Abstract

Magnetic Resonance Elastography for Measuring the Compliance of Chronic Total Occlusions

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Percutaneous coronary revascularization of chronic total occlusions (CTOs) is difficult due to the presence of a hard proximal fibrous cap and lack of image guidance. The use of x-ray fluoroscopy alone makes it difficult to identify vessel boundaries and occlusive constituents which would aid the process of revascularization. It also can be difficult to keep a guidewire intraluminal without puncturing the vessel wall. Although several imaging modalities are being developed, a technique for measuring the stiffness of occlusions would facilitate revascularization by helping the process of guidewire selection and placement. In this study, a technique known as static magnetic resonance elastography is explored as a method of determining the compliance of CTOs. A finite element simulation was used to determine the response of an artery to deformation, and displacement images were obtained from an artery phantom using a stimulated echo MR imaging pulse sequence and a pneumatic compression system.
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Acronyms

CT computed tomography.

CTO chronic total occlusion.

FOV field of view.

IVUS intravascular ultrasound.

MRE magnetic resonance elastography.

MRI magnetic resonance imaging.

OCT optical coherence tomography.

PCI percutaneous coronary intervention.

PFC proximal fibrous cap.

RF radio-frequency.

STEAM stimulated echo imaging sequence.
Chapter 1

Background and Motivation

1.1 Introduction

Since the early to mid 1990s, a number of different techniques have been developed for determining the stiffness of tissue using magnetic resonance imaging (MRI). These techniques are collectively referred to as methods of magnetic resonance elastography (MRE). In addition to applications for determining the stiffness of tissue in various parts of the body, it was speculated that MRE would be a useful technique for determining the stiffness of blocked arteries [1]. Despite the interest in such techniques, there have yet to be studies focusing on MRE for cardiovascular applications. This is most likely due to some of the challenges encountered when using MRI for imaging cardiovascular systems, including difficulty in acquiring high resolution images of small blood vessels. In addition, MRE is difficult to perform on tissue deep within the body, and would likely require some kind of intravascular device to access blood vessels such as coronary arteries.

Although there are some potential challenges, MRE still shows promise as a technique for assessing the stiffness of blocked arteries. In particular, it may be useful as a guiding modality when performing percutaneous coronary intervention. Enhanced
image guidance techniques would be especially useful in difficult cases, such as in the revascularization of a chronic total occlusion (CTO). This is a very difficult procedure for interventional cardiologists, mainly due to the degree of hardness of such lesions, and the lack of imaging guidance provided by x-ray fluoroscopy.

The purpose of this work is to develop a technique for determining the stiffness of CTOs, in order to help guide percutaneous coronary intervention. This chapter outlines some of the current techniques used to help cross CTOs with a guidewire and the methods used to assess the stiffness of tissue using MRI. In Chapter 2, a technique used to determine the thickness of the proximal fibrous cap of a CTO is presented, with testing of the methods on an agar/gelatin phantom. The final section outlines some of the future work that will be necessary in order to develop the technique further for use in clinical applications.

1.2 Chronic Total Occlusions

Coronary artery disease, which is the leading cause of mortality in the western world, results from the accumulation of plaque in the walls of coronary arteries [2]. The disease can be treated by percutaneous coronary intervention (PCI), or in more severe cases by performing a coronary artery bypass graft. With PCI, constrictions or blockages in coronary arteries are crossed with a wire and catheter, and plaque is compressed against the walls of the vessel using a balloon.

Atherosclerotic plaques vary considerably in their composition and size. Chronic total occlusions (CTOs), which have proven to be the most difficult type of occlusions to cross by PCI, are defined as total occlusions blocking the entire cross section of the artery that are greater than one month old [2]. The process of crossing a CTO with a guidewire is shown schematically in Figure 1.1. Although chronic total occlusions are less common, as many as 20% of patients who undergo diagnostic coronary artery
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Figure 1.1: Schematic of a CTO being crossed by a wire as performed by percutaneous coronary intervention (PCI). The catheter provides a sheath around which the wire is inserted and pressed through the lesion. [Image Courtesy: Dr. Renu Vermani]

catheterization are found to have one or more CTO [3]. Since they are difficult to cross, the presence of one or more CTO usually leads to referral for coronary bypass surgery or for other forms of medical therapy. Additionally, only the most skilled operators will attempt to perform percutaneous revascularization on CTOs. Bypass surgery is much more invasive than PCI, since it requires splitting of the sternum, and diversion of the patient’s blood supply to a heart-lung machine, which artificially oxygenates and pumps blood while the bypass graft is being sutured. This type of surgery requires hospitalization, a much longer recovery time, and can potentially lead to significant complications such as stroke or postperfusion syndrome. Ideally, less invasive methods of treatment such as PCI would be preferable to bypass surgery for these reasons. Recanalization of CTOs has proven to be beneficial by reducing angina [4], improving left ventricular function [5, 6], and improving quality of life [7]. It has also been shown to reduce the risk of mortality due to subsequent cardiac events [8, 9, 10]. The development of improved techniques for successfully crossing CTOs is essential to providing improved patient care with less invasive treatment methods.

One of the biggest concerns when performing percutaneous revascularization of CTOs is in making sure that the guidewire stays within the true lumen of the vessel, rather than perforating the vessel walls. This, combined with the presence of hard
calcified or fibrous tissue at the proximal end of the occlusion, makes revascularization of a CTO much more difficult when compared to PCI of a non-occluded artery. This means that in addition to a requirement for greater operator skill, revascularization of a CTO requires longer procedural times, which in turn uses more resources, and involves higher doses of radiation delivered to the patient during x-ray fluoroscopy [7]. Procedural difficulty is made worse by the fact that x-ray fluoroscopy is the only imaging method used currently to help guide interventional cardiologists while performing PCI. Because of poor soft tissue contrast, x-ray fluoroscopy does not provide images of blocked sections of an artery. The operator must try to position the guidewire properly by looking at the proximal and distal ends of the blockage, which are visible due to iodinated contrast in the blood and bridging collaterals supplying blood to the distal end.

1.2.1 Development and Composition of a CTO

Research efforts in recent years have focused on understanding the pathophysiology of CTOs in order to determine why some are easier to cross than others. Early studies focused on understanding the collagen-rich extracellular matrix, which is largely responsible for impeding guidewire crossing [2]. It has been shown that calcium deposits can also form within a CTO, which tend to be difficult obstacles to pass when attempting to cross a CTO. Recent studies have shown, however, that in addition to collagen and calcium which hinder CTO crossing, microvessels can also be present, which may aid in the process of revascularization. Figure 1.2 shows a cross section of a fibrocalcific lesion, as well as a lipid rich CTO. The lipid rich lesion would typically be softer, and much easier to treat by PCI.

The development of a CTO can happen either as a result of atherosclerotic plaque rupture which leads to thrombus formation, or due to the gradual growth of an atherosclerotic plaque over time as it begins to occlude the entire lumen of
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An artery. Few studies have been done on human CTOs to determine the various stages in CTO development; however, different animal models have been developed to help characterize the process. In animal models of venous occlusions, it has been shown that the process of CTO formation is similar to the process of wound healing, especially in the early stages [12]. An initially formed thrombus consists of platelets and erythrocytes within a fibrin mesh. This is soon followed by acute inflammatory cells, which invade the fibrin mesh [13]. At first these consist primarily of neutrophils, which are the most abundant types of white blood cells, but eventually these are replaced by mononuclear cells [14]. Endothelial cells, which are usually present on the inner lining of blood vessels, are also present within the fibrin mesh, and form tube-like structures or microvessels [15]. Other cells such as macrophages, foam cells, and lymphocytes form in the mesh, but mostly around the innermost part of the artery near the lumen [16]. Foam cells can accumulate in the centre of a lesion, making up the lipid rich centre of a soft occlusion. As the lesion progresses, collagen starts to become the major structural component of the extracellular matrix. The lipid-rich cholesterol and foam cell deposits are eventually replaced by collagen and calcium deposits, which are responsible for the increased stiffness of lesions with age.
Additionally, the thick fibrous tissue that forms is particularly dense near the proximal and distal ends of the occlusion. The proximal end of an occlusion that forms thick fibrous tissue is referred to as the proximal fibrous cap (PFC), and is shown in Figure 1.3 [17]. Experience by interventional cardiologists has shown that this section can be the most difficult part of a CTO to cross. It is usually found that a stiff wire used to push through the PFC of an occlusion is more than adequate to traverse the rest of the lesion. The difficulty after puncturing the PFC is in keeping the guidewire intraluminal, rather than in being able to penetrate the rest of the lesion. As mentioned before, it is also believed by some that microvessels formed by endothelial cells may decrease the stiffness of an occlusion and provide a route for recanalization [18].

![Figure 1.3: (A) Trichrome-stained longitudinal section of a 12-week-old chronic total arterial occlusion (CTO) showing the proximal fibrous cap (PFC) at the entrance of the CTO, and the lumen (L). The magnified section is shown in (B). Green represents collagen in this type of stain. Image adapted from [17]](image)

### 1.2.2 Imaging and Guidance for Crossing CTOs

As mentioned previously, x-ray fluoroscopy is the primary imaging modality used for revascularization of CTOs. Despite its limitations, it can help identify features that may affect the likelihood of successful guidewire crossing. Some of the features
that may hinder the success of PCI include lesions longer than 15-20 mm, multi-vessel disease, and the presence of calcifications [4, 9, 10, 19, 20]. Other factors such as the presence of bridging collaterals, proximity to a side branch, and poor visibility of the distal vessel, can make the procedure more difficult [4, 9, 19, 20, 21]. As shown in Figure 1.4, fluoroscopy only provides a 2-D projection through the body, where visualization of key features is limited by detector resolution and poor soft-tissue contrast [2]. The entry and exit points can usually be identified, but the path between both points, and the boundary between the vessel wall and the occlusion are not visible. Other imaging techniques are being explored to help guide the revascularization of CTOs, including CT (computed tomography) angiography, intravascular MRI, forward-looking intravascular ultrasound (IVUS), and optical coherence tomography (OCT).

![Image of X-ray fluoroscopy](image)

Figure 1.4: X-ray fluoroscopy image of a chronic total occlusion (CTO) in the right coronary artery (RCA). An x-ray opaque contrast agent has been injected through a catheter into the proximal end of the RCA. A portion of the RCA distal to the occlusion is visible due to contrast supplied downstream by collateral vessels. [Image courtesy of Dr. Alexander Dick]
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Computed tomography (CT) angiography is currently gaining popularity as a method of assessing coronary artery lesions. It has been shown that CT angiography is more accurate at detecting severe stenoses compared to mildly diseased segments [22]; however, high levels of calcification can limit the ability to distinguish between calcium deposits and the lumen of the vessel [23]. The 3-D nature of CT angiography allows for improved measurement of occlusion length, and identification of features such as vessel tortuosity, bridging collaterals, and calcification. Unfortunately, CT angiography also lacks soft tissue contrast, and involves relatively high doses of radiation. An example of a CT angiography image of a CTO with minimal calcification is shown in Figure 1.5, displaying the entry and exit points of the occlusion.

Figure 1.5: A volume rendered computed tomography (CT) angiogram of a native right coronary artery (RCA) is shown in (A) with a long chronic total occlusion (CTO) shown by the white arrow. Longitudinal images in various planes are shown in (B-D) demonstrating the entry (En) and exit (Ex) points of the occlusion, with minimal calcification. [23]

Intravascular MRI is another imaging modality that shows promise due to its soft tissue contrast. Unfortunately, the technique is limited by low resolution and by cardiac motion artefacts. However, various studies have proven that MRI can
be used to differentiate between the vessel wall and the occlusion. Clarke et al. have shown that high-resolution MR images using multiple contrast weightings can be acquired, which accurately reflect and can help differentiate various plaque constituents [24, 25, 26]. Current efforts in intravascular MRI development are focused on forward-looking coils to be able to guide revascularization. Anderson et al. have developed a forward looking intravascular coil for imaging in occlusive arterial disease [27]. Previously designed intravascular imaging coils suffered from signal nulls and were designed for side-viewing. The proposed coil consists of two independent orthogonal solenoids located at the tip of a catheter. By using two solenoidal ellipses oriented at $45^\circ$ with respect to the catheter axis, and perpendicular to each other, signal nulls are eliminated, and imaging is possible in front of the catheter.

Other forward-looking intravascular imaging techniques include ultrasound and optical coherence tomography (OCT). Intravascular ultrasound (IVUS) is appealing due to high resolution, good penetration depth, and the ability to differentiate between occlusive constituents and the vessel wall. Unfortunately, IVUS is limited by the inability of ultrasound to propagate through calcified tissue, and the difficulty of orientating the beam in the appropriate direction intravascularly. OCT is a very similar technique to ultrasound that uses light instead of sound waves. It is capable of very high resolution, but is unable to penetrate very far ahead of the device. Despite this limitation, OCT may be helpful in guiding the placement of a wire at increments along the length of a CTO [23]. In this way it could be possible to apply laser ablation, along with balloon angioplasty at each increment as guided by OCT.

An important note about image guidance for crossing CTOs is that it is much different than what is required when traversing less severe non-occluded lesions [23]. The lumen present in a non-occluded artery provides a tunnel which naturally helps contain a wire as it traverses an artery. With fully occluded arteries however, there is no natural boundary to help guide a wire as it is passed through a lesion. Heavily
calcified or fibrotic lesions could deflect a wire and direct it through the vessel wall. It is therefore important to detect the position and composition of tissue within a CTO in order to guide a wire through the true lumen of the vessel. It is even more important to know how stiff sections of a CTO are in order to predict the proper path for wire placement.

1.2.3 CTO Compliance

Although there have been studies on the development and composition of CTOs, few have examined the stiffnesses of occlusive constituents and how they can hinder wire crossing quantitatively. One study published recently by Thind et al. focused on determining the force required to puncture the proximal fibrous cap of CTOs [28]. Although not directly related to the stiffness of lesions and their constituents, the puncture force required to push through the PFC of various CTOs is a useful measure for characterization of CTO age and composition, and is potentially helpful for assessing therapies to facilitate guidewire crossing.

The study used arterial occlusions created in the femoral artery of Male New Zealand white rabbits, sacrificed at 2, 6, 12 and 15 weeks following occlusion creation via the injection of thrombin solution. After sacrifice, the femoral artery segment containing the CTO was removed and positioned in a holding apparatus using a stent and pin as shown in Figure 1.6. A load cell connected to a force tester was used, with the inner mandrel from an 18G spinal needle used as the puncture probe. For each CTO sample, the probe was lowered very slowly toward the PFC of the occlusion, and the force per displacement of the probe was recorded at a sampling rate of 4 Hz. A sample of one of the force displacement curves for a 6 week old CTO is shown in Figure 1.7. The puncture force was recorded in all cases as the force required to reach the first major peak in the curve, after which the force would drop off. The results of the study showed that there was a definite trend of increasing puncture
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Figure 1.6: Schematic of a puncture force measurement setup used by A. Thind. The stent at the proximal end of the vessel, and a pin through the distal end, are used to secure the vessel. The puncture probe is lowered slowly towards the proximal fibrous cap (PFC). The force is measured by the load cell as the probe displaces the PFC and eventually punctures through. [Image courtesy of Amandeep Thind]

force with increasing occlusion age as expected. It was also noted that there was a significant increase in puncture force between 6 and 12 weeks, indicating that there was a change from what would be considered a "soft" to a "hard" lesion occurring within this time frame. These changes can be attributed to an increase in collagen, and a decrease in the level of proteoglycan material, creating dense fibrotic tissue.

The technique outlined in this study may be useful in assessing the efficacy of different treatment methods for reducing the stiffness of CTOs. Studies by Strauss et al. have shown that collagenase can be delivered locally to CTOs in order to soften the collagen in the proximal fibrous cap and to ease guidewire crossing [29, 30].
In this case, a measure of puncture force can be used to determine the effect of collagenase on PFC stiffness at various time points.

This study provides a novel technique for measuring the stiffness of the proximal fibrous cap of CTOs ex vivo; however, it is limited by dependency on the size of the puncture probe, and on the location at which the probe is applied along the surface of the PFC. Development of additional techniques are necessary in order to be able to characterize the stiffness of lesions in vivo. An imaging technique known as elastography has been used in numerous applications, especially in recent years, and has potential as a method of assessing the stiffness of CTOs in vivo.
1.3 Magnetic Resonance Elastography

A number of different approaches have been used to measure the mechanical properties of tissue using MRI. Although there are different ways of implementing these techniques, they are all forms of elastography, and are referred to in the case of MRI as methods of magnetic resonance elastography (MRE). With each method the information obtained is slightly different; however the goal is the same: to obtain information about the strength or stiffness of tissue. Considering that many tissues are complex and consist of regions of varying stiffness, MRE allows for the determination of stiffness within all sections of tissue, rather than an overall averaged value.

Two main types of MRE techniques have been employed to measure tissue properties. The first and more common approach used in recent years involves application of dynamic, or harmonic, stresses at high frequencies on the order of hundreds or thousands of hertz. The dynamic stresses produced help create images of shear waves travelling through tissue at different time points. The second approach relies on the application of static compression to tissue. Spin displacement measured before and after compression is compared to obtain a map of displacement, which leads to a strain image. In the case of static elastography using MRI, a quasi-static approach is necessary, where low excitation frequencies around 1 Hz are used, and displacements are measured within each period.

1.3.1 Dynamic MRE Methods and Challenges

Dynamic MRE was first described by Muthupillai et al. as a method of determining the elastic modulus of tissue [31]. It has since been applied to determining changes in stiffness of soft tissues for the diagnosis of cancerous tumours and liver fibrosis [32, 33]. The technique is based around the induction of shear waves, combined
with synchronized imaging of the shear waves travelling through tissue. A bipolar
gradient is applied at the same frequency as the shear excitation, which provides
motion sensitization in the resulting phase images. The phase of nuclear spins is
therefore increased or reduced depending on the direction of motion of a specific
voxel moving through a shear wave. The resulting images represent the variation in
displacements seen at a snapshot in time as the shear waves travel through tissue.
These displacement maps can then be used to measure the wavelength of the shear
waves.

Since shear waves travel faster in hard materials and slower in soft materials, the
wavelengths throughout an image can help transform displacement patterns into
stress patterns. Several inversion algorithms have been developed to numerically
determine the shear modulus at different positions based on displacement images
[34, 35]. As opposed to palpation, which is used by physicians to help diagnose
cancer and other diseases, dynamic MRE is capable of determining the stiffness of
tissue deep within the body. It also provides a much more objective measurement
of tissue stiffness. An example of dynamic elastography is shown in Figure 1.8,
comparing the stiffness of a normal and a fibrotic liver [33]. The wave image is
obtained from applying dynamic elastography using an acoustic driver, and shows
the displacement due to the propagation of shear waves through the liver. The
wavelength of shear waves, which can be seen as the distance between two points
of equal displacement from the wave image, is visibly larger in the fibrotic case,
indicating a higher shear modulus. This is verified in the elastogram, where the
fibrotic liver is found to have significantly higher stiffness values throughout the
image.

Although dynamic MRE is an excellent technique for non-invasively imaging me-
chanical properties of soft tissue, it is not necessarily ideal in cases where harder
tissue is being studied, or in situations requiring smaller fields of view [36]. Unfortu-
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Figure 1.8: Sample dynamic MRE images of the liver in a normal volunteer and a patient with cirrhosis. The wave images show that the shear wavelength was higher in the fibrotic case than in the normal liver. This corresponds to higher shear stiffnesses in the fibrotic liver as shown in the elastograms. [33]

nately the determination of stiffness for chronically occluded arteries runs into both of these problems. The shear modulus of a CTO has not yet been measured in the literature; however, it is suspected that due to the variety of different constituents within a given CTO, and the high variability between the stiffness of the proximal fibrous cap in different cases, a wide range of stiffness values would be observed for any given CTO. Compared to soft tissue which has a shear modulus on the order of 50 kPa, hard calcified lesions could have have shear moduli on the order of hundreds or thousands of kPa [36]. Cartilage for example, which is a relatively hard tissue, has a high shear modulus between 0.2 and 2.0 MPa.

The frequency necessary for shear excitation can be determined based on the required wavelength of shear waves, which ultimately depends on the required field of view. Since shear waves attenuate much quicker at higher frequencies, and most MRE applications require larger fields of view, low frequencies have generally been
used. Values as low as 50 Hz and 125 Hz have been used for breast tissue and skeletal
muscle respectively [37]. Few clinical applications involving measures of stiffnesses
on small fields of view have been studied. One recent study, which looked at MRE of
hyaline cartilage, used samples of less than 5 mm, and required frequencies of up to
8 kHz [38]. Although cartilage is likely stiffer than an arterial occlusion, this study
suggests that high frequencies would be required for the application of dynamic
MRE to CTOs.

The frequency of excitation is determined by the required field of view, but
it is also limited by the slew rate and gradient amplitude of the scanner. This
is because the motion-sensitizing gradients are required to switch polarity at the
same frequency as the mechanical excitation. The gradients have to be able to
switch fast enough to reach full gradient amplitude within each cycle. With a
typical 1.5 T scanner for example (Signa; GE Healthcare, Milwaukee, WI, USA),
the gradient amplitude is 40 mT/m, and the slew rate is 150 mT/m/msec. The
equation governing the maximum allowable frequency for a given gradient amplitude
and slew rate is given by

$$f_{\text{max}} = \frac{SR}{4 \cdot GA}$$

(1.1)

where $SR$ is the slew rate, and $GA$ is the gradient amplitude. In this case, the
maximum allowable frequency is 937.5 Hz. With a frequency of 937.5 Hz, and
a shear modulus of 0.2 MPa, the wavelength observed would be around 15 mm.
Considering most features in blocked arteries are on the order of micrometers, this
approach would be incapable of discerning between hard and soft regions within a
blocked artery. In the study done by Lopez et al., these problems were overcome
by producing an actuator capable of large displacement amplitudes, as well as a
customized z-axis gradient coil capable of higher gradient strengths at fast switching
rates [38]. Using the modified gradient coil, dynamic elastography was performed at frequencies of 1000 - 10,000 Hz, capable of producing detailed displacement maps of small cartilage samples. Dynamic MRE of a blocked artery is therefore possible, but would require significant modifications to both the gradient coils and the actuator used to create shear waves. Due to these challenges, static MRE has been chosen in this study as a technique to explore for performing elastography on chronic total occlusions. This does not mean that dynamic MRE of CTOs is not a possible option, but rather that it would require more resources, and would be more difficult to implement.

1.4 Static Elastography

As in dynamic elastography, the goal of static elastography is to determine the stiffness of tissue based on the response to applied deformation. In the dynamic case, deformation is applied at higher frequencies to produce shear waves traveling through tissue. In static elastography however, the tissue is subjected to deformation at lower frequencies such that wave propagation is assumed to be negligible, and the tissue is considered to be in a state of static stress [39]. The resulting image in static elastography is a phase image representing the displacement between two compressive states at all positions within a cross section of tissue. The displacements due to deformation can then be converted into an image of strain, which ultimately represents the deformation of all points due to the applied stress. Although the resultant image in static elastography is not a direct measurement of tissue stiffness as in dynamic elastography, the derived strain is potentially more useful and a more common measurement as compared to shear modulus [36].

Despite the prevalence of more commonly used methods of dynamic elastography, static elastography has been used successfully in a number of situations. Plewes et al.
used this method successfully to obtain strain images of the breast, as a preliminary study for identifying lesions in breast cancer [39]. The focus of the study was on improving methods of inverse strain mapping for determining the Young’s modulus of the breast with high accuracy. This was accomplished by limiting the tissue to three measures of Young’s moduli, representing fibroglandular, adipose, and tumour tissue in separated regions. Further studies were done by Samani et al. developing the technique further, leaving the Young’s modulus of all three tissues as unknowns before solving iteratively for their values [40, 41]. A more recent study by Hardy et al. used static elastography to determine the strain response of articular cartilage under compression [36].

1.4.1 Static MRE Technique and Theory

The methods of obtaining displacement images using MRI for static elastography are similar to the methods used in dynamic elastography in that they are both phase contrast techniques using gradients to sensitize the phase of nuclear spins to motion. Phase contrast techniques are advantageous compared to other techniques used for detecting motion due to their sensitivity. A study done by Walker et al. was used to detect motion on the order of tens of nanometres due to ultrasound fields [42]. In dynamic elastography, actuators have been used that produce motion on the order of micrometers [32, 37, 43, 44]. More recently, phase contrast methods for static elastography have been developed, making use of two lobes of a bipolar gradient cycle, separated in time to allow for a specified displacement to occur [45, 46]. In the study by Chenevert et al., a stimulated echo imaging sequence (STEAM) was used to produce phase shifts relative to tissue displacement [46]. In all cases, the process of quasi-static MRE involves a number of steps including: compression of the sample with an actuator, imaging the compression with an MRI pulse sequence, converting the phase images to displacement and strain, and finally inverse strain
1.4.1.1 Stimulated Echo Imaging Sequence (STEAM)

A typical STEAM sequence is outlined in Figure 1.9. The main benefit of a STEAM sequence compared to other phase contrast methods is that it allows for transients due to compression to come to rest within a window of time, called the mixing time. This ensures that the final phase image obtained represents displacement due to static compression. The sequence consists of three 90° radio-frequency (RF) pulses separated in time, with the latter two pulses separated by $T_m$, defined as the mixing time. During this time the sample is compressed from state A to state B, and allowed to come to rest, such that all transients due to compression have dissipated by the third RF pulse. The spins are tagged after the first RF pulse and before compression by applying a sensitization gradient, $G_s$. After the mixing time and the sample has come to rest in the compressed state, a second sensitization gradient is applied to tag the phase relative to displacement. The two lobes of the sensitization gradient are applied in such a way that nuclear spins remaining stationary receive zero net phase [39]. The position of nuclear spins is defined as:

$$
    r(t) = \begin{cases} 
        0, & t < (TE + T_m)/2 \\
        d, & t > (TE + T_m)/2 
    \end{cases}
$$

where the spins undergo a step displacement of $d$ units between the uncompressed and compressed states. The resulting phase from the sensitization gradient $G_s$ is then defined as:

$$
    \phi = \gamma \int G_s(t)r(t)dt \\
    = \gamma dG_0 \tau
$$
Background and Motivation

Figure 1.9: Schematic of a basic stimulated echo pulse sequence used for static MRE. Figure adapted from [39]

where $\gamma$ is the gyromagnetic ratio of protons, $G_0$ is the amplitude of the gradient $G_s$, and $\tau$ is the width of each sensitization lobe [39]. The displacement can be detected along any axis by setting the sensitization gradient along the same axis as the desired displacement. The entire sequence is acquired twice for each line of k-space, alternating the sign of $G_0$, and the corresponding phases are subtracted from each other in order to eliminate errors due to $B_0$ inhomogeneity.

A typical phase image created from a single acquisition in static MRE contains multiple bands of phase, a condition known as phase wrap. This occurs when the
phase of a voxel increases past 360°, which ends up being recorded as somewhere between 0° and 360°. This problem can be eliminated by carefully selecting the magnitude of the sensitization gradients such that when the two phase images are subtracted from each other, the image contains zero phase wrap. A study by Aletras et al. used this method to encode large displacements with no visible phase wrap in the resultant images [47]. Assuming the maximum displacement, \( d_{\text{max}} \), is known based on the specifications of the actuator used for compression, the gradients for two phase acquisitions can be determined from the equation:

\[
\phi_2 - \phi_1 = \gamma d_{\text{max}} \tau (G_2 - G_1)
\]

where \( G_1 \) and \( G_2 \) are the amplitudes of the gradients selected for each alternating phase acquisition respectively. The difference between \( \phi_2 \) and \( \phi_1 \) must be kept below \( \pi \) such that \( +d_{\text{max}} \) and \( -d_{\text{max}} \) correspond to a phase difference between \( -\pi \) and \( +\pi \).

A sample of some of the images obtained in a typical acquisition using static MRE is shown in Figure 1.10, taken from one of the original studies on elasticity imaging by means of a STEAM sequence [46]. The images are of a urethane rubber phantom with two hard inclusions. The magnitude image shows that there are clearly two regions within the phantom: the surrounding material and two distinct inclusions. However, the image does not give any information about the relative stiffnesses of the separate regions. This illustrates the necessity for elastography imaging to obtain true information about the mechanical properties of a sample. The phase image shown in Figure 1.10(b) shows the phase shift proportional to the vertical displacement of the phantom. In this case phase wrap is visible in the image, due to the specific choice of gradients used in this study. The displacement sensitivity was chosen as 15.33 \( \pi/mm \), which is large enough to produce multiple phase bands at a displacement of 1.4 mm. Finally, the strain was calculated from
Background and Motivation

Figure 1.10: Images obtained from static elastography experiments on a phantom with two inclusions. The magnitude image of the phantom is shown in (a), followed by the phase image representing displacement in the vertical direction in (b), and the derived strain image in the vertical direction in (c). Figure adapted from [46].
the displacement image, and is shown in Figure 1.10(c). Because the equations for strain involve the differential of displacement, it was deemed unnecessary to remove the phase bands from the displacement image in order to obtain a representative map of sample stiffness.

1.4.1.2 Determining Strain

The property of strain is defined as the percentage deformation of a material, and can be represented mathematically in any direction as a tensor defined by:

$$\epsilon_{ij} = \frac{1}{2} \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right)$$  \hspace{1cm} (1.5)

where $u$ is the displacement vector, and $x$ is the coordinate vector. In the vertical direction $x_2$, the equation becomes:

$$\epsilon_{22} = \frac{\partial u_2}{\partial x_2}$$  \hspace{1cm} (1.6)

where $\epsilon_{22}$ represents the component of the strain tensor in the vertical direction.

A plane strain condition can also be used in some instances to describe deformation in an object with one dimension that is much longer than the others. In this case it is assumed that the cross-sectional state of stress is independent of the strain in the long dimension. This is sometimes applied to simplify the process of inverse strain mapping, which is defined in the following section [48]. In the case of plane strain, the strain tensor $\epsilon$ is defined by:

$$\epsilon = \begin{pmatrix} \epsilon_{11} & \epsilon_{12} & 0 \\ \epsilon_{21} & \epsilon_{22} & 0 \\ 0 & 0 & 0 \end{pmatrix}$$  \hspace{1cm} (1.7)
where \( x_3 \) is the longer dimension considered to have zero strain.

1.4.1.3 Inverse Strain Mapping

There have been a number of studies that have shown how strain imaging alone is useful as a method of visually identifying different regions of stiffness [49, 50]. However, in some cases it is necessary to determine accurate stiffness values by calculating the Young’s moduli of separate tissue regions; a process known as inverse strain mapping. In studies by Plewes et al, inverse strain mapping was performed to determine the stiffness of breast tissue [39]. This process involves using existing contrast-enhanced magnetic resonance images to identify and segment different regions of tissue. An initial estimate for the modulus of suspicious tissue is applied, and finite element modelling is used to obtain strains and stresses. The calculated strains and stresses at each voxel are then used to find the corresponding Young’s modulus. All calculated moduli are averaged for a given region, and a new elastic modulus value for the tumour is assumed for the next iteration. The process is repeated until the solution converges so that the averaged modulus matches that from the previous iteration. In clinical applications, full three dimensional models are usually required, due to complex geometry. A two dimensional plane strain analysis is more appropriate when dealing with tissue phantoms, or simpler geometries.

1.5 Summary and Thesis Aims

Percutaneous coronary revascularization of chronic total occlusions is a very difficult procedure to perform when compared to management of less severe forms of atherosclerosis. This is due to the presence of a hard proximal fibrous cap which can be difficult to cross with a guidewire, and due to the challenge of keeping a wire intraluminal during the procedure. Image guidance is limited for the most part to
x-ray fluoroscopy, which provides a two dimensional projection with poor soft tissue contrast. Other imaging modalities are being developed, but they each have different limitations. A technique for imaging the stiffness of tissue, known as magnetic resonance elastography, has been developed and used in several applications. The static form of the technique shows promise as a method of imaging the compliance of CTOs, by providing a method of analyzing the response of a CTO to deformation.

The aim of this thesis is to develop a technique for determining the thickness of the proximal fibrous cap of chronic total occlusions. The theory behind indentation of the surface of a CTO at the proximal fibrous cap is studied by performing finite element analysis on a simple model. The technique for analyzing the compliance of CTOs involves using static MR elastography to measure the displacement and strain through a cross-section of an artery phantom. The results are compared with theory obtained from finite element analysis, and the thickness of the proximal fibrous cap is estimated.
Chapter 2

Development of a Technique for Studying the Compliance of Chronic Total Occlusions Using MR Elastography

2.1 Introduction

Patients with chronic total occlusions (CTOs) are usually referred for bypass surgery, rather than being treated by percutaneous coronary intervention (PCI). Due to the potential complications and extremely invasive nature of bypass surgery, it would be ideal to develop techniques for improving the success rate of CTO revascularization. A number of different imaging modalities have been suggested and developed for image guidance; however each method has its own limitations. X-ray fluoroscopy, which is the most prominent technique used for image guidance, only provides a 2-D projection through the body, and is limited by poor soft tissue contrast and poor detector resolution [2]. This makes it difficult to identify key features such as the
occlusion itself, the vessel wall, or the constituents within the occlusion. Without proper image guidance for crossing CTOs, pushing a guidewire through an occlusion blindly can lead to perforation of the vessel wall. Although a soft guidewire may be insufficient to penetrate hard occlusions, a stiffer guidewire is more likely to perforate the vessel wall. Also, constituents such as calcium deposits and collagen can deflect a wire in the wrong direction [23]. It would be helpful not only to have better image guidance for crossing CTOs, but also to have some information about the stiffness of an occlusion before attempting to perform revascularization.

A technique known as magnetic resonance elastography (MRE) has been used in a number of applications to determine the stiffness of tissue for the diagnosis of cancerous tumours and liver fibrosis [32, 33]. It has been suggested that this technique may be useful at determining the stiffness of atheromas [1]; however there have yet to be studies on this application. A static form of the technique has been used for determining the location and stiffness of breast tumours, as well as the stiffness of articular cartilage [39, 40, 41, 36]. The technique is based around imaging the displacement induced by compression of tissue. The displacement is then converted into deformation, or strain, and ultimately into values of stiffness.

The aim of this study is to develop a technique for determining the thickness of the proximal fibrous cap of CTOs, using static MR elastography. Compression loading is applied to the surface of the proximal fibrous cap of a simulated artery phantom. The displacement and strain due to compression are analyzed using a phase contrast MRI pulse sequence. The technique is evaluated based on its ability to distinguish between the hard and soft regions of the phantom, such that the thickness of the proximal fibrous cap can be identified.
2.2 Materials and Methods

2.2.1 Finite Element Analysis

A three dimensional finite element model was developed in order to predict the response of an artery phantom to applied deformation. Information about the shape of the displacement and strain curves obtained from finite element models of an artery were used to help analyze the curves obtained from experiments on agar/gelatin phantoms. The model was developed using ABAQUS, a commonly used software for doing finite element simulations. The model consisted of four simulated regions of tissue including the lipid-rich inner core of a CTO, the proximal fibrous cap (PFC), the artery wall, and a surrounding layer of pericardial fat. The entire model was created as a 2cm by 2cm by 5cm block of pericardial fat, imbedded with a 5mm inner diameter vessel at its centre. The artery wall was set to be 0.5mm thick, and the PFC was set to be 1mm thick. In order to save computational time, one quarter of the model was examined in detail, and extrapolated to a whole section by using symmetry boundary conditions. The model was meshed using small elements in the regions of interest such as the PFC, and larger elements near the end of the vessel and for the pericardial fat. The fully meshed quarter-model is shown in Figure 2.1, with colour coded regions.

The stiffnesses of each of the regions were assigned values based on publications and estimates of tissue stiffness. The vessel wall was assigned a Young’s modulus of 100kPa, based on a recent study measuring the stiffness of the abdominal aorta in healthy volunteers [51]. The fat and lipid-rich core of the CTO were assigned a value of 2kPa, based on measurements of adipose and fibroglandular breast tissue [52]. Finally, the stiffness of the PFC was assumed a high value of 300kPa, by estimating that collagen and calcium could potentially lead to high stiffness values well above the stiffness of soft tissue and that of the vessel wall. Although these
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The model is represented as one quarter of the full CTO in order to save computational time. The lipid-rich inner core of the CTO is shown in blue, the proximal fibrous cap in green, the vessel wall in red, and the pericardial fat in yellow. Values may not represent exactly what would be present in an actual CTO, it was noted that there could be a wide range of tissue stiffnesses present in any given CTO depending on the age and type of lesion. Therefore the values used in this simulation provide an estimate of one possible situation. A series of three additional models were simulated using stiffer values for the inner core of the CTO relative to the PFC. This provided information about the sensitivity of displacement to differences in stiffness between occlusive constituents. The Poisson’s ratio, which is the ratio of transverse to axial strain, was set to 0.495, representing a near incompressible material as assumed by other investigators [40].

Different boundary conditions were applied in order to simulate as closely as possible to a real CTO imbedded in fat. The sides of the block that were removed to reduce the size of the model to one quarter were assigned symmetry boundary conditions in order to simulate a full artery imbedded in fat. The bottom surface of the model was assigned a fixed boundary condition in order to restrain the model.
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The load case for the model was defined as a 2mm displacement along the surface of the PFC alone. This simulated the compression of a CTO with a rigid piston applied at the surface of the blockage. An additional scenario was modeled simulating indentation with a smaller device by applying a 2mm displacement across a 1mm diameter surface on the face of the occlusion.

2.2.2 Compression Apparatus

A loading apparatus was designed as a pneumatic system connected to an electronically controlled valve in order to time cyclic displacements with the MRI scanner. A schematic of the entire compression system is shown in Figure 2.2, and is described as follows. The pneumatic system consisted of a tank of compressed air (Medical E size), a fluid dispensing system (EFD Ultra 2400, Nordson, Westlake, OH) to control delivery of compressed air, and a custom made pneumatic cylinder. The compressed air tank was attached to a regulator to keep the pressure below 100psi for safe delivery to the EFD system. Although the fluid dispensing system was designed for applying fluids such as epoxy and other solvents, it was chosen in this study due to its ability to apply controlled bursts of compressed air for any application. The dispensing unit contains a high-speed solenoid system, which when activated by an external trigger opens a valve to release gas at a specified pressure through the output pressure line. The output pressure was set to 30psi for a duration of 500ms in order to compress the sample for the duration of the mixing time and the readout gradients for each cycle of the STEAM sequence. The pressure was released after each burst in order for the pneumatic cylinder to reset itself between compressive cycles.

The pneumatic piston was made out of materials that were compatible with use inside the bore of an MRI scanner, and connected to the EFD fluid dispenser. The main cylinder and piston rod were made out of polycarbonate, and the end piece
Figure 2.2: Schematic of the loading system, and corresponding image below. The solenoid valve in the fluid dispenser is triggered by the MRI to release compressed air at 30psi for 500ms. The compressed air is delivered to the cylinder from the computer room to the MRI room using 1/8in ID urethane tubing. The cylinder is then displaced by the pressurized air, causing compression of the artery phantom by approximately 1.5mm.
and piston head were made out of Delrin, which is a material that has been shown to be safe for MRI applications [53, 54]. The piston head was fitted with a rubber 0-ring used to seal the inside of the cylinder chamber. A 1/8in NPT threaded hole was drilled into one end of the cylinder chamber in order to provide a connection for 1/8in ID urethane tubing connecting the output of the EFD fluid dispensing system with the input of the cylinder chamber. The tubing connected the cylinder and fluid dispenser through the wave guide between the computer room and the MRI room. The opposite side of the chamber was fitted with a copper beryllium spring, which provided a means of resetting the cylinder after release of pressurized air. This type of cylinder is known as a single acting pneumatic cylinder, due to the release of pressurized gas into only one side of the piston head. The spring was compressed within the cylinder while at rest, such that enough force would be generated to push the piston head back to its original position after pressure release. A 13in long piston rod with a 1/4in diameter was placed against the surface of the artery phantom at the opposite end of a wooden base. The rod was fitted with a cylindrical piece of spare plastic and passed through a block of Delrin glued to the wooden base such that compression was controlled by the distance between the two components. This acted as a stopping device, and was set to a displacement of \( \sim 1.5 \text{mm} \). The holder for the artery phantom was screwed to the wooden base using nylon screws set on a track in order to adjust the position of the phantom relative to the piston rod.

The EFD fluid dispensing system was connected to the scope trigger of the MRI scanner in order to trigger compression of the artery phantom. The fluid dispenser required a 5V external trigger pulse greater than 10ms in length in order to trigger the solenoid valve. A function generator was connected in between the MRI scope trigger and the input of the fluid dispenser using two BNC cables in order to provide the appropriate external trigger. The function generator was set to deliver a 5V pulse
with a width of 100ms, and an edge time of 5ms. The pulse was set to trigger 30ms after the rising edge of the second RF pulse in the STEAM sequence, as described in Section 1.4.

### 2.2.3 Image Acquisition

The wooden base of the compression apparatus, containing the artery phantom and the pneumatic cylinder, was placed within the bore of a GE Signa 3T EXCITE system scanner (GE Healthcare, Milwaukee). Tubing was passed through the wave guide into the computer room and attached to the compressed air and EFD fluid dispenser. Compression of the sample was imaged using a STEAM sequence as defined in Section 1.4.1.1. Phase images of the phantom were acquired in the coronal plane, through the centre of the artery section of the phantom in the middle of the gel holder. The orientation of the piston rod in the corresponding images was pushing upwards against the hard gel within the cylindrical cavity of the artery. The TR, TE, and mixing time \( T_m \) were chosen as 3s, 19ms, and 300ms respectively. The field of view (FOV) was 12cm, with a resolution of 256x128 pixels, and a slice thickness of 6mm. The total acquisition time was 6 minutes and 24 seconds. The mixing time of 300ms was chosen based on the T1 of the gel, which was found to be around 700 - 750ms. The mixing time should be considerably smaller than the signal decay of the stored magnetization given by T1 in order to obtain adequate signal in the readout of the pulse sequence. It was noted that there was a delay between triggering of the EFD fluid dispenser and compression of the pneumatic cylinder, however, the delay was small enough that compression of the sample occurred within the mixing time. Two image acquisitions were made, and subtracted from each other according to Equation 1.4 such that a phase difference of \( \pi \) would be observed for a maximum displacement of 2.03mm.
2.2.4 Artery Phantom Preparation

The artery phantom was prepared in an acrylic holder large enough for a 65mm by 65mm by 65mm gel. It consisted of a soft agar/gelatin mixture imbedded with a hard inclusion of agar to mimic the proximal fibrous cap of an artery. To prepare the base gel, a 0.5% agar and 2.5% gelatin mixture was added to 400 mL of distilled water using 2g of agar (Sigma A7002, St. Louis, MO) and 10g of porcine skin gelatin (Sigma G-2625, St. Louis, MO). The agar was added first to the distilled water, and heated in the microwave until boiling was observed. The agar mixture was then placed on a hot plate and stirred while adding the gelatin until all particles had dissolved. The agar/gelatin mixture was poured into the acrylic holder, and a 6.35mm diameter polycarbonate rod was inserted into the centre of the gel by approximately 25mm. The gel was allowed to set for an hour in the refrigerator, while the second gel was prepared. The gel representing the PFC was prepared in the same manner as for the previous gel, but with 4% agar and no gelatin. After cooling to about 40°C to avoid melting the previous gel, the second gel was poured into the cylindrical cavity created by the polycarbonate rod by about 10mm. The entire gel was then placed in the refrigerator and allowed to set overnight.

2.2.5 Image Analysis

Phase images were acquired as described in Section 2.2.3. The phase of each pixel was scaled by a ratio of 0.6462mm/rad in order to obtain a map of displacement. The image of displacement was then smoothed using a smoothing spline with the smoothing parameter set to \( p = 0.26 \). A smoothing spline is defined as a function \( f(x) \) for which the expression

\[
p \sum_{j=1}^{n} |y(j) - f(x(j))|^2 + (1 - p) \int |D^2 f(t)|^2 \, dt
\]

(2.1)
is minimized. The parameters in Equation 2.1 include the smoothing parameter $p$, column of data $y(:, j)$, position of data points $x(j)$, and second derivative operator denoted by $D^2$. The spline was applied to each column in the displacement matrix individually, since the data was analyzed on a per-column basis in the vertical direction. A strain image was derived from the smoothed displacement image by taking the first derivative of displacement along each column. This was calculated numerically and applied at the mid-point between each set of adjacent pixels as:

$$\epsilon_n = \frac{u_{n+1} - u_n}{y_{n+1} - y_n} \quad (2.2)$$

where $u_n$ is the displacement of the $n^{th}$ pixel, and $y_n$ is the position of a pixel in the vertical direction.

### 2.3 Results

#### 2.3.1 Finite Element Simulation

The absolute value of strain is shown in Figure 2.3 as a three dimensional contour map displayed over the compressed state of the simulated artery model. As described in Section 1.4.1.3, information about the strain alone is sometimes enough to be able to understand the distribution of stiffness in a sample. In this case, some of the key features are clearly visible due to the relatively simple geometry, and the uniform loading across the face of the occlusion. The lowest strain is experienced near the edges of the model around the fat, and at the face of the occlusion throughout the PFC. This is due to the distribution of stress during loading of the model. Since the PFC itself is quite hard relative to the other tissue types, it experiences a small deformation relative to its surroundings. The fat on the other hand is easily deformable, and experiences a high degree of strain near the interface between the
Figure 2.3: Contour map of the absolute strain mapped over a close-up view of the fully compressed state of the artery model. The interface between the proximal fibrous cap (PFC) and the inner core of the chronic total occlusion (CTO) is easily identifiable at the surface where strain increases abruptly.

vessel wall as it is pulled by vessel movement. These high strains are quickly absorbed at further distances from the vessel wall, due to the fat’s low elastic modulus. One of the key features to notice in the contour map is how the strain increases almost instantly at the interface between the lipid-rich core of the CTO and the PFC. This again is due to the difference in elastic moduli between the hard PFC and the soft core of the CTO. Like the surrounding fat, the inner core is easily deformable and absorbs most of the deformation near the interface between the two materials. This provides a feature that can be used to identify the boundary between hard and soft materials. High strains are also observed at the boundary between the inner core and the vessel wall, also due to the difference between the two elastic moduli.

A graph of the displacement across the length of the model at the centre of the artery is shown in Figure 2.4. This represents the displacement in the same direction as the compression, which is in the \(-z\) direction with respect to the global coordinate system used by ABAQUS, shown at the bottom left corner of Figure 2.3. The graph of displacement is placed above a cross-section of the artery model for
Figure 2.4: Displacement of the artery model along its centreline. A cross section of the modelled artery is shown below as a reference for the different regions. The direction of displacement is positive towards the left with respect to the cross section shown. Compression is towards the right, meaning that the displacement is displayed as a negative value. The dotted line indicates the interface between the proximal fibrous cap (PFC) and the soft inner core behind it.
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reference, with the dotted line indicating the position of the interface between the PFC and the CTO core. One of the key features to note is that the displacement remains relatively unchanged throughout the PFC of the model. This is mainly due to the high modulus of the PFC relative to the CTO core. Since the PFC is not easily deformable, it moves almost as an entire unit, transmitting the displacement induced by movement of the piston rod throughout the region. At the interface between the PFC and the CTO core, the displacement begins to be absorbed, and starts to drop towards zero. The soft inner core absorbs most of the displacement along the length of the artery in a predictable manner.

![Figure 2.5: Strain of the artery model along its centreline, with compression considered as negative strain. A cross section of the modelled artery is shown below as a reference for the different regions. The dotted line indicates the interface between the proximal fibrous cap (PFC) and the soft inner core behind it.](image)

A graph of the strain across the length of the model is shown in Figure 2.5. The graph shown is basically a first derivative of the displacement curve shown in Figure
2.4. Compressive strain in this case is shown as a negative value, due to the negative slope of the displacement curve. This curve displays some of the same information as was seen in the displacement curve, but with different noticeable features. Since the PFC transmits most of the compression to the inner core of the model, it experiences little strain throughout its length. At the interface between the PFC and the inner core behind it, indicated by the dotted line, the strain increases rapidly. This is due to the low elastic modulus of the inner core, which is more easily compressed. The strain is then absorbed along the rest of the length of the model, as the inner core experiences less and less transmitted displacement.

2.3.2 Compression of the Artery Phantom

The magnitude image of the artery phantom is shown in Figure 2.6(a). With a field of view of 12cm, the depth of the hard gel was measured to be around 10mm. Compression was applied in the vertical direction upwards, with the polycarbonate rod applying pressure at the surface of the simulated PFC. It was also noticed that the simulated PFC had penetrated the soft gel around it, and had been pushed through the gel on a slight angle. This was likely due to excess pressure applied to the surface of the occlusion when setting the polycarbonate rod in place against the surface. There was also a slight artefact in the image which appeared as an 'X' with bands around it. It was unclear exactly what caused this artefact, but it only resulted in a slight increase in phase around the soft gel in a specific area. The overall trends were still evident in the data, despite the slight distortion of phase due to the artefact. The magnitude image represents the compressed state of the phantom, and was used as a mask to eliminate noise in the empty space around the phase image.

The phase image was obtained by subtraction of two phase acquisitions such that a phase of \( \pi \) radians corresponded to a displacement of 2.03mm. The magnitude
Figure 2.6: Images of magnitude, displacement, and strain, obtained from an agar/gelatin phantom of a chronic total occlusion (CTO) using a STEAM sequence. The magnitude image of the phantom is shown in (a), followed by the phase image representing displacement upwards in the vertical direction in (b), the smoothed displacement using a smoothing spline with a parameter $p = 0.26$ applied on each column of data in (c), and the derived strain image in the vertical direction taken from the smoothed displacement data (d).
Figure 2.7: Plot of displacement along the artery axis from the 66th column of data in the displacement image, through the centre of the artery phantom. The displacement is plotted as a reflection along the x-axis as a means of visual comparison with Figure 2.4. The vertical distance along the artery centre is plotted upwards starting from the surface of the hard gel at 48mm from the bottom of the displacement image. The red dotted line indicates the estimated transition point between the hard and soft gels within the phantom.

image was used to mask any surrounding noise, and an image of displacement was created by scaling the phase by $2.03/\pi$, as shown in Figure 2.6(b). The displacement image shows that there was a fairly consistent displacement throughout the harder gel, which tended to drop off at the interfaces between the hard and soft gel. Although the compression rod was displaced by around 1.5mm, only about 0.6mm displacement was actually applied to the surface of the PFC, most likely due to positioning of the rod, and the angle at which it was pressing against the occlusion. Despite these problems, the overall change in displacement between the hard and
soft gels is still evident in the resultant phase image. A column of data was taken through the centre of the artery from which displacement data and strain data was plotted against vertical distance along the artery. The displacement data, plotted between the surface of the occlusion and the edge of the gel, is shown in Figure 2.7. Although displacement was recorded as a positive value in the direction of compression, the plot was flipped about the x-axis, as a means of comparison with the finite element theory. The raw displacement data is shown as well as a smoothed curve of displacement using a smoothing spline with a smoothing parameter \( p = 0.26 \). The trend of the data shown by the smoothed curve indicates a fairly flat section near the hard PFC of the occlusion, followed by a sudden drop in displacement and a gradual change towards zero. The flat section in displacement indicates the presence of a hard lesion, and the sudden drop indicates a transition to a much softer gel. From this transition, the interface between the hard and soft gels is shown to be anywhere between 7 - 9mm from the surface of the occlusion. This is in good agreement with the measured PFC length of about 10mm.

A smoothed image of the displacement in the vertical direction is shown in Figure 2.6(c). The image was smoothed with the same smoothing spline used for the single column of displacement, but applied on all columns of the image individually. The smoothed image shows more clearly the higher displacement in the hard region, followed by less displacement further away from the simulated PFC. Smoothing was performed both as a method of analyzing trends, and also to provide a more continuous curve to apply differentiation for imaging the resultant strain. The first derivative of displacement with respect to distance in the vertical direction was performed on each column in the smoothed displacement image as per Equation 2.2. The data in the strain image shown in Figure 2.6(d) is a bit difficult to analyze from the image alone, however it can be seen that there is a region of high strain near the surface of the PFC, followed by a relatively low strain around zero, followed
Figure 2.8: Plot of strain from the 66th column of data in the strain image, through the centre of the artery phantom. Negative strain in this case represents compressive deformation. The vertical distance along the artery centre is plotted upwards starting from the surface of the hard gel. The red dotted line indicates the estimated transition point between the hard and soft gels within the phantom.

again by a region of negative strain, indicating compression near the transition between hard and soft gel. The high strain near the surface is due to the smoothing of the displacement between the empty space surrounding the occlusion and its surface. The more important information is around the interface between the gels where a high amount of negative strain is seen. This indicates the location of high deformation of soft gel transmitted by the hard PFC. A clearer plot of strain is shown in Figure 2.8 as a plot of strain along the centreline of the artery from the surface of the PFC to the edge of the gel. A 2nd order gaussian curve was also fit to the strain data in order to more easily view the important information. It can be seen that there is a region of almost no strain followed by a high value of negative
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2.4 Discussion

The purpose of this study was to determine whether static elastography could be performed on a simple phantom of a chronic total occlusion in order to determine the thickness of the proximal fibrous cap. This was proven by finite element analysis on a simple model, as well as by static elastography performed on an artery phantom. The theory presented using finite element methods showed that certain key features indicated a transition between hard and soft tissue types. This included a change in slope in the displacement plot from low values for hard tissue to high values for soft tissue. In addition to changes in slope, the displacement approached zero the further tissue was from the compression or indentation point. A displacement of zero at the opposite end of the artery would be approached faster or slower depending on how constrained the tissue was. In the case of the finite element model which was less constrained, the displacement approached zero very slowly. In the case of the artery phantom which was encased in an acrylic holder, the far end of the artery was constrained by the walls of the holder, meaning that the displacement had to be zero at the far end of the gel, and reached this value much quicker. In both cases however, any sharp changes in the slope of the displacement curve indicated changes in tissue stiffness, and gradual changes were due to overall absorption of displacement with tissue length. Since the strain is essentially the first derivative of the displacement curve, which is equal to the slope of the displacement curve at each point, similar information was obtained in the strain plot. Instead of visualizing changes in slope by looking at the displacement curve, a strain plot displays changes
in slope directly. An analysis based on the strain plot involves looking for sudden changes in strain as indicators of tissue boundaries. Since the difference in stiffness between the two tissue types in the finite element model was fairly large, the change in strain was dramatic, from a low value for hard tissue to a high value for soft tissue. The strain was also absorbed near the end of the tissue due to absorption of displacement, causing little to no deformation. Sudden changes in strain therefore indicate changes in tissue type, whereas gradual changes are due to absorption of displacement. In a full analysis, ideally the stress distribution would also be known throughout the length of the model. In an indentation scenario such as the one used for this experiment, the stress would also decrease with distance along the model such that the ratio of stress to strain would remain constant for a given tissue type.

As opposed to most static elastography experiments, which compress the entire tissue of interest from both ends, the application to CTOs involves indentation loading on only one end of the occlusion. In this experiment the entire face of the simulated PFC was compressed by a flat surface, however smaller indentation surfaces could potentially be used. Since the application of static MRE to CTOs involves applying compression while performing intravascular procedures, it is possible that a stiff guidewire or similar tool could be used to indent the surface of the occlusion. Compression behind the indentation surface would follow a similar pattern as was observed in this study. Indentation could potentially be applied at various points along the surface of a CTO, in order to determine the best location for the guidewire to pierce through. Alternatively, laser ablation could be applied up to a certain distance depending on the measured thickness of the PFC.

The differences in slope observed at the transition point between hard and soft parts of the occlusion in the finite element simulation were highly visible due to the large difference between the modeled stiffnesses for the two materials. In order to determine the sensitivity of displacement curves to different stiffness variations,
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Figure 2.9: Plot of displacement along the centre of the finite element model for different ratios of stiffness between the proximal fibrous cap (PFC) and the inner core. The four curves correspond to PFC stiffnesses of 150, 3, 1.5 and 1 times higher than the stiffness of the inner core. The dotted black line indicates the position of the transition between the two materials, which was placed at 5mm for ease of comparison.

A number of additional scenarios were evaluated using different ratios of stiffness between the PFC and CTO core. The additional models were assigned PFC to CTO core stiffness ratios of 3, 1.5 and 1. This was compared to the original model, which used a ratio of 150 between 300kPa for the PFC and 2kPa for the inner core. The displacement along the centre of the simulated artery for each of the four scenarios is shown in Figure 2.9. The transition point, indicated by the dotted black line at 5mm, is more apparent with the highest stiffness ratio. Ratios of 3 and 1.5, which were obtained by increasing the modulus of the inner core, lead to displacement curves with subtle changes in slope at the transition point between hard and soft materials. As expected, a ratio of 1 leads to zero change in slope at the transition point, since both the PFC and inner core are assigned equal stiffness values. For lower ratios of stiffness, the transition point is difficult to observe from displacement alone, and would be more easily visible in a strain curve representing the slope of displacement directly. In simple situations where there are two materials of different stiffnesses, the transition point can be determined as long as the signal-
to-noise ratio (SNR) is high enough that error is kept at a minimum. This allows for
the extrapolation of curve data based on known characteristics of the curve shape
within the hard and soft regions of the sample. Extrapolation of curve shapes for the
hard and soft regions can be made such that the intersection of the two curves points
to the transition between the two constituents. Ultimately how well these points
can be identified depends also on the displacement induced and how constrained the
entire artery is within the body. The higher the induced displacement, and the more
constrained an artery is, the greater the difference will be between displacement at
the proximal and distal end of an occlusion. A large range of displacement between
both ends of an occlusion will lead to more information contained within that range.
In more realistic situations with complex geometry and multiple transition points,
displacement and strain information may be too complicated to use as a method
of identification of regions of stiffness. In those situations, a more complete 3-D
analysis is most likely necessary to obtain strains and stresses, and corresponding
Young’s moduli at each respective position.

In order to obtain accurate information in the displacement data about the
transition point between hard and soft materials, the SNR must be relatively high.
Magnitude SNR can be obtained from the magnitude image by taking the ratio of
the mean signal in a region of interest by the standard deviation of noise in the
background of the image. This is then converted to phase noise by

\[
\sigma_{\text{phase}} = \tan(\sigma/\mu)
\]

(2.3)

where \(\sigma_{\text{phase}}\) is the noise in phase, \(\sigma\) is the standard deviation of noise in the mag-
nitude image, and \(\mu\) is the mean signal in the magnitude image. The phase noise
can then be converted to displacement noise by scaling proportionately with the
induced displacement. The calculated magnitude SNR in this experiment is roughly
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650, which corresponds to a phase noise of 0.0015 radians, and a displacement noise of 0.001mm. Since the noise is very low in this case, the transition between hard and soft materials can be identified with high accuracy, even in cases where the ratio of stiffness between the two regions is fairly low. The low noise also suggests that the variability in the data causing oscillation in the displacement and strain curves is a result of other factors. The artefact in the centre of the gel is likely the cause for this oscillation. The artefact pattern seems to be caused by interference of compression waves as they meet in the centre of the gel after reflecting off the acrylic walls of the gel holder. This is suggested by the direction of the bands in the pattern, as they are parallel to the sides of the acrylic walls. Any delay in compression due to air traveling through tubing will have to be eliminated in future experiments in order to ensure adequate time is given in the mixing time for any waves due to compression to dissipate. Additionally, a different gel holder may need to be developed to ensure waves do not reflect off all sides of the acrylic walls. A gel holder should also be less restrictive to allow for more movement near the sides of the gel. This will help the experimental data more accurately reflect displacement patterns given by finite element analysis.

Although compression was applied across the entire surface of the occlusion in the finite element simulation, it is possible that smaller devices could be used to indent the occlusion across a smaller area. To investigate this scenario, an additional simulation was run in which the compression was applied on the surface of the occlusion across a 1mm diameter circular area at the artery centre. The resulting displacement curve along the centre of the artery is shown in Figure 2.10. The curve shows a region near the surface where a drop in displacement is seen, followed by a region of change in slope as observed when compressing the entire surface of the occlusion. The sudden drop in displacement at the surface is likely due increased stress and strain caused by indentation directly behind the indented surface. This
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indentation also causes displacement of the entire surface of the occlusion, but by a lesser amount than the delivered compression. This creates an effective delivered displacement, which in this case is around 1.8mm across the entire surface of the occlusion. There is therefore a loss of 0.2mm of transferred displacement due to compression of the indented surface. In clinical applications, it would be easier to analyze the resulting displacement data by applying a uniform compression to the surface of the occlusion. This could be accomplished by using a balloon attached to a catheter delivering uniform pressure across the entire surface of the occlusion.

The distance between the fluid dispenser valve and the pneumatic cylinder within the MRI room was long enough that there was a delay between triggering and compression of the cylinder. This delay was difficult to quantify, due to it being on the order of tens of milliseconds. Some preliminary experiments were done prior to testing the artery phantom, which showed that despite this delay, a mixing time of 300ms was long enough to ensure compression of the sample before the third RF pulse. It is possible, however, that the delay between triggering of the fluid dispenser valve, and compression of the sample was longer than necessary to eliminate...
transients due to compression waves. This may have been responsible for the arte-fact present in the resultant phase image. The delay will have to be quantified in the future to either prove that a mixing time of 300ms is sufficient for steady-state analysis, or to show that the solenoid valve will have to be triggered earlier in the sequence to account for the delay. Alternatively, the delay due to tubing length can be calculated theoretically based on fluid flow theory.

In addition to the artefact behind the hard occlusion, the magnitude image in Figure 2.6(a) shows a susceptibility artefact around the occlusion and near the walls of the artery cavity. This is caused by differences in magnetization between the gel and surrounding air. Since the harder gel penetrated the softer gel as it was being compressed, air pockets were most likely introduced at the interface between the two gels. As a result, there is a small amount of signal loss surrounding the hard gel. There also appear to be air bubbles in the hard gel, which also contribute to some signal loss. It will be important for future experiments to create a gel that has as few air bubbles as possible, and good adhesion at the interface between the two types of gels. The susceptibility artefact can also be removed by submerging the entire sample in water, so that there are as few air/gel interfaces as possible.

The finite element analysis showed that it is not necessary to perform inverse strain mapping on a simple artery model in order to determine the thickness of the proximal fibrous cap of a CTO. However, inverse strain mapping would be necessary if the goal were to obtain values for the Young’s modulus of different tissue regions. Additionally, real CTOs are likely to be more complex both in tissue geometry and in the number of different tissue regions with separate stiffnesses. The technique presented in this paper is essentially a one-dimensional analysis, by analyzing the displacement and strain along a single line through the plane of interest. With more complex geometry and with the added requirement of quantifying tissue stiffness, a full three-dimensional analysis should be considered. The techniques outlined in
publications on static MRE for breast cancer are useful methods for performing a more complex analysis [39, 40, 41]. Finite element analysis could be performed in tandem with static elastography on a CTO in order to quantify the stress induced in tissue due to indentation loading, and to calculate the average stiffness of segmented regions within a CTO. An iterative technique to determine the stiffness of CTO regions could prove to be an excellent method of developing a three-dimensional map for PCI guidance.

2.5 Conclusions

A new technique for determining the thickness of the proximal fibrous cap of a CTO has been proposed, based on existing methods of static MRE. The theory for the compression of tissue using indentation loading has been determined using finite element analysis on a simple CTO model. An agar/gelatin phantom of a simple blocked artery was also tested using a STEAM sequence and a pneumatic compression system to deliver indentation loading at the surface of the occlusion. The results of the finite element analysis show that indentation loading at the surface of an occlusion leads to a displacement pattern such that the transition between hard and soft regions can be identified by changes in slope. In simple geometries, displacement and strain provide enough information to determine the location of different regions of tissue stiffness. The phantom experiment shows similar results as determined by finite element theory in that the thickness of the proximal fibrous cap can be determined by changes in slope in the displacement curve. Future work will be necessary to develop techniques for characterizing the stiffness of occlusive constituents. Methods of inverse strain mapping combining finite element analysis and static elastography will most likely need to be developed in order to fully characterize the stiffness of CTOs in three dimensions.
Chapter 3

Summary and Future Work

This thesis has dealt with the development of a technique for determining the thickness of the proximal fibrous cap of CTOs, by using static elastography to map the response of an artery phantom to compressive deformation. The experiment outlined in Chapter 2 evaluated this technique based on its ability to identify the length of the hard and soft sections within an artery phantom with a hard proximal fibrous cap and a soft inner core. A finite element analysis was done on a simple CTO model to determine the types of displacement and strain patterns that would be observed. With displacement applied along the surface of the PFC, the resultant displacement patterns showed that changes in slope corresponded to transition interfaces between hard and soft regions. The strain patterns were a direct reflection of these changes in slope, since strain is essentially the first derivative of displacement, or the instantaneous slope of displacement at any point along the model. Phase images were also acquired from compression of an artery phantom made of different stiffness of agar/gelatin mixtures. The phase image was converted to displacement by a scaling factor, and a line of data was taken through the centre of the artery as a means of comparison with the finite element theory. A strain image was also derived based on the first derivative of each column within the displacement image. Although
there were some problems with artefacts and susceptibility, the overall smoothed data showed trends similar to those predicted by the theory. The thickness of the hard gel within the artery phantom was estimated based on the changes in slope of displacement, and was found to be close to the actual thickness measured from the magnitude image.

The work outlined in the previous sections has shown that it is possible to measure the patterns of deformation resulting from indentation type loading on a CTO. It therefore provides an introduction to the development of a technique for characterizing the compliance of CTOs. Future work will be necessary before static elastography can be used as a method of guidance for performing revascularization of CTOs. First of all, additional experiments will be needed to complete the work presented in this thesis. The technique must be improved such that artefacts are eliminated in the resultant images. This includes creating gels with less air bubbles, better adhesion between soft and hard gels, controlled loading to prevent penetration of one gel through the other, and optimized compression delay and mixing times. Better adhesion between different gels can be accomplished by using more gelatin in the agar/gelatin mixtures, and by waiting for the hard gel to cool to $40^\circ C$ before pouring into the cavity left by the softer gel. Controlled loading can be improved by creating a model without a cavity or lumen, such that compression can be visualized on the outside of a block of gel. Additionally, submerging the gel in water will eliminate problems with susceptibility artefacts. Finally, the delay between triggering of the solenoid valve and compression of the cylinder will be measured and accounted for in the pulse sequence, such that adequate mixing times are used to allow the gel to return to steady-state between compressive cycles.

A number of different experiments will need to be done in the future in order to develop the technique of static elastography applied to CTOs further. These include tests to characterize the compliance or stiffness of CTO constituents, to
develop methods of inverse strain mapping, and to test devices in vivo.

3.1 Characterizing the Stiffness of CTOs

The work outlined in this paper used a phantom with gels of different stiffnesses to represent hard and soft lesions; however, the percentages of agar and gelatin were selected more on the basis of having a large difference between the stiffness of the two gels, rather than having an accurate representation of CTO stiffness. Attempts have been made to determine the stiffness of CTOs, as described in Section 1.2.3, using a force tester and rabbit model CTOs. The results of the study showed that puncture force of CTOs increases with the maturation of lesions. It is difficult however to correlate values of puncture force with actual values of Young’s modulus. This is due to a number of factors, including the piercing shape of the puncture probe, and difficulty in separating the components of deformation due to the proximal fibrous cap and vessel wall.

Experiments were attempted to try to correlate puncture force of various gels with the results of the study by Thind et al [28]. This involved making gels of different percentages and testing them using the same force tester and puncture probe. One of the curves taken from a puncture force test on 2.5% agarose is shown in Figure 3.1. The shear modulus of each gel was also tested using dynamic elastography in order to correlate stiffness values with values of puncture force. A number of problems were encountered in the tests relating to the properties of puncture force curves of agarose gels. Whereas the tests on rabbit CTO models had definite peaks representing puncture force, the gels had multiple peaks which were hard to interpret. A pattern was noticed whereby the force would increase to a certain value, drop off suddenly, and then increase again to a higher value. It was thought that this behaviour was due to fracturing of the gel. The forces measured
were therefore not necessarily puncture forces, but rather points at which fracture planes would be opened up within the gel. There was also considerable variation in gel behaviour depending on the batch made.

A better test for measuring the stiffness of CTOs would be to use an indentation force testing setup used by Samani et al [52]. This test is very similar to puncture force tests, except that it involves indentation using a flat indenter, and does not puncture the sample. The theory for this method states that there is a conversion factor dependent on the geometry and boundary conditions of a sample, for which the slope of the force displacement curve during indentation can be converted to Young’s modulus. This method was used successfully to determine the Young’s modulus of breast tissue. Although the geometry of the samples were fairly large, this technique could be modified to determine the stiffness of CTOs.
3.2 Scaling and SNR

The experiment outlined in this study deals with a simulated artery with a fairly large diameter. The resolution used based on the available 5” surface coil and size of the agar/gelatin phantom was 0.5mm by 1mm by 6mm. Based on the size of human CTOs, with typical diameters in the range of 2mm and a proximal fibrous cap thickness of around 0.2mm, the target resolution for clinical applications would be around 0.2mm by 0.4mm by 1mm. Since SNR is proportional to voxel volume, the target resolution would result in a decrease in SNR by 0.027. A magnitude SNR of 650 as determined in this experiment would be decreased to about 17. In order to make up for the lost SNR due to resolution, clinical applications would need to use improved devices and increased scan time. Intravascular coils have been shown to provide at least 10 times better SNR than a 5” surface coil, at the expense of field-of-view (FOV). This is not necessarily a problem in this situation, since smaller FOVs would still be able to surround the region of interest in a CTO. Additionally, amplifiers are being developed which can increase SNR by 4. With both an intravascular coil and an amplifier, the SNR can be increased to 680, which is higher than the current SNR obtained in this study. Without the use of amplifiers, the scan time could also be increased to improve SNR further. Since SNR is proportional to $\sqrt{\text{time}}$, a scan time of 1:36 could be increased to 22:30 rather than using amplifiers. This is not likely practical however, since long imaging time introduces logistical challenges in a clinical scenario, particularly making the system more sensitive to patient motion and patient fatigue.

3.3 Inverse Strain Mapping

As described in Section 1.4.1.3, inverse strain mapping is the process of determining the Young’s modulus of tissue based on maps of strain and known boundary con-
ditions. For realistic applications involving complex geometry, such as elastography with real CTOs, a full 3-D analysis is often necessary, integrating static elastography imaging to obtain strain images, with finite element analysis to obtain maps of stress. A flowchart outlining the process is shown in Figure 3.2. Since the governing equations of continuum mechanics are fairly complex when dealing with 3-D geometry, the equations tend to be ill defined and difficult to solve. To overcome these problems, values of elastic modulus are averaged for a given tissue type with each iteration.

Future work will likely involve using inverse strain mapping techniques to determine the elastic moduli of different constituents within a CTO. Key features will
include the proximal fibrous cap, soft inner core, calcium deposits, and the vessel wall. Magnitude images can be used to segment different regions in a CTO based on the key tissue types. An iterative procedure using finite element analysis can then be used to determine the averaged modulus values for each region, providing an accurate map of the stiffness of CTOs in three dimensions.

3.4 In Vivo Testing

The use of static elastography for determining the compliance of CTOs can only be truly verified by performing preclinical studies using models of occlusive disease. Due to the size of vascular anatomy in humans, and the resolution limitations of MRI, it would be advantageous to use large animals such as swine for models of occlusive disease. One model in particular has been developed successfully and has been applied to both peripheral and coronary vessels. In order to create occlusive lesions, a collagen sponge from a vascular closure device (Angio-Seal, St. Jude Medical, USA) is inserted into a vessel with a catheter guided by x-ray fluoroscopy. The sponge expands after exposure to blood, and forms a thrombus which develops over time. The collagen sponge itself degrades as the lesion develops. More advanced models will need to be developed as well to create occlusions that contain calcium deposits and significantly hard collagen fibrous networks in order to test the efficacy of elastography for characterizing lesion compliance.

Devices for delivering compression and acquiring static elastography images will need to be borrowed from other areas of MRI research as well as current practices in interventional cardiology. Devices similar to guidewires or balloons that can be inserted in a catheter will be essential for delivering indentation to the surface of CTOs in vivo. Load cells can be integrated into the tip of a device to measure the pressure exerted by indentation. Additionally, improved coils and imaging devices
will help improve the technique. Future work on the development of forward-looking intravascular coils will be essential for providing displacement images of CTOs with improved resolution [27].
References


