end-systolic phase as a result of the complete constriction (i.e., zero coronary blood flow) was also accurately depicted (Figures 5.4(f) and 5.6(f)).

Validation of the radial strain estimates in the anterior wall region at each ischemia level was performed in vivo against the direct measurement of sonomicrometry. The temporal radial strain profiles of the first canine left ventricle (Figure 5.5) exhibited similar trends in the anterior wall region between the two methods at each constriction
level. At 40% constriction, reduced radial thickening (or, hypokinesia) during systole and delayed radial thickening relative to baseline were observed in both Myocardial Elastography and sonomicrometry (Figure 5.5(a)). Up to 80% constriction, radial thinning (or, dyskinesia) was first observed during systole, followed by delayed radial thickening (Figure 5.5(b)). This delayed deformation phenomenon was also observed in Figure 5.7 and has been reported by several groups and termed as postsystolic shortening and thickening, which might be able to serve as an indicator of myocardial variability. Myocardial Elastography was thus shown capable of quantifying and localizing the postsystolic shortening.

Figures 5.4(g) and 5.6(g) present the myocardial deformation in two canine left ventricles after reperfusion. The observation from the first example (Figure 5.4(g)) that the systolic deformation of the ischemic (i.e., anterior-lateral wall) region after reperfusion did not fully recover and achieve its normal level was confirmed by the quantitative temporal radial strain profile shown in Figure 5.5(b), where radial thinning was noted in both complete constriction and reperfusion cases. This finding, i.e., that the negative radial strain or radial thinning in the anterior wall region exhibited after reperfusion (Figure 5.4(g)) was also confirmed in pathology (Figure 5.4(h)). However, the infarcted septal region shown in Figure 5.4(h) could not be compared to the radial strain image in Figure 5.4(g) since the pathology slice was not exactly taken through the myocardium where this short-axis echocardiogram was acquired.

Moreover, the postsystolic shortening/thickening feature was not clearly seen in the complete constriction level, possibly explaining the sustained radial thinning in the ischemic wall region during systole, namely, the lack of myocardial viability even after
reperfusion. On the other hand, radial thickening was observed in the lateral wall region at end-systole after reperfusion whereas radial thinning was noted in the same region at end-systole at 100% constriction. Radial thinning in the lateral wall in the complete constriction case might have resulted from lack of adequate perfusion in this canine heart. This phenomenon may reveal that the lateral wall segment transiently underwent reduced blood supply at several constriction levels since the lateral wall segment restored its myocardial deformation after reperfusion.

In the second reperfusion example presented in Figure 5.6(g), the mechanical function of the anterior wall segment was shown to be partially restored after reperfusion. This demonstrated the potential of Myocardial Elastography for providing myocardial deformation at variable levels of coronary blood flow. Nonetheless, reduced radial thickening and radial thinning were respectively observed in two regions (indicated by the solid and dotted circles) of the remote myocardium (i.e., posterior wall) in the Myocardial Elastography radial strain image in the reperfusion case (Figure 5.6(g)). Evident damage caused by an implanted crystal in the posterior junction between the right and left ventricles was noted (indicated by the solid circle in Figure 5.6(h): left image), and the surrounding myocardium shown in the pathology image was pale in color (Figure 5.6(h): left image); this explained the reduced radial deformation in the region indicated by the solid circle shown in Figure 5.6(g) and further confirmed the accuracy of the strains depicted. Another crystal implanted in the subendocardium of the posterior wall region was not only observed on the strain image indicated by the dotted circle (Figure 5.6(g)), but also justified in pathology (dotted circle in Figure 5.6(h): right image). This explained the atypical radial deformation, akinesia or dyskinesia, present in
the normal (i.e., posterior) region in the Myocardial Elastography radial strain image of this canine model.

In addition, the lateral wall region of the left ventricle in Figure 5.6(g) exhibited systolic radial thinning, while the rest of the myocardium underwent radial thickening after reperfusion. In fact, reduced radial thickening and subepicardial radial thinning in the same region was also noted starting at the 20% constriction level. This dyskinesia of the lateral wall region may be attributed to its lack of coronary blood supply; therefore, insufficient perfusion during coronary constriction and even after reperfusion led to its impaired myocardial deformation. Although no sonomicrometers were implanted in this region to validate this finding, the radial thinning in the lateral wall of the same canine left ventricle was verified by the radial strain in the four-chamber view reported in another study by our group\textsuperscript{134}. These results corroborate that Myocardial Elastography could identify the ischemic wall region at variable levels of coronary blood flow through precise 2D transmural strain imaging at high spatial resolution.

As far as the deformation of the canine left ventricle shown in Figure 5.6 is concerned, conspicuous radial thinning occurred at the 40% constriction level. The extent of the ischemic region increased with the level of coronary constriction. In addition, at 20% constriction, radial thinning in the sub-endocardium and reduced radial thickening in the sub-epicardium were observed in the anterior wall region. The difference in radial strains between subendocardial and subepicardial regions was in agreement with the fact that the subendocardial region was more susceptible to reduced coronary blood flow\textsuperscript{38}. This might indicate that non-transmural ischemia was induced at the 20% constriction level (i.e., 20% flow reduction) and shows that Myocardial Elastography could depict this
transmural variation and differentiate subendocardial from subepicardial deformation. The impaired regional myocardial function, i.e., significant decrease in the shortening of the endocardial third of the ventricular wall, at 20% coronary constriction level (or, coronary flow reduction) was also observed by Vatner\(^{43}\), whose study was performed on conscious dogs. Lekven et al.\(^{111}\) also showed that myocardial contractility was significantly diminished when the coronary blood flow was reduced by approximately 23%.

The success rate of this study, completing graded levels of constriction and reperfusion, was 50% as mentioned in the methods section due to differences in the collateral distribution and responsiveness to ischemia among the dogs used. Therefore, data obtained from successful experiments are all of high value even though the baselines among dogs varied. For example, the systolic radial strains at 0% constriction in Figure 5.5 ranged from -10% to 10% strain, which was low compared to the strain values shown in Figure 5.6 as well as previously reported in literature\(^{30,125}\). This canine left ventricle was found to be hypokinetic at the baseline prior to surgery as visually assessed by an echocardiography expert. Despite the lower strain values at the baseline, the graded ischemia experiment was successfully performed, and the dyskinetic anterior wall region was observed at greater constriction levels from the 2D elastographic radial strain estimates, which were in good agreement with the sonomicrometry measurements (Figure 5.5).

Table 5.1 shows that both the end-systolic ME radial strain and the WMSI decreased at greater LAD flow reduction. Similarly, the ejection fraction exhibited this trend in the fifth case except for the others shown in Table 5.1. Unlike the ME radial strains and
WMSI, the ejection fraction is a global volumetric measure and was shown less sensitive to the detection of myocardial abnormality at mild and intermediate ischemic levels (below 40% LAD flow reduction). Further compared to the WMSI, the ME radial strains and their images detailed quantitative and transmural myocardial deformation.

This study demonstrated that Myocardial Elastography could reliably estimate and image transmural strains in a full left-ventricular short-axis view in vivo, confirming our previous investigations in a theoretical framework and a clinical setting. Most importantly, for the first time, Myocardial Elastography could non-invasively identify and characterize the region of altered myocardial deformation starting at 40% and possibly as small as 20% coronary constriction (i.e., 20% coronary blood flow reduction) in vivo. The greater the reduction in coronary blood flow induced, the larger the extent of the ischemic myocardial segment on the strain images present with dyskinesia. Moreover, the estimated radial strain using Myocardial Elastography (Figure 5.6(b)) showed that the anterior wall region underwent non-transmural ischemia formed at 20% constriction. This may reveal the potential of Myocardial Elastography as a reliable diagnostic tool to detect early myocardial ischemia and warrant more complete investigations. Future work will include a similar study using circumferential strains, the association of high quality strain estimation with the echocardiography system parameters (e.g., beam density, beamwidth, and focal location), and the performance and specificity of detecting the severity of stenosis and its subsequent treatment in a clinical setting.

The finding that the ischemic myocardial regions exhibited opposite deformation (i.e., radial thinning, instead of radial thickening) from the non-ischemic ones was consistent with the results shown in the theoretical framework (Figures 4.7 and 4.8). This further
confirmed the reliable use of Myocardial Elastography for angle-independent strain estimation as an imaging tool to detect and identify the ischemic region as a result of coronary flow reduction. In Chapter 6, Myocardial Elastography is therefore performed in a clinical setting, the ultimate configuration, to evaluate its reliable capability of detecting abnormal myocardial regions in human left ventricles.
Chapter 6

Clinical Validation of Myocardial Elastography against MR Tagging

6.1. Background

Strain estimation techniques range from Tissue Doppler Imaging (TDI)\textsuperscript{23,135,136}, Strain Rate Imaging (SRI)\textsuperscript{24-26, 73} to Myocardial Elastography (ME)\textsuperscript{4, 32, 137, 138}. Among those, Myocardial Elastography (see Chapter 4), which is a radio-frequency (RF)-based ultrasound speckle tracking technique, has been shown capable of assessing normal myocardial deformation\textsuperscript{4, 139} and detecting abnormal myocardial function \textit{in vivo}\textsuperscript{138}, as a result of ischemia or infarction, through estimation of the myocardial deformation resulting from the natural contraction of the myocardium in each cardiac cycle. Myocardial Elastography has also been shown fundamentally capable of accurately estimating and imaging in-plane deformation in full short-axis views in a previously proposed theoretical framework (Chapter 4)\textsuperscript{32, 66}, using an ultrasonic image formation model and an established three-dimensional (3D), finite-element canine left-ventricular model, in both normal and left-circumflex (LCx) ischemic states. Furthermore, using the same framework, Myocardial Elastography (ME) could differentiate abnormal from normal myocardium based on angle-independent estimates. Not only was Myocardial Elastography shown to accurately
estimate and image the myocardial displacements and strains using the theoretical model, but it could also differentiate abnormal from normal cardiac muscle without a beam-to-muscle angle dependence\textsuperscript{32,66,90,91} in full view.

Myocardial Elastography has also been validated against direct measurement, sonomicrometry, in an animal study presented in Chapter 5, where progressive coronary flow reduction was performed to simulate coronary stenosis and cause regional myocardial ischemia and thus abnormal myocardial deformation. Again, opposite angle-independent strain patterns were observed in the myocardial ischemic region compared to the normal one. The changes in the angle-independent strain patterns facilitate the detection, identification and localization of the ischemic or dysfunctional myocardial region. However, an important remaining question is how the performance of Myocardial Elastography is as a potential diagnostic tool in a clinical setting.

As far as clinical applications are concerned, MR tagging, or tagged Magnetic Resonance Imaging (tMRI)\textsuperscript{33, 34}, is still regarded as the noninvasive gold standard of assessing myocardial deformation. Tags function as virtual markers embedded in the myocardium, and the deformation of their shape during the cardiac cycle is associated with myocardial motion. Since MR tagging was invented in the late eighties, efforts have been made to quantify myocardial motion/strain from tagged images; ranging from tracking tag lines or grids\textsuperscript{85,140-144} to extracting harmonic phase (HARP) information\textsuperscript{145,146}.

Several previous studies have compared the estimates from echocardiography with those from MR tagging\textsuperscript{74, 79, 147-149}. Edvardsen et al.\textsuperscript{74} first validated echocardiographic strains using Tissue Doppler against MR tagging (tMRI) and showed high correlation for radial strains (r=0.96) between the two modalities. However, this tissue Doppler method
merely estimates a one-dimensional (1D) strain component, namely radial strain, and no 2D images were shown. In addition, their estimated systolic strains were defined as the percent change of the segment length, while the actual Lagrangian normal strains include second order displacement gradient terms. Konofagou et al.\textsuperscript{149} showed that axial displacement ($r=0.81$) and strain ($r=0.65$) estimated from B-mode based Myocardial Elastography were well correlated with those from 1D MR tagging in the septum in an apical four-chamber view of human left ventricles. Only the axial estimates, which coincided with the beam direction and were displayed in an M-mode format, were shown. Notomi et al.\textsuperscript{147} used an ultrasound B-mode based speckle tracking technique to measure ventricular torsion and validated it against MR tagging. Basal and apical short-axis images were acquired from human subjects using both ultrasound and MR tagging. Their temporal average torsion profile proved that torsional deformation estimated from the ultrasound speckle tracking was in good agreement with that from the HARP analysis of MR tagging images. Helle-Valle et al.\textsuperscript{148} also showed the feasibility that ultrasound speckle tracking could assess ventricular rotation in healthy human subjects with findings consistent with those using MR tagging. Similar to the methods presented by Notomi et al., basal and apical level short-axis images were acquired, and B-mode speckle tracking and HARP were employed to analyze rotation in ultrasound and MR tagging, respectively. Average mid-endocardial and sub-endocardial rotation values were estimated and compared during a cardiac cycle across the two imaging modalities. Amundsen et al.\textsuperscript{79} proposed a B-mode based speckle tracking echocardiography (STE) technique to track the displacement of segment endpoints and to calculate strain from the change in wall thickness. Echocardiograms were acquired from two- and four-chamber apical views. The
longitudinal strain measured using their B-mode-based STE was in good agreement with MR tagging estimates.

Nevertheless, none of the aforementioned reports provided a one-to-one comparison of displacement and strain fields obtained in echocardiograms and MR tagging in full view in a clinical setting. Our group has implemented Myocardial Elastography in a clinical setting, and preliminarily validated in-plane displacement (i.e., lateral and axial) and strain (i.e., lateral, axial, radial and circumferential) estimates against MR tagging estimates by color-coding and overlaying those estimates on both echocardiography and tagged MR images\textsuperscript{32, 67, 139}.

In this section, we focus on the full depiction of the nonuniformity of 2D transmural myocardial displacement and deformation (i.e., strains) in short-axis views from the Myocardial Elastography technique with the additional implementation of principal strain estimation in a clinical setting. In order to evaluate myocardial motion and strain estimates, Myocardial Elastography is compared against MR tagging.

6.2. Methodology

6.2.1. Human Subject Recruitment

A total of thirty-six (n=36) human subjects were recruited: twenty-five (n=25) normals (13 males and 12 females, 33.1±7.7 y.o) and eleven (n=11) subjects with history of heart disease and, more specifically, history of partial constriction in the left anterior descending (LAD) or left circumflex (LCx) coronary artery that was stent-treated (7 males and 4 females, 55.2±9.5 y.o). The results in 9 out of the 36 human left ventricles were reported in
this chapter due to exclusion criteria, including poor acoustic window, poor sector matching, claustrophobia and incompatible stent (see details in section 6.2.3.1.). The human subject study protocol was approved by the Institutional Review Board of Columbia University, and informed consent was obtained from all human subjects prior to scanning.

6.2.2. Magnetic Resonance Tagging

Since the invention of MR tagging as an imaging method to analyze cardiac motion and deformation, other types of sequences have also been developed for the same purpose, such as velocity-encoded MRI\textsuperscript{150}, strain-encoded MRI\textsuperscript{151,152}, and Displacement Encoding with Stimulated Echoes (DENSE)\textsuperscript{153,154}. Since MR tagging has been well established and was available for further sequence optimization in the MR scanner used (see section 6.2.2.1), MR tagging was considered as the gold standard in this clinical study.

As mentioned in the background, quantification of the myocardial motion/strain from tagged MR images range from tracking tag lines or grids\textsuperscript{85,140-144} to extracting harmonic phase (HARP) information\textsuperscript{145,146}. The tag analysis process with HARP is computationally efficient, but its accuracy may be jeopardized compared to the tag tracking method presented in section 6.2.2.2 based on previously reported preliminary studies\textsuperscript{155,156}. The bandpass filter used in HARP presents a trade-off between spatial constraints and the frequency bandwidth used. This may lead to difficulties in the estimation of large local deformation. Moreover, HARP may not be as robust in estimating fast myocardial deformation in the presence of low frame rate due to its phase-wrapping artifact\textsuperscript{146}.
6.2.2.1. Tagged MR Image Acquisition

Tagged MR images were obtained on a Philips Intera 1.5T scanner (Philips Medical Systems, Best, The Netherlands) equipped with a five-channel SENSE cardiac coil and master gradients of strength 30 mT/m and slew rate 150 T/m/s. A multi-slice and multi-phase true short-axis tagged image was acquired under free-breathing with a combination of fast-field echo excitation and a multi-shot echo-planar readout (EPI-FFE) technique (FOV=350 mm, TE=4 ms, TR=30, NSA=4, resolution acquired/reconstructed =192/256, flip angle =13 degrees, EPI factor=3 and full ECG gating scan duration=4.77 min). The receiver bandwidth was 401.9 Hz, and the time to fill the k-space was 23.85 seconds. Two-dimensional grid tagging was performed yielding a 9-mm, in-plane tag resolution. The short-axis orientation was also acquired at the papillary muscle level from the same subjects. The nominal frame rate was 33 fps.

The reason we focused on short-axis views was that the anterior, posterior, lateral and septal wall regions which are affected by LAD or LCx occlusions could be imaged at the same time and that angle-independent strains were estimated based on polar coordinates, which were more appropriately represented in short-axis views than other views, e.g. long-axis, four-chamber and two-chamber views, given the associated left-ventricular quasi-circular shape. In addition, preliminary studies indicated that higher contrast between normal and abnormal myocardial deformation could be depicted in short-axis views.
6.2.2.2. MR Tag Tracking

A tagged MRI sequence generates two perpendicular sets of equally spaced parallel tagging planes as temporary markers within the myocardium through spatial modulation of the magnetization at end-diastole (ED)\(^{33, 158}\). Imaging planes are perpendicular to the two sets of tagging planes so that the tags appear as dark grids on the MR images and deform with the underlying myocardium during the cardiac cycle \textit{in vivo}. This yields detailed motion information of the myocardium.

In order to track the tagging grids and obtain the localized myocardial displacement and strain values, we implemented a template-based tracking algorithm on a 2D grid-shaped mesh to obtain the displacement vectors of the crossing points (or, nodes) on the tagging grids\(^{143, 144, 159, 160}\). Each crossing point (or, node) on the mesh was tracked by calculating the similarity between templates, which were modeled using two tunable Gabor filters and the underlying images\(^{144, 160}\). The crossing points on the mesh were driven iteratively by forces from those neighboring image patches, whose texture patterns were the most similar to a reference template. The coordinates of the crossing points were further smoothed in a time sequence by a cubic spline function, and the displacements were thus calculated through subtraction. Finally, a cubic B-spline-based method was employed to obtain a dense displacement distribution throughout the myocardium\(^{161}\). The cumulative 2D systolic displacement was also obtained.

6.2.2.3. Strain Calculation

Cumulative 2D (i.e., lateral and axial) systolic Lagrangian finite strain was derived from the cumulative 2D displacement to evaluate the systolic function \textit{in vivo}\(^{66, 103}\). Positive and negative 2D strains indicate extension and shortening, respectively.
6.2.3. High Frame-Rate RF Echocardiographic Data Acquisition and Analysis

6.2.3.1. Data Acquisition

A clinical echocardiography ultrasound system (General Electric (GE) Vivid FiVe, GE Vingmed Ultrasound, Horten, Norway) with a phased array probe (FPA 2.5MHz 1C) was used to acquire cardiac ultrasound in-phase and quadrature (I/Q) data in 2D short-axis views at the papillary level at a frame rate of 136 fps, which was the maximum achievable in the clinical setting using the aforementioned system. The I/Q data were further upsampled to retrieve the RF signals. The lateral and axial resolutions are approximately 1.92 mm and 0.77 mm, respectively.

The frame rates of commercial ultrasound systems typically range between 30 fps and 70 fps. This GE system allowed a maximum frame rate of 50 fps in a default setting. However, RF-based speckle tracking and strain imaging requires higher frame rates (Figures 4.9 and 4.10) for myocardial motion estimation\(^4,\,26,\,73\). In order to increase the frame rate without sacrificing the beam density or the size of the region-of-interest (ROI), a novel electrocardiogram (ECG)-gated composite imaging technique, which assembled multiple small sector images into a full-view echocardiogram, was implemented by our group\(^{162}\). Because of the limited control on the GE system used, different from the fully automated method proposed by Wang et al., five or six sectors with a reduced field of view (FOV) were selected manually and combined off-line based on the spatial (i.e., depth and angle) and ECG information to depict the entire cardiac short-axis view up to 136 fps. RF data within three cardiac cycles were acquired for each sector. All the sectors were
acquired under separate breath-holds and free-hand scanning, and the total acquisition time was approximately six minutes. Owing to the separate breath-holds and free-hand scanning, discontinuities between neighboring sectors were impossible to correct in some subjects and thus deteriorated the image reconstruction and subsequent motion estimation. Other subjects had non-optimal acoustic windows, so the ultrasonic RF signal quality was not suitable for motion tracking. Due to the deeper imaging fields of view needed in some subjects and the limited control on the system used, the RF frame rate was insufficient for the RF-based Myocardial Elastography as assessed in Chapter 4 (Figures 4.9 and 4.10). Among the 11 patients who satisfied the criteria and agreed to participate in the study, two experienced claustrophobia in the MRI scanner, two had stents incompatible with MRI, and another four had no short-axis echocardiograms because they fell under the earlier protocol that did not require the short-axis echocardiograms. In short, results based on six normals and three subjects with history of myocardial infarction are reported in this study.

At the frame rate of 136 fps, the decorrelation of RF signals resulting from through-plane motion was reduced. In other words, sufficiently high correlation between two consecutive RF frames was achieved\textsuperscript{163}. The theoretical framework, evaluating the performance of Myocardial Elastography at multiple short-axis views, proposed by our group\textsuperscript{32, 66} also showed that Myocardial Elastography retained good performance, even in the presence of through-plane motion. Furthermore, the data presented in this chapter were acquired at the papillary muscle level, which served as a marker for registration purposes in a standard echocardiographic, short-axis view\textsuperscript{164}.
6.2.3.2. Data Analysis

Two-dimensional, in-plane orthogonal (lateral and axial) displacement components were estimated using one-dimensional (1D) cross-correlation and recorrelation of RF signals in a 2D search. The cross-correlation technique employed a 1D matching kernel of 7.7 mm with an 80% overlap. In a preliminary study, several different 1D matching kernel sizes were tested. It was concluded that the larger the kernel, the less noisy the displacement estimates, and the lower the precision of the estimates. Since the overlap was directly defined by the 1D matching kernel size, the larger the kernel, the lower the resolution of displacement estimates. In other words, the trade-off between precision and resolution of displacement estimates, owing to the kernel size, was identified. According to the results from clinical data, the optimal 1D matching kernel used was approximately 10 times higher than the wavelength. The 80% overlap can be adjusted according to the need of resolution of displacement estimates. In other words, the window shift was assumed to indicate the expected elastographic resolution as reported in the literature. The reference and comparison frames included the RF signals before and after deformation, respectively. The RF signal segment in the comparison frame corresponding to the maximum cross-correlation value was considered to be the best match with the RF signal segment in the reference frame. Cosine interpolation was then applied around the peak of the cross-correlation function for a more refined peak search. Thus, the lateral and axial shifts between the reference and comparison RF segments with the highest cross-correlated value were the lateral and axial displacements, respectively.

A correction (or, recorrelation) in the axial displacement estimation was performed to reduce the decorrelation resulting from axial motion for improved lateral displacement.
estimation. It was implemented by shifting the RF signal segments by the estimated axial displacement in the comparison frame, prior to the second lateral displacement estimation (Figure 4.3). This estimated lateral displacement was then further normalized using the actual beam spacing, which varied with depth owing to the polar coordinates used in the phased array configuration. This normalization is detailed in Appendix A.

The incremental 2D displacements that occurred from ED to ES were further integrated to obtain the cumulative 2D systolic displacement. For each pixel, appropriate registration between consecutive displacement images was performed in order to ensure that the cumulative displacement depicted the motion of the same tissue region. The end-diastolic phase was pinpointed by the peak of the QRS segment (i.e., R wave) in the ECG signal.

Since the phased-array configuration is used for echocardiography (see Appendix A), the strains were calculated in polar coordinates (see Appendix B). In Myocardial Elastography, a least-squares strain estimator (LSQSE) with a kernel of 11.7 mm in both the lateral and axial directions was used in order to improve the signal-to-noise ratio (SNR) in the strain image and compensate for the lower sonographic SNR compared to the dog case (Chapter 5).

Table 6.1 summarizes the main image parameters for Myocardial Elastography and MR tag tracking used in this study. The SNR of the tagged MR images was approximately 5.45, while that of MR strain images was approximately 10.15.
Table 6.1. Strain imaging parameters for both Myocardial Elastography and MR tag tracking.

<table>
<thead>
<tr>
<th></th>
<th>Myocardial Elastography</th>
<th>MR tag tracking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal resolution of strain elements (fps)</td>
<td>136</td>
<td>33</td>
</tr>
<tr>
<td>Lateral resolution of strains (mm)</td>
<td>1.76</td>
<td>9</td>
</tr>
<tr>
<td>Axial resolution of strains (mm)</td>
<td>1.38</td>
<td>9</td>
</tr>
<tr>
<td>Data acquisition temporal resolution (fps)</td>
<td>136</td>
<td>33</td>
</tr>
</tbody>
</table>

However, the aforementioned 2D finite strain was dependent on the orientation of the ultrasound transducer relative to the ventricle and on the coordinates of the imaging systems. In addition, the coordinate systems used in the two modalities were different as shown in Appendix A. This angle dependence and differences in the coordinate system might complicate the interpretation of myocardial deformation in the left ventricle as well as comparison between the two imaging modalities. Therefore, angle-independent, polar (i.e., radial and circumferential) strains, were additionally obtained by defining an angle, $\theta$, about the centroid of the left ventricle and by coordinate transformation of the 2D finite strain. Positive and negative radial strains indicated myocardial thickening and thinning, respectively, while myocardial stretching and shortening were represented by positive and negative circumferential strains, respectively.

Even though the polar strains are independent of the transducer orientation, the selection of the centroid is critical. Principal strains have been proven to be angle-independent as well as less centroid-independent than the polar strains\textsuperscript{90, 91}. Considering a 2D short-axis slice of the myocardium, solving the eigenvalue/eigenvector problem using equation (6.1) for the 2D finite strain tensor could yield two principal strains (eigenvalues)
corresponding to two principal axes (eigenvectors), which closely approximated strains in
the polar directions.

\[ \mathbf{E}^p = \begin{bmatrix} \varepsilon_1 & 0 \\ 0 & \varepsilon_2 \end{bmatrix}, \tag{6.1} \]

where \( \mathbf{E}^p \) is the principal strain tensor, and \( \varepsilon_1 \) and \( \varepsilon_2 \) are the classified 1st and 2nd principal
components, respectively. Note that the two principal strains were classified according to
their angles between the principal (i.e., eigenvectors) and polar directions\(^91\). The classified
1st and 2nd principal strains closely approximated radial and circumferential strains,
respectively\(^91\).

### 6.2.3.3. Automated Contour Tracking

Segmenting the myocardium from the neighboring tissue is essential in the depiction
and detection of the extent of the pathological myocardium. Myocardial segmentation on
the elastographic images throughout the entire cardiac cycle was performed and extended
from 1D (i.e., axial) to 2D using a semi-automated method developed by our group\(^167\). The
endo- and epicardial contours on the first acquired RF echocardiogram (i.e., at ED) were
initially manually traced using 20 points for each as the reference, while in all subsequent
frames, the contours were automatically segmented according to the estimated 2D
displacement components. Automated contour tracking was thus implemented using 2D
elastographic estimates.

### 6.3. Results

Only the cumulative systolic deformation (i.e., displacements and strains) from ED to
ES was considered in this chapter, since systolic function is relevant to the active
contractility of the myocardium, and the analysis of tagged MR images during diastole was
not feasible owing to tag fading. The cumulative lateral and axial displacement images from ED to ES estimated using MR tagging and Myocardial Elastography at the papillary muscle level in a short-axis view of the left ventricle of a normal human subject (female, 28 y.o., heart rate 80 bpm) are shown in Figure 6.1(i) at the end-systolic phase. The anterior, lateral, posterior and septal walls are in the upper right, lower right, lower left and upper left regions, respectively. Positive displacement values indicate rightward or upward motion, while negative displacement values represent leftward or downward motion. Figure 6.1(ii) shows the corresponding cumulative systolic lateral and axial strains estimated from MR tagging ((a) and (c)) and Myocardial Elastography ((b) and (d)). As expected for a normal left ventricle being imaged in an echocardiographic short-axis view, extension in the lateral direction appears in the lateral and septal myocardial regions, and axial extension in the anterior and posterior walls.

Figure 6.1 (Continued on the next page)

(i)
Figure 6.1: Cumulative systolic 2D (i) displacements and (ii) strains of the left ventricle of a normal human subject (female, 28 y.o., heart rate 80 bpm) between ED and ES: (a) and (c) are the lateral and axial components from MR tagging (tMRI), respectively; (b) and (d) are the lateral and axial components from Myocardial Elastography (ME), respectively. All the displacement and strain images are acquired approximately at the papillary muscle level and shown at ES. The white rectangles indicate where the temporal displacement and strain profiles shown in Figure 6.3 are obtained. The arrows indicate the motion directions.
Figure 6.2 (Continued on the next page)
Figure 6.2: Cumulative systolic (i) polar and (ii) classified principal strains of the same normal human left ventricle between ED and ES: (a) and (c) are the radial/classified 1st principal and circumferential/classified 2nd principal strains from MR tagging (tMRI), respectively; (b) and (d) are the radial/classified 1st principal and circumferential/classified 2nd principal strains from Myocardial Elastography (ME), respectively. The white rectangles in (ii) indicate where the temporal strain profiles shown in Figures 6.7(a) and (b) were obtained.
The cumulative systolic polar and classified principal strains estimated from both imaging modalities are shown in Figures 6.2(i) and (ii), respectively. Figure 6.2 shows positive radial (i.e., myocardial thickening in (a) and (b)) and negative circumferential (i.e., myocardial shortening in (c) and (d)) strains. The maps of the polar and classified principal strains were visually indistinguishable.

The temporal axial displacement and 2D polar and classified principal strain profiles in a posterior wall region of 7.5×7.5 mm², which is indicated by the white squares in Figure 6.1 during systole, are shown in Figure 6.3. The temporal lateral displacement profiles of MR tagging and Myocardial Elastography averaged within the white rectangles shown in Figure 6.1(i) (a-b) are shown in Figure 6.3(a). Note that the errorbars represent the transmural variations of displacements, or strains, within the white rectangle on each image in Figures 6.1 and 6.4. Compared to the other myocardial regions, the posterior wall is within a sector and thus less affected by the manual composite imaging method. However, the posteroseptal region, where larger lateral motion occurred, is more suitable for obtaining temporal lateral displacement profiles. Figures 6.3(a)-(d) show the temporal (i.e., from ED to ES) profiles of the cumulative lateral and axial displacements and strains. The magnitude and the increasing trend of cumulative Myocardial Elastography lateral and axial displacements (Figure 6.3(b)) during systole are in excellent agreement with the MR tagging estimates. However, the lateral strain (Figure 6.3(c)) obtained by the two modalities has a larger discrepancy than the axial strain. The temporal axial (Figure 6.3(d)), radial (Figure 6.3(e)) and the classified 1st principal component (Figure 6.3(g)) strain profiles show better agreement between MR tagging and Myocardial Elastography than the lateral (Figure 6.3(c)), circumferential (Figure 6.3(f)) and the classified 2nd principal strain
components (Figure 6.3(h)) in the normal case. This is because the lateral strain (Figure 6.3(c)) in the selected location contributes to a larger degree to the circumferential and the classified 2nd principal strains and thus results in their larger disagreement (Figure 6.3(f) and (h)) between two modalities. The strains obtained from Myocardial Elastography are also higher than the equivalent MR tagging values (Figure 6.3(c-h)). Increased standard deviations in the Myocardial Elastography with time, due to accumulation errors, and higher standard deviations of the Myocardial Elastography estimates compared to those of the MR tagging ones were noted in the normal left ventricle (Figure 6.3).

Figure 6.3 (Continued on the next page)
Figure 6.3: A normal human left ventricle: temporal displacement and strain profiles from Myocardial Elastography (ME) and MR tagging (tMRI) in the postero-septal or posterior wall region of 7.5 mm by 7.5 mm from ED to ES in the case of (a) lateral, (b) axial displacements, (c) lateral, (d) axial, (e) radial, (f) circumferential, (g) classified 1\textsuperscript{st} principal, and (h) classified 2\textsuperscript{nd} principal strains. The displacement profile is displayed between -2 mm to 6 mm. The strain profile is displayed between -0.3 to 0.5, namely -30\% to 50\% strain.
An example of the deformation in an infarcted left ventricle is shown in Figures 6.4 and 6.5. This human subject (male, 69 y.o., heart rate 73 bpm) suffered a myocardial infarction caused by partial constriction of the distal left anterior descending (LAD) coronary artery and exhibited subsequent motion abnormalities in both the septal and anterior walls. Figure 6.4 shows the estimated cumulative systolic 2D strains and indicates that the axial component has better agreement than the lateral one. Not only does the infarcted left ventricle (Figure 6.4) show hypokinetic behavior in the post-infarcted (i.e., anterior and anteroseptal) region and hyperkinesia in the non-pathological (i.e., lateral and lateral-posterior) wall region compared with the normal left ventricle (Figure 6.1(ii)), but the 2D strain patterns of the infarcted one (Figure 6.4) are highly asymmetric compared to those of the normal one (Figure 6.1(ii)). The cumulative systolic radial (Figure 6.5(i) (b)) and classified 1st principal (Figure 6.5(ii) (b)) Myocardial Elastography strain estimates for the infarcted left ventricle show myocardial thickening in the posterior and anterior-septal walls but not in the septum or anterior region. In contrast, the radial (Figure 6.5(i) (a)) and classified 1st principal (Figure 6.5(i) (a)) MR tagging strains show thickening throughout the entire myocardium with augmented thickening in the posterior wall but with reduced thickening in the other walls. The circumferential (Figure 6.5(i) (d)) and classified 2nd principal (Figure 6.5(ii) (d)) Myocardial Elastography strain estimates show myocardial shortening in the posterior wall and slight stretching in the other regions, while the MR tagging estimates (Figures 6.5(i) (c) and (ii) (c)) indicate slight stretching in the lateral, anterior and anterior-septal walls. Overall, good agreement in the circumferential and classified 2nd principal strains between two imaging methods was shown.
Figure 6.4: Cumulative systolic 2D strains of an infarcted human left ventricle of a patient with a history of partial LAD constriction (male, 69 y.o., heart rate 73 bpm) between ED and ES: (a) and (c) are the lateral and axial strains from MR tagging (tMRI), respectively; (b) and (d) are the lateral and axial strains from Myocardial Elastography (ME), respectively. All the displacement and strain images were acquired approximately at the papillary muscle level and shown at ES. The white rectangles indicate where the temporal strain profiles shown in Figure 6.6 were obtained.
Figure 6.5 (Continued on the next page)
Figure 6.5: Cumulative systolic (i) polar and (ii) classified principal strains of the same infarcted human left ventricle between ED and ES: (a) and (c) are the radial/classified 1<sup>st</sup> and circumferential/classified 2<sup>nd</sup> principal strains from MR tagging (tMRI), respectively; (b) and (d) are the radial/classified 1<sup>st</sup> principal and circumferential/classified 2<sup>nd</sup> principal strains from Myocardial Elastography (ME), respectively. The white rectangles in (ii) indicate where the temporal strain profiles shown in Figures 6.7(c) and (d) were obtained.
Similar to the normal human left ventricle, the temporal axial displacement and 2D polar and classified principal strain profiles in a posterior-lateral wall region of 7.5×7.5 mm², which is indicated by the white squares in Figure 6.4 during systole, for the infarcted case are shown in Figure 6.6. The temporal lateral displacement profiles of MR tagging and Myocardial Elastography are obtained from a posteroseptal wall region of 7.5×7.5 mm² and are shown in Figure 6.6(a). Overall, the displacements and strains obtained from Myocardial Elastography are larger in magnitude than the equivalent MR tagging values. Increased standard deviations in the Myocardial Elastography estimates over time and higher standard deviations of the Myocardial Elastography estimates compared to those of MR tagging were also noted in the infarcted case (Figure 6.6).

![Figure 6.6](Continued on the next page)
Figure 6.6: An infarcted human left ventricle: temporal displacement and strain profiles from Myocardial Elastography (ME) and MR tagging (tMRI) in the posteroseptal (for the lateral displacement) or posterior-lateral wall region (for the other estimates) of 7.5 mm by 7.5 mm from ED to ES in the case of (a) lateral, (b) axial displacements, (c) lateral, (d) axial, (e) radial, (f) circumferential, (g) classified 1st principal, and (h) classified 2nd principal strains. The displacement profile is shown from -3 mm to 8 mm. The strain profile is shown from -0.4 to 0.8, namely -40% to 80% strain.

Figures 6.7(a) and (b) show the temporal classified 1st and 2nd principal strain profiles in an anterior wall region of 3.5×3.5 mm² in the normal left ventricle, which is indicated by the white rectangles in Figure 6.2(ii), respectively. Figures 6.7(c) and (d) show the temporal classified 1st and 2nd principal strain profiles in a comparable anterior wall region.
of 3.5×3.5 mm² in the infarcted left ventricle, respectively. The normal left ventricle appears to experience radial thickening (Figure 6.7(a)) and circumferential shortening (Figure 6.7(b)); in contrast, the infarcted one undergoes radial thinning (Figure 6.7(c)) and circumferential stretching (Figure 6.7(d)). This further confirms that the abnormal myocardium undergoes opposite deformation compared with the normal myocardium as indicated in both simulations (Chapter 4) and canine experiments (Chapter 5).

**Figure 6.7**: Temporal systolic Myocardial Elastography (ME) and MR tagging (tMRI) classified principal strain profiles in the anterior wall region of 3.5 by 3.5 mm² in the case of a normal human left ventricle: (a) classified 1ˢᵗ and (b) classified 2ⁿᵈ systolic principal strains and of an infarcted human left ventricle: (c) classified 1ˢᵗ and (d) classified 2ⁿᵈ principal strains.
Good correlation (r=0.75) in the end-systolic radial and circumferential strains of the posterior wall region of 7.5 by 7.5 mm$^2$ between Myocardial Elastography and MR tagging in six normal and three infarcted left ventricles was found (Figure 6.8). The agreement between the two methods was further evaluated through Bland-Altman analysis, which estimates the bias and jitter errors by plotting the difference between the two methods against the average between the two methods. A Bland-Altman plot based on the aforementioned nine human left ventricles (Figure 6.9(a)) shows good agreement in the end-systolic radial strain between the two methods with a bias of 5.59% strain and 95% limits of agreement (or, confidence interval) (-6.24% to 17.41% strain). In the end-systolic circumferential strain (Figure 6.9(b)), a bias of 0.57% strain within 95% limits of agreement (-16.53% to 17.68% strain) was found.

**Figure 6.8**: The scatter plots of estimated end-systolic (a) radial and (b) circumferential strains in the posterior wall region of 7.5 by 7.5 mm$^2$ in six normal (labeled with the circle) and three infarcted (labeled with the asterisk) human left ventricles from Myocardial Elastography (ME) and MR tagging (tMRI).
Figure 6.9: The Bland-Altman plots of estimated end-systolic (a) radial and (b) circumferential strains in the posterior wall region of 7.5 by 7.5 mm² based on six normal (labeled with the circle) and three infarcted (labeled with the asterisk) human left ventricles using Myocardial Elastography (ME) and MR tagging (tMRI).
6.4. Discussion and Conclusion

Imaging of the 2D transmural displacement and deformation (or, finite strain) components, using lateral and axial, polar, and principal coordinates, in a full short-axis view acquired in a clinical echocardiography setting, was shown for the first time. A comparison of 2D images of all aforementioned estimated displacements and strains between ultrasound and MRI tagging in a clinical setting was also performed for the first time to our knowledge. Qualitatively, all these Myocardial Elastography estimates were in excellent agreement with those of MR tagging in both normal (Figures 6.1-6.2) and infarcted (Figures 6.4-6.5) human left ventricles. More specifically, the 2D displacements (Figures 6.3(a) and (b)), axial (Figure 6.3(d)), radial (Figure 6.3(e)) and the classified 1st principal (Figure 6.3(g)) Myocardial Elastography strain estimates were found to be in good quantitative agreement with the MR tagging estimates in the posterior wall region of the normal human left ventricle. As for the infarcted human left ventricle, axial (Figure 6.6(d)) and classified 1st principal (Figure 6.6(g)) strains across the two imaging modalities had the best quantitative agreement compared to other estimates.

In the normal human left ventricle shown in Figure 6.1, estimates from both MR tagging and Myocardial Elastography correctly depicted physiologic motion and deformation in the systolic phase. However, the orientation of the MR tagging 2D displacements (Figure 6.1(i), (a) and (c)) and strains (Figure 6.1(ii), (a) and (c)) did not exactly match with that of the Myocardial Elastography estimates (Figures 6.1(i)-(ii), (b) and (d)). This may have resulted from the fact that the image planes acquired using MR tagging and echocardiography were not adequately co-registered and that the coordinate systems were different between these two imaging modalities (Appendix A). Moreover, the
size and the shape of the right ventricle shown in the tagged MR image (Figure 6.1(i), (a) and (c)) did not correspond to those shown on the echocardiography images (Figure 6.1(i), (b) and (d)). In order to reduce the discrepancy due to image misregistration and to more fairly compare the estimates between the two imaging modalities, polar (Figure 6.2(i)) and classified principal (Figure 6.2(ii)) strains were imaged, showing myocardial wall thickening and circumferential shortening during systole in the normal human left ventricle.

The temporal profiles of the MR tagging radial (Figure 6.3(e)) and classified 1st principal (Figure 6.3(g)) strains showed excellent agreement with the equivalent Myocardial Elastography profiles, while the circumferential (Figure 6.3(f)) and classified 2nd principal component (Figure 6.3(h)) profiles show the lowest agreement. However, the classified 2nd principal strain was associated with a lower discrepancy than the circumferential strain across the two modalities in cases studied. In general, classified principal strains showed comparable results to those of polar strains in the clinical cases studied, but the former could be used to further reduce the centroid dependence, and thus, may constitute a more reliable tool for the accurate depiction of myocardial deformation.

The MR tagging and Myocardial Elastography strain estimates in the posterior wall of the infarcted ventricle were higher than those in the anterior wall (Figures 6.4 and 6.5). This may indicate that the post-infarcted (i.e., anterior and antero-setpal) region experienced the reduced contractility and that the normal region (i.e., posterior) compensated for the reduced systolic function of the abnormal region (i.e., anterior) with hyperkinesia, i.e., larger motion and deformation. However, this effect of compensation
was more pronounced in the Myocardial Elastography, not in the MR tagging, estimates. The cumulative systolic axial, radial and the classified 1st principal strain estimated from Myocardial Elastography in the posterior wall were approximately on the order of 50%, while those estimated from MR tagging ranged from 20% to 30% (Figures 6.6(d), (e) and (g)). This large discrepancy may have been due to the different short-axis planes acquired in the two imaging system and still needs further investigation. In addition, the infarcted left ventricle exhibited a more asymmetric geometry and deformation pattern than the normal case. This further complicated the comparison between the strain estimates from the two imaging systems, especially in the presence of imperfect image registration. The polar and classified principal strains still showed comparable results.

In the case of the infarcted human left ventricle (Figures 6.4 and 6.5), manual composite RF sector data acquisition was also employed to increase the frame rate, with potential, albeit small, mismatches between neighboring sectors in the septal and outside the lateral walls due to free-hand scanning, inconsistency in breath-hold duration and volume, and different lengths of cardiac cycles involved for the different sectors. Thus, the MR tagging and Myocardial Elastography strain estimates in the septal region of this infarcted myocardium appeared to have larger discrepancy than those in the other regions due to the septal discontinuity in the ultrasound data (Figures 6.4 and 6.5). Synchronizing breathholds was more difficult for the pathological subjects than for the normals, and additional trials for an optimized data acquisition were avoided in the former group. Moreover, the example of the infarcted human left ventricle shown was the only one that still showed myocardial dysfunction after treatment from our patient pool, and was therefore used here as an example to contrast with the normal case.
Temporal classified principal strain profiles in the anterior wall region of both normal (Figures 6.7(a) and (b)) and infarcted (Figures 6.7(c) and (d)) left ventricles showed similar systolic strain trends with both imaging methods. Smaller spatial variations of strain estimates in MR tagging than in Myocardial Elastography were still noted. Overall, increased radial thickening (Figure 6.7(a)) and circumferential shortening (Figure 6.7(b)) over time in the anterior wall of the normal left ventricle were noted. The slight radial thinning (Figure 6.7(c)) and circumferential stretching (Figure 6.7(d)) in the anterior region of the infarcted left ventricle confirmed the myocardial abnormality in the anterior region caused by partial LAD constriction. Compared with the posterior wall region, the anterior wall region in the infarcted left ventricle underwent paradoxical deformation according to both the Myocardial Elastography and MR tagging estimates. This was consistent with the qualitative observation of reduced, and even opposite, deformation in the anterior wall and of the hyperkinetic posterior wall, in compensation for the loss of contractility in the pathological region, in the infarcted case. Moreover, the anterior wall region of the infarcted left ventricle was thinner than that of the normal one. Therefore, only 25% of the ROI in the normal case was used to obtain the temporal strain profiles in the infarcted case. The same kernel size in the least-squared strain estimator was used in both normal and infarcted cases. Therefore, the kernel size relative to the myocardial thickness determined the smoothness effect on the strains. Furthermore, Myocardial Elastography can provide more detailed deformation owing to its higher temporal resolution than MR tagging.

The spatial resolution (1.92 mm and 0.77 mm in the lateral and axial directions) of an RF ultrasound frame was higher than that (9 mm in both lateral and axial directions) of a tagged MR image in the cases considered in this study. This constituted a discrepancy in
spatial resolution (and thereby spatial variability) of the strain estimates between the two modalities. Figures 6.3 and 6.6 show the average strain values with the standard deviations depicting the spatial variations of strain estimates in the posterior wall region. A larger number of original signal samples were available transmurally in echocardiography than in MR tagging due to the higher spatial resolution. Therefore, the larger standard deviation of Myocardial Elastography compared to that of MR tagging (Figures 6.3 and 6.6) indicated that the spatial strain variation increased with spatial resolution as expected. The higher the spatial resolution, the larger the number of strain estimates that can be obtained within the myocardium, and thus a larger spatial strain variation can be unveiled transmurally\textsuperscript{165}. This spatial strain variation was consistent with the transmural non-uniformity previously reported in the canine and human left ventricles\textsuperscript{125, 168}. The temporal resolution of echocardiography was four times higher than that of MR tagging in the cases studied, so smoother temporal profiles of cumulative displacements and strains were shown (Figures 6.3, 6.6, and 6.7).

Overall, the trends of MR tagging and Myocardial Elastography temporal cumulative displacement and strain profiles were in very good agreement, while the strain values showed lower agreement. An approximate 10\% (20\%) discrepancy of the strains in normal (treated) subjects with Myocardial Elastography compared to that with MR tagging was observed. This discrepancy may have resulted from several reasons as indicated above, such as the lower SNR of the ultrasound RF signals, sector discontinuities due to manually performed composite imaging, inexact registration between ultrasound and MR images, and a low transmural tagging resolution.
Despite the fact that higher Myocardial Elastography than MR tagging strain values were observed here (Figures 6.3 and 6.6), several groups\textsuperscript{168-170} have shown similar radial and/or circumferential strain values of normal human left ventricles with the Myocardial Elastography estimates reported in this study. Bogaert and Rademakers (2001) showed total wall thickening of 32.8\%±1.0\% during systole estimated from MR tagging in the normal posterior wall. Herbots et al. (2003) showed average peak radial strain of 62\%±11\% estimated with SRI, and their results were in good agreement with those estimated from both ultrasound and MRI M-modes, in the basal infero-lateral wall. Hurlburt et al. (2007) presented average radial strains of 37\%±17\% and circumferential strains of 21\%±7\% using B-mode speckle tracking in the posterior wall region. Although the strains obtained from Myocardial Elastography were overall higher compared with those from MR tagging in both normal and infarcted left ventricles, these preliminary results showed that the two imaging modalities were in good agreement and that Myocardial Elastography is capable of differentiating abnormal from normal myocardium even in a post-infarcted, treated left ventricle. Correct co-registration and study of the role of inherent resolution and SNR differences across the two modalities are currently ongoing.

Good correlation (Figure 6.8) as evidenced by the scatter plots and good agreement (Figure 6.9) with the Bland-Altman plots in the end-systolic radial (r=0.75; bias of 5.59\%) and circumferential (r=0.75; bias of 0.57\%) strains between Myocardial Elastography and MR tagging in six normal and three infarcted normal left ventricles were found. The result that greater bias was found in the radial strain might be due to the fact that fewer tag lines were present in the radial than circumferential directions, resulting in underestimated radial strain. Overall, compared to the range of the average radial (between 0\% and 35\% strain)
and circumferential (between -35% and 0% strain) strains measured, the bias reported was deemed acceptable. This was in agreement with reported MR tagging literature where circumferential strains are shown to be more reliable than radial ones\textsuperscript{154}.

Several groups have validated their cardiac function assessment techniques in echocardiography against the direct measurement of sonomicrometry\textsuperscript{30, 117, 171}. However, sonomicrometry cannot be used as the gold standard in a clinical study (as it was used in Chapter 5) due to the requirement of an invasive procedure. In terms of a non-invasive, clinical validation of Myocardial Elastography, MR tagging was selected as the gold standard given that the methods used have been more established and its findings validated. On the other hand, to confirm the validity of the new tag tracking method, as part of a separate study, the tagging sequence is being further optimized, and the tracking algorithm\textsuperscript{155, 172} is being evaluated against more established techniques such as HARP\textsuperscript{146} and velocity-encoded MRI\textsuperscript{173}.

Finally, since the MR and echocardiography data were not necessarily acquired from the same myocardial region or image plane, and were not accurately co-registered due partially to the lack of 3D data, the ROIs selected for plotting temporal strain profiles might not have represented the same material points across the MR images and echocardiograms. In this preliminary study, we mainly concentrated on the regional transmural deformation after a global match of the papillary-level short-axis view between the two imaging configurations. Ongoing investigations on image registration are currently being performed to optimize cross-modality comparisons.

Myocardial motion and deformation in two orthogonal directions were accurately assessed using angle-independent Myocardial Elastography. In-plane, 2-D transmural
(lateral and axial) displacement and (lateral, axial, polar and classified principal) strain fields were comparable to those obtained with MR tagging, in both normal and pathologic human hearts \textit{in vivo}. The axial displacement as well as the radial and classified 1st principal strain estimates depicted the strongest agreement between the two modalities in the normal case. Most importantly, the abnormal anterior region in the infarcted left ventricle was successfully depicted by the qualitative and quantitative classified principal strain results, showing passive deformation behavior during active contraction (i.e., systole). Classified principal strains did not appear to be superior, but were comparable to polar strains in the infarcted case, so they may serve as an alternative tool in the detection of abnormal myocardium. Although preliminary results show that higher strain values were obtained with Myocardial Elastography compared to MR tagging, the overall trends of the temporal cumulative displacement and strain profiles obtained from these two imaging modalities were in excellent agreement. The presented results constituted a preliminary validation of high-frame-rate RF ultrasound data acquisition, and subsequently 2D imaging of full-view, in-plane, orthogonal displacement and strain components against tagged MR imaging. To our knowledge, this is the first time that a side-by-side comparison of the displacement and strain images has been performed in a clinical setting between MR tagging and echocardiography.
Chapter 7

Conclusions and Future Directions

7.1. Conclusions

The objective of this dissertation was to fully develop Myocardial Elastography\textsuperscript{4,65}, a radio-frequency (RF)-based strain imaging technique, as a potential diagnostic tool for the early detection of coronary artery disease, particularly myocardial ischemia. The assessment of Myocardial Elastography was performed using a theoretical framework (Chapter 4)\textsuperscript{32,66,120}, \textit{in vivo} animal studies (Chapter 5)\textsuperscript{174}, and clinical settings (Chapter 6)\textsuperscript{76,120}. The main contribution and findings in these three chapters are highlighted as follows.

As introduced in Chapter 4, a theoretical framework was established for the complete development and evaluation of Myocardial Elastography. It was comprised of 1) a 3D finite-element model of the left ventricle in normal and left-circumflex ischemic cases; 2) a 2D/3D ultrasonic image formation model to simulate 2D/3D ultrasonic RF frames; 3) development of Myocardial Elastography in 2D and 3D; and 4) validation of Myocardial Elastography estimates against the finite-element model solutions. Several novel technical components were developed and incorporated into Myocardial Elastography: 1) 1D cross-correlation in a 2D search configuration; 2) displacement estimation extended from one- to two-dimensional and a bi-plane configuration; 3) a recorrelation to correct axial (lateral) displacement for lateral (axial) displacement estimation; 4) estimate cumulative 2D displacements; and 5) compute cumulative (Lagrangian) 2D and angle-independent strains.
The simulation results showed that Myocardial Elastography can estimate and image 2D displacements (Figures 4.5 and 4.7), 2D strains and angle-independent strains of the short-axis myocardium in both normal and LCx ischemic cases with good accuracy and at high spatial resolution. The results also showed that the axial displacement estimation required a frame rate approximately two-fold higher than the lateral displacement estimation (Figures 4.9 and 4.10). Moreover, identification and differentiation of the ischemic (at its early onset) from the normal myocardium was reliably mapped using the angle-independent strains in Myocardial Elastography. Opposite angle-independent strain patterns were found in the ischemic myocardial region compared to the normal one based on the theoretical framework.

As demonstrated in Chapter 5, Myocardial Elastography was further evaluated in an in vivo non-survival canine study (n=10), where gradual flow reduction in the left anterior descending coronary artery at 20% increments was performed. To our knowledge, this is the first study in which an ultrasound-based strain imaging technique was investigated at variable graded levels of coronary flow reduction to examine the performance in detecting myocardial ischemia at distinct stages starting from its very early onset. Myocardial strains estimated using Myocardial Elastography were shown to be in good agreement (Figures 5.4, 5.6 and 5.7; bias of 0.22% strain) with those computed in sonomicrometry, held here as the ground truth for the direct measurement in vivo. Furthermore, Myocardial Elastography was demonstrated to be capable of detecting the ischemic region at 40%, even possibly as low as 20%, flow reduction based on the radial strain estimated and imaged, which was identified as a more detailed, localized, and quantitative parameter than the conventional wall motion score index, ejection fraction, etc. The opposite strain patterns observed in the
ischemic regions compared to the normal region at progressive levels of coronary flow reduction were in excellent agreement with the findings in the theoretical framework.

Presented in Chapter 6, a preliminary clinical study was conducted to assess the performance and clinical value of Myocardial Elastography in the diagnosis of myocardial ischemia caused by coronary artery disease. As a first step of the clinical study, myocardial deformation of the human left ventricle (in 6 normals and 3 subjects with history of heart disease) was estimated by Myocardial Elastography and subsequently validated against MR tagging, the assumed gold standard for in vivo cardiac strain imaging. To our knowledge, side-by-side comparison of strain images between these two modalities was, for the first time, presented in the human left ventricle in full echocardiographic views in vivo. Qualitatively (Figures 6.1-6.2 and 6.4-6.5) and quantitatively (Figures 6.3 and 6.6-6.9), good agreement in the displacements and strains (bias of 5.59% and strain in the radial direction) was shown in both normal and infarcted human left ventricles. In addition, reduced systolic radial thickening was found in the infarcted (anterior) compared to the remote (posterior) wall region in the infarcted left ventricle. This further demonstrated that Myocardial Elastography could not only image motion and deformation in a full ventricular view, but also identify the infarcted myocardial region in a clinical setting based on the comparison with the non-ischemic or remote regions.

Based on the findings from the aforementioned theoretical framework, in vivo canine ischemic model, and clinical study, Myocardial Elastography’s good accuracy in estimating and imaging 2D displacement and strain components in both normal and ischemic myocardium was demonstrated. Opposite angle-independent strain patterns in the ischemic region were demonstrated in the theoretical framework, in vivo animal experiments, and the
clinical study. Myocardial Elastography, an RF-based strain imaging technique, may thus serve as a potential computer-aided diagnostic tool of myocardial ischemia caused by coronary artery disease.

7.2. Future Directions

The findings presented in this dissertation encompass the full scope of evaluating myocardial deformation using Myocardial Elastography for the detection of myocardial ischemia caused by coronary artery disease, from theoretical to animal and clinical evaluation and validation. Inspired by the theoretical and in vivo findings, future investigations can be classified into short-term and long-term goals, where the latter can be further divided into basic science and clinical studies.

In the short term, Myocardial Elastography requires additional evaluation, such as 1) a novel motion tracking scheme adaptive to the complex cardiac motion and spatially-variant image resolution, 2) displacement and strain estimation in the parasternal long-axis and apical echocardiographic views in addition to the presented short-axis view for a complete 3D representation, and 3) advancement of fast echocardiographic RF data acquisition design, while maintaining the high frame rate, to shorten the breath-hold duration in a clinical setting. Moreover, Myocardial Elastography is not limited to the 2D imaging configuration and can in principle easily be extended to 3D should the 3D RF data be accessible in commercial echocardiography systems.

The long-term goal is to seek applications of Myocardial Elastography in both basic science and the clinic. In basic science, understanding and modeling the mechanical behavior of the intact heart in vivo in a variety of disease states can benefit from the
employment of our proposed strain imaging technique of Myocardial Elastography. Through knowledge on the strains \textit{in vivo}, the stress-strain relationship can be inferred and constructed in finite-element modeling for \textit{in vivo} assessment of the mechanical properties provided additional information on myocardial stress is available.

In finite-element modeling, myocardial stress is typically computed based on the strains and material properties through constitutive laws. Strains are measured from experiments, and material properties are obtained from experiments on isolated tissue and computational models of muscle activation \textsuperscript{37, 95, 175}. This dissertation (Chapters 4-6) has shown that accurate strain estimation and distribution at high spatial resolution are available via Myocardial Elastography. They can thus help establish the stress-strain relationship, which is difficult to evaluate directly \textit{in vivo}, and can aid the computational estimation of myocardial stress \textsuperscript{46} to assess the mechanical properties under normal and ischemic conditions.

In addition, conflicting findings in previously published reports concerning the stiffness in the ischemic case were summarized in section 2.2.2., while the types of changes in mechanical properties during ischemia remain to be resolved \textsuperscript{96}. Hence, \textit{in vivo} evaluation of material properties of myocardium in both normal and ischemic cases becomes important to understand the relationship between the alteration of mechanical properties and the progression of myocardial ischemia. In order to assess mechanical properties \textit{in vivo}, myocardial stress measurement as well as strain estimation from the imaging methods is required.

Even though it is difficult to measure myocardial stress \textit{in vivo} without damaging the muscle \textsuperscript{46}, certain methods that can approximate stress by left ventricular pressure based on
Laplace's law or its modification have been developed \(^{176-178}\) with associated assumptions on the cylindrical geometry and isotropy. Should the \textit{in vivo} myocardial stress measurement be available and reliable, the mechanical properties may be retrieved with the strains estimated by Myocardial Elastography \textit{in vivo}. The cardiac mechanics may thus be studied \textit{in vivo} in both normal and ischemic conditions.

The preliminary clinical study presented in this dissertation was successfully performed on infarcted human left ventricles. Myocardial Elastography, a non-invasive and reliable strain imaging technique, can now be evaluated as a potentially reliable pre-diagnostic tool for the detection of the early onset of myocardial ischemia as a result of coronary artery disease to localize and map the associated ischemic region. Stress echocardiography, contrast administration or diagnostic catheterization may be avoided when accurate strain images are found to be capable of reliably associating symptoms, like angina, with coronary artery disease while excluding other conditions or symptom cases. This can further help avoid unnecessary invasive and costly diagnostic tests, such as coronary angiography using fluoroscopy. In order to investigate the degree of association of abnormal myocardial deformation with the presence and severity of coronary stenosis, a clinical study using both Myocardial Elastography and coronary angiography by fluoroscopy is currently being conducted under the approval by the Institutional Review Board of Columbia University. Patients who are selected to undergo catheterization with or without a history of heart disease or myocardial infarction are being recruited for such a study. It is anticipated that the relationship between the strain estimates in the myocardium and the location and severity of coronary stenosis may constitute the niche of Myocardial Elastography in the clinical diagnosis of coronary artery disease.
Finally, throughout the dissertation, Myocardial Elastography was mainly investigated for left-ventricular function. However, this technique may be employed to evaluate right-ventricular or atrial function using appropriate echocardiographic views, for instance, subcostal views, and even aid the diagnosis of other types of heart diseases, such as dilated cardiomyopathy, associated with abnormal myocardial deformation.
List of Abbreviations

2D: two-dimensional
3D: three-dimensional
ANT: anterior
CAD: coronary artery disease
CHD: coronary heart disease
CO: cardiac output
ECG: electrocardiogram
ED: end diastole
EDLVP: end-diastolic left-ventricular pressure
EF: ejection fraction
ES: end systole
FE: finite-element
FWHM: Full Width Half Maximum
HR: heart rate
LAD: left anterior descending
LAT: lateral
LSQSE: least-squares strain estimator
LV: left ventricle
SEP: septal
LCx: left circumflex
MAE: mean absolute error
ME: myocardial elastography

MRI: magnetic resonance imaging

POST: posterior

PSF: point spread function

PV: pressure-volume

RCA: right coronary artery

RF: radio-frequency

ROI: region of interest

SAD: sum-of-absolute differences

SM: sonomicrometry

SNR_s: sonographic signal-to-noise ratio

SNR_e: elastographic signal-to-noise ratio

SRI: strain rate imaging

SSD: sum-of-squared differences

TDI: tissue Doppler imaging

tMRI: MR tagging

TTC: triphenyltetrazolium chloride

WMSI: wall motion score index
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Appendix A

Coordinate Systems in Echocardiography and MR tagging

In ultrasound imaging, the axial direction is defined as the beam direction, and the lateral direction is also in-plane but perpendicular to the axial direction. In a linear array configuration, the lateral and axial directions correspond to the abscissa ($x$-) and the ordinate ($y$-) axes in Cartesian coordinates, respectively. On the other hand, the lateral ($x_{us}$-) and axial ($y_{us}$-) directions in a phased array configuration (i.e., polar coordinates), as employed in echocardiography, coincide with the angular and radial axes, respectively (Figure A.1(a)).

In Myocardial Elastography, lateral and axial displacements are first obtained (see section 4.2.3). In a simplified case, assume that a material point moves from the P1 to the P1’ location as shown in Figure A.1(b). The axial displacement is denoted as $v_{ax}$ (mm). Due to the depth-varying RF signal spacing in the phased array configuration (Figure A.1(a)), the unit of the initial lateral displacement estimate is the number of RF signals involved in the lateral direction, through which the target material point passes. Thus, the actual lateral displacement (mm) needs to be further obtained by multiplying the initial lateral displacement (number of the interpolated RF signals) with the actual beam spacing as follows:
\[ u_{us} = u_{tmp} \cdot r \cdot \beta, \]  

where \( u_{tmp} \) and \( u_{us} \) are the initial and actual lateral displacements, \( r \) is the radius at an RF sample point, and \( \beta \) (radians) is the angular increment of the RF signals involved in the azimuthal direction (Figure A.1).

Figure A.1: (a) the coordinate system used in the ultrasound phased array configuration, where solid lines show representative RF signals, \( x_{us} \) and \( y_{us} \) are the lateral and axial directions, respectively, solid blue arrow shows the motion vector of a material point, P1; (b) the magnification of the motion vector in (a): \( x_{us} \) and \( y_{us} \) are the actual lateral and axial displacements, respectively, and \( \beta \) is the angle increment between two neighboring RF signals (Figure 4.3).
The lateral and axial coordinates/displacements ($u_{us}$ and $v_{us}$) can be transformed into Cartesian ones using the following equations:

\[
R = \begin{bmatrix}
\cos \alpha & \sin \alpha \\
-\sin \alpha & \cos \alpha
\end{bmatrix}
\]

(A.2)

\[
\begin{bmatrix}
x \\ y
\end{bmatrix} = R \begin{bmatrix}
x_{us} \\ y_{us}
\end{bmatrix}
\]

(A.3)

\[
\begin{bmatrix}
u \\ v
\end{bmatrix} = R \begin{bmatrix}
u_{us} \\ v_{us}
\end{bmatrix},
\]

(A.4)

where $\alpha$ is the counterclockwise angle between the two coordinate systems, and $u$ and $v$ are the Cartesian displacements (Figure A.2(a)).

In MR tagging, Cartesian coordinates are instead used, and the horizontal and vertical axes are defined as the lateral and axial directions throughout this dissertation, respectively. Clearly, different coordinate systems, as used in these two imaging modalities, contribute to discrepancies between the 2D displacement estimates (Figure 6.1).
Figure A.2: (a) the ultrasound phased array configuration with $x_{us}$ and $y_{us}$ being the lateral and axial directions, respectively, $x$ and $y$ composing Cartesian coordinates, and $\alpha$ being the counterclockwise angle between two coordinate systems; (b) the illustration of the Cartesian coordinate system used in the tagged MR images. $(x, y)$ represent the Cartesian coordinates in both (a) and (b), and P1 indicates the same material point in both imaging modalities.
Appendix B

Strain Calculation in Polar Coordinates

As explained in Appendix A and shown in Figure A.1, lateral and axial displacements correspond to circumferential and radial displacements, respectively, in the ultrasound phased array configuration. Therefore, the strain calculation derived from the displacement gradient has to be performed in the same configuration, namely polar coordinates. In other words, the displacement gradient calculation in Eq. (4.4) is no longer valid in the phased array configuration. Here is an example. First, following the notation used in Appendix A, we assume that the displacement vector of a material point is formulated as

\[ u_{us} = u_{us} \mathbf{e}_{us}^{ux} + v_{us} \mathbf{e}_{us}^{uy} \]  

When a balloon inflates uniformly, not only does the radius increase, but the circumference also stretches. When we follow the same material point, it only exhibits radial motion, \( v_{us} \). If we continue to use the displacement gradient formula in (4.4), we will conclude

\[ \frac{\partial u_{us}}{\partial x_{us}} = 0, \quad \frac{\partial u_{us}}{\partial y_{us}} = 0, \quad \frac{\partial v_{us}}{\partial x_{us}} = 0 \]  

\[ \nabla u = \begin{bmatrix} 0 & 0 \\ 0 & \frac{\partial v_{us}}{\partial y_{us}} \end{bmatrix} \]
\[ E = \begin{bmatrix} 0 & 0 \\ 0 & \frac{\partial v_{us}}{\partial y_{us}} + \frac{1}{2} \left( \frac{\partial v_{us}}{\partial y_{us}} \right)^2 \end{bmatrix} \] (B.4)

Clearly, only the axial strain, or radial strain in the phased array configuration, is present in (B.4). However, the balloon example demonstrates that there exists circumferential deformation. Consequently, the displacement gradient (\( \nabla u_{us} \)) calculation should be adapted to the phased array configuration (or polar coordinate system) as follows:

\[
\nabla u_{us} = \begin{bmatrix} \frac{\partial v_{us}}{\partial y_{us}} & \frac{1}{y_{us}} \left( \frac{\partial v_{us}}{\partial x_{us}} - u_{us} \right) \\ \frac{\partial u_{us}}{\partial y_{us}} & \frac{1}{y_{us}} \left( \frac{\partial u_{us}}{\partial x_{us}} + v_{us} \right) \end{bmatrix} \] (B.5)

Then, the full strain tensor (\( E_{us} \)) can still be calculated, similar to (4.5) as follows:

\[
E_{us} = \frac{1}{2} \left( \nabla u_{us} + (\nabla u_{us})^T + (\nabla u_{us})^T \nabla u_{us} \right) \] (B.6)

Note that the lateral and axial strain in the ultrasound phased array coordinate system are obtained in (B.6). In order to compute the strain tensor in Cartesian coordinates, the rotation matrix in (A.2) is used for the Cartesian strain transformation as follows:

\[
E_{cart} = RE_{us}R^T \] (B.7)

Finally, the angle-independent polar strains defined in cardiac coordinates can be computed using (4.6) and (4.7).