Chapter 2 : Human Health Significance

In this chapter, the role diagnostic medical ultrasound plays in addressing public health needs related to carotid plaque burden are discussed. Specifically, focus is placed on stroke or transient ischemic attacks (TIA) due to carotid atherosclerotic disease with increased vessel stenosis or embolization being primary causative factors. First, the prevalence and pathology of stroke is described. The current status of prevention and treatment measures are reviewed. Current methods to assess stroke risk are reviewed by describing these techniques, the physiological target they aim to quantify, status of development, and effectiveness. In this chapter, focus is placed primarily on imaging methods. A thorough literature review describes research efforts in medical ultrasound imaging for carotid plaque detection and characterization. Finally, the approach taken in this dissertation is presented in the context of prior research efforts.

2.1 Etiology of stroke and the role of atherosclerotic plaque

Stroke is a disease that effects the most defining and critical organ of the human body, the brain. Stroke is a result of prolonged hypoxia to neural tissue resulting in cell death that can occur because of infarction, hemorrhage, or subarachnoid hemorrhage [1]. Symptoms include compromised movement, speech, cognition, and death. Location and extent of neuronal injury determine the resulting neuronal dysfunction. While stroke is an acute ischemic cerebrovascular event with long lasting effects, there are similar ischemic cerebrovascular pathologies with

different time-courses. For example, transient ischemic attacks (TIA), usually last from 2-15 minutes. They result in cerebral impairment that subsides in under twenty-four hours [1]. In addition, there also may be chronic ischemic events resulting from microemboli that may explain some dementias due to vascular cognitive impairment [1]. According to Hachinski et al., one in three people will experience stroke or dementia, but twice as many individuals will incur cognitive impairment to a lesser degree [2]. Hachinski reported on the efforts of the National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network's (CSN) effort to create a standard way to identify and report on the degree of cognitive impairment. Vascular cognitive impairment is likely to become a productive area of future research since it has been a largely unrecognized detriment to human health. Its widespread presence and increasing importance to quality of life as life expectancy continues to be prolonged cannot be understated [2, 3]. Recent evidence has also emerged suggesting that cerebral emboli may be a cause or accelerator for cognitive decline associated with Alzheimer's disease [4, 5, 6]. Some researchers have termed the Alzheimer's/vascular disease combination as 'mixed dementia', and it has gained increased recognition as the cause of mild cognitive impairment observed with aging [7, 8, 9]. Mild cognitive impairment, which may be a precursor to Alzheimer's, is thought to occur in 10 to 20 percent of the elderly. Alzheimer's disease is one of the fastest growing causes of death in the United States: the number of deaths per year increased by 47% from 2000 to 2006 [10]. Furthermore, a correlation between migraine and ischemic stroke has led to the suggestion that embolic ischemia may increase migraine risk [11, 12, 13]. For example, Jesurum et al. [14] found that migraine with aura can be relieved when the source of ischemia causing emboli, a right-to-left shunt via a patent foramen ovale (PFO), is closed even partially with surgery.

While the effects of stroke are varied, there are only a few basic causes. The pathogenesis of stroke can be classified into four categories [1], namely: brain hemorrhage, subarachnoid hemorrhage, intracranial hemorrhage from an arteriovenous malformation, and brain infarction, which is also referenced as *ischemic stroke*. Mechanisms of cerebral infarction are further divided into subcategories, namely, thrombotic, embolic, and hemodynamic. Thrombotic infarction usually occurs with a thrombosis that forms around an atherosclerotic plaque, which occludes blood flow. This can occur with the larger cerebral arteries that possess extensive cerebrovascular disease.

Emboli causing brain infarction can have many origins. One source of emboli is the heart. Cardio-embolic stroke can be due to many conditions. Atrial fibrillation, recent myocardial infarction, congestive heart failure, valve disease or mechanical valve replacement can result in thrombosis with free passage to the brain. Strokes that were previously labeled idiopathic, paradoxical, or crypotogenic, are now thought to be primarily caused by a patent foramen ovale (PFO). A PFO occurs when the shunt in the fetus's atrial septum, which bypasses circulation to the lungs, fails to close after birth. A clot within the shunt or a peripheral venous thrombus that has bypassed the lungs could then find its way to cerebral tissue [1]. Finally, hemodynamic brain infarctions refer to hypoperfusion due to plaque stenosis or occlusion.

The stroke pathogenesis targeted in this work are primarily emboli originating from carotid plaque. This is one of the more common causes of stroke, underlying over 50% of strokes [15, 16]. The carotid artery is the main conduit of blood to the brain. In humans there is a left and right common carotid artery (CCA) that bifurcates in the upper neck into the internal carotid artery (ICA) and the external carotid artery (ECA). The diameter of the CCA is typically 0.5 mm although age and atherosclerosis can increase diameter through remodeling [17]. Large

muscular arteries are prone to develop atherosclerosis, and areas of hemodynamic disturbance are inherently susceptible to atherosclerosis, so plaque invariably develops around the bifurcation at the carotid bulb.

Carotid endarterectomy (CEA) is a surgery performed to reduce the risk of stroke from carotid atherosclerosis. It involves accessing the carotid in the neck near the carotid bulb. An incision is made longitudinally along the carotid, the plaque is scraped out, and the surgical site closed. CEA has been performed since 1954, and approximately one million surgeries have been performed between 1974 to 1985 [18]. Two large scale clinical trials were performed in the 1990s to test the safety and effectiveness of CEA, namely the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and the Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS) [19, 20, 18]. The metric for stroke risk used during the trials was the extent of stenosis. In patients with severe stenosis, defined to be 70 to 99%, the results demonstrated that CEA had significant ipsilateral benefit over medical treatment alone. However, stenosis from 50 to 69% had a moderate reduction in stroke risk, and there was no significant statistical benefit for patients with stenosis less than 50%. It was estimated that for patients with 50 to 69% stenosis, it took 15 surgeries to prevent one stroke in a five year period. Another study from the European Carotid Surgery Trial concluded that CEA was beneficial in only 16% of patients with 70-99% stenosis. [21]

Surgical complications and costs also solicit increased specificity in the selection of CEA candidates. In general, CEA has low rates of death and morbidity, but patients with a history of tobacco use, substantial angina, contralateral occlusion, or preoperative TIA have elevated risk of complications [22]. Most patients with significant carotid plaques are older and have other symptoms of cardiovascular disease, and the surgical risks must be weighed carefully. Yet,

stroke is a widespread detriment to public health and increased sensitivity to stroke risk is desired for appropriate prophylactic treatments. The risk factors for stroke are well known and include diabetes, hypercholesterolemia, hypertension, coronary heart disease, tobacco use, large artery disease, atrial fibrillation, PFO or atrial septal defect, and cervical artery dissection [23]. In 2005, 780 thousand new cases of stroke occurred in the United States [24]. There were 150 thousand deaths in the United States during 2004. While mortality rates have decreased over the years, morbidity is a public health and financial burden because of the recovery and rehabilitation required. Around 5.8 million stroke survivors are alive today. It is estimated that the direct medical costs in the United States due to stroke were $43.7 billion dollars in 2008 [24]. Therefore, the most effective method of addressing stroke is prevention. The purpose of the proposed research is to develop methods to more effectively identify and stratify stroke risk from embolic carotid plaque.

2.2 Clinical carotid ultrasound and plaque characterization

2.2.1 Vulnerable plaque

Vulnerable plaque is defined as "a plaque which has a high tendency to cause ischemic events due to cerebral emboli originating from a thrombus on the plaque surface or from plaque rupture." [25] There have been many hypotheses presented on the property or properties that make a plaque vulnerable. These include a large lipid necrotic core or intraplaque hemorrhage with a thin overlying fibrous cap, inflammatory infiltrate, and other factors [26].

Morphologically, the appearance of ulceration is also associated with plaque vulnerability [27, 28]. Ulceration is an irregularity in the surface of the plaque. In addition to inducing stress concentrations, ulcerations expose thrombogenic layers of the plaque and provide a surface for thrombus to develop on. Another factor that can lead to increased plaque vulnerability is

angiogenesis. Neoangiogensis refers to the formation of small blood vessels from the vasa vasorum that result from large and complex atherogenesis [29]. These small fissures in the plaque also create additional stress concentrations. Plaques that appear heterogeneous in composition as indicated by ultrasound B-Mode echogenicity are also associated with amaurosis fugax, TIA, and stroke symptoms [27, 30, 31]. Heterogeneity can cause stress concentrations due to material property distribution discontinuity, similarly to how ulcerations or neovascularization can cause stress concentrations due to morphological discontinuities. Thrombus in the plaque is considered a risk for future rupture since it not only can result in mechanically weak conditions but also is a marker of previous rupture events. Thrombus formation, healing, and remodeling can be an ongoing process in vulnerable plaques.

Chemical markers of inflammation are also associated with plaque instability [32, 33]. These markers are used for the justification and development of pharmacological treatments such as statins. These markers tag for macrophage infiltration, the presence of matrix metalloproteinase-9 (MMP-9), and the presence of inflammation. Macrophage infiltration plays a role in plaque formation along with indicating an acute inflammatory response [34, 35]. Buildup of lipid initiates inside macrophages that then distend until they cannot escape into the circulation, forming 'foam cells', and eventually lipid crystals. Macrophages secrete proteolytic enzymes that weaken the extracellular matrix. MMP-9 functions as an enzyme that breaks down the extracellular matrix [36]. As such, it plays a role in weakening the plaque material, which can have a positive-feedback influence on the presence of MMP-9. Smooth muscle cells usually produce extra-cellular collagen that strengthens, though it can also produce the elastases capesin S or K in diseased intima [37, 38].

Finally, while all these factors can make plaques intrinsically vulnerable to rupture, rupture

is caused by extrinsic hemodynamic forces [26, 39]. Computational finite element analysis has shown that peak wall shear stress is roughly proportional to flow rate at the carotid bifurcation in healthy arteries [40]. Cyclic hemodynamic pulse pressure has been associated with carotid plaque ulceration [41]. Hypertension, as quantified with central systolic blood pressure, correlates with ischemia as quantified with fluid-attenuated inversion recovery (FLAIR) MRI images, where the white matter hyper-intensities correlate independently from carotid plaque score [42]. Turbulent flow resulting from severe stenosis can increase root mean square pressure fluctuations by 3.6 fold when stenosis increases from 80 to 90% [43]. Hemodynamic forces vary from patient to patient with hypertension, pulsatility, and turbulence influenced by the bifurcation and plaque morphology.

All these factors that have been intuitively associated with plaque vulnerability are explained formally by a quantity arising from solid mechanics models of the underlying physical behavior, local stress concentration. Stress concentrators have received exhaustive attention in the Materials Science and Engineering discipline because of their relationship to material failure. They define a *stress concentration factor* to be [44]

$$K = \frac{\sigma_{max}}{\sigma_{avg}}$$

Eqn. 2.1

The stress concentration factor, K, is the maximum stress caused by the disturbance in uniformity, σ_{max}, divided by the reference stress, σ_{avg}. This concept is relevant not only to industrial materials such as metals and ceramics, but biological tissues including plaque [45].

2.2.2 Plaque characterization with other methods and imaging modalities

Ultrasound is currently the most common method for plaque investigation because it is noninvasive, easily accessible, and has a relatively low cost. While most prevalent clinically, other methods have a clinical and research role in determining plaque vulnerability.

2.2.2.1 Histology

Histological classification of excised plaques have shown that hemorrhage, ulceration, and lipid rich plaques have an association with amaurosis fugax, TIA, or stroke. [27] Fresh thrombi, especially, have a connection with ischemic infarction. [29] Also, as previously mentioned, inflammatory markers are related to stroke symptoms. Histology is the most common gold standard for imaging modalities that try to determine tissue composition, ulceration, microstructure, and biochemical markers.

2.2.2.2 Computed Tomography

Angiography is the current gold standard for quantifying stenosis, and the high resolution is good for identifying ulcerations [19, 46]. Single slice computed tomography (CT) has had limited success in carotid plaque classification [47], but recently multidetector-row computed tomography (MRCT) have attempted to quantify total plaque volume, calcification, fibrous, and lipid or hemorrhage areas [48, 49].

2.2.2.3 Magnetic Resonance Imaging

High resolution magnetic resonance imaging (MRI) has better composition determination capabilities than MRCT because of the increased soft tissue contrast [50, 25, 51, 52, 53, 54]. This contrast is not only used to identify volume and degree of stenosis but also provides a noninvasive method to identify components of lipid, fibrous, calcium, or thrombus. Relative to

the surrounding muscle, calcium appears hypointense on T_1-weighted, very hypointense on proton-density weighted, and very hypointense on T_2-weighted images. Lipids are very hyperintense on T_1-weighted, hyperintense on proton-density weighted, and hypointense on T_2-weighted images. Finally, fibrous tissue is isointense to slightly hyperintense on all three parameter-weighted images. T_1 shortening causing increased signal intensity is associated with the protein-water interactions of the extracellular matrix content found in fibrous tissue. A short T_2, which causes low signal intensity in T_2-weighted images, is found in primarily lipid areas where there is increased interaction between free and bound water. The calcium areas will have low signal intensity because of low proton density and diffusion-mediated susceptibility effects. [55] The calcium susceptibility and paramagnetic ferric iron in hemorrhage may alter atherosclerotic appearance in 3.0 T magnets slightly, but the general characteristics still apply from 1.5 T magnets. [56] In a study of *ex-vivo* plaque specimens, Fabiano et al. found that 1.5-T MRI had sensitivities and specificities of 92% and 74% for the lipid core, 82% and 94% for fibrous tissue, 72% and 87% for fibrous/loose connective tissue, and 98% and 99% for calcifications [52].

The quality of MRI images of the carotid bifurcation will continue to improve as hardware, excitation sequences, and image processing is modified for this application. Balu et al. indicated a 1.7 fold improvement in SNR and larger coverage with a 8 channel phased array coil at 3T [57]. In a study of 60 patients, high resolution MRI was able to detect greater plaque hemorrhage in acute symptomatic vs. recently symptomatic vs. asymptomatic patients [58]. The application of black-blood MR imaging sequences increases the detection of ulceration [59]. Even though MRI imaging of composition holds promise, there is room for improvement: an attempt to correlate plaque morphology and composition as measured on both arteries of 40

patients did not find that the MRI images alone could not predict the severity of white matter ischemia as measured using FLAIR MRI images [60].

Contrast can be further improved and neovascularization visualized with contrast-enhanced MRI [61]. Since methemoglobin is associated with thrombus and hemorrhage and with a shortening of T_1, intraplaque hemorrhage can be detected with MRI [62]. Another thrombus detecting MRI agent is the fibrin targeted peptide EP-2104R. [63] Thrombus age can be inferred from T_1-weighted or T_2-weighted signal intensity, although thrombus generally has better T_1 intensity. [64] The gadolinium-based MRI contrast agent P947 MMPs may be a tool for detecting plaque inflammation [65].

Another MRI functional imaging approach is strain imaging. The technique used to calculate displacements in MR strain imaging is similar to the technique used to calculate blood velocity in phase-contrast magnetic resonance angiography. Dephasing that occurs during a bipolar gradient is proportional to the displacement of tissue. Early work studied the porcine aorta and found that when displacements estimated were compared to fiducial markers on the luminal wall, a strain of 10% would have an error standard deviation of 3.6% [66]. In a study of *ex-vivo* porcine aortas comparing a control group to renovascular hypertension group, it was found that the Young's Modulus-wall thickness product, derived from MR strain images, differentiated the hypertensive group because of the increased wall stiffness [67]. Lin et al. used displacement encoding with stimulated echoes (DENSE) pulse sequence to get the circumferential strain of the carotid artery [68]. High temporal resolution is obtained by utilizing steady-state free-precession (SSFP) along with high in-plane resolution, 0.6 mm. Good repeatability was seen between acquisitions at 1.5 T and 3 T. Changes in circumferential strain can even be observed in the aorta of a murine model of atherosclerosis when high field strength

MRI is applied [69].

2.2.2.4 Nuclear imaging

Plaque inflammation is targeted in many of the newer nuclear imaging techniques [70]. ^{18}F-FDG positron emission tomography (PET) detects the increased glycolytic activity of inflammatory cells. [71, 72, 73] Single-photon positron emission computed tomography (SPECT) imaging can be performed to trace oxidized low density lipoproteins (^{99m}Tc-LDL), or apoptosis (^{99m}Tc-annexin A5). [74, 75, 76, 77] Annovazzi et. al. have attempted to use ^{99m}Tc-IL2 scintigraphy to detect chronic inflammatory response have indicated that T-cell and macrophage activation as a marker for Crohn's disease [78]. ^{111}In platelet scintigraphy is sensitive to thrombosis, but it cannot distinguish other tissue types [79].

2.2.2.5 Thermal

Increased metabolic activity associated with inflammation can be detected with a needle thermistor, although this requires interrogation with a catheter, which is an invasive procedure. Inflammation is associated with thrombosis generation on both ruptured and non-ruptured surfaces [80]. In a study of 50 CEA samples, Casscells et al. found that some plaques have focal regions that are warmer by 0.4-2.2 ºC, and they can be very close to one another, less than 1 mm apart [80]. Increased cell density correlated with macrophage cell density and proximity to the luminal surface. In general, the thermal profile is heterogeneous. Temperature is also found to be higher in areas where local pH is lower, and it is inversely correlated with smooth muscle cell density [81].

There are two methods to measure temperature variations *in vivo*: using either thermistors or infrared techniques. A thermistor placed at the tip of a catheter must come into direct contact

with tissue's luminal surface. A fiber-optic cable in a catheter can transmit infrared energy that indicates local temperature. In both cases, blood flow may redistribute local spikes in temperature [82].

2.2.2.6 Optical

There have been a variety of optical techniques that have demonstrated diagnostic capabilities, which measure various optical characteristics of the plaque. Like thermal methods, these methods require interrogation with a catheter because they generally have lower penetration than the other imaging modalities. On the other hand, they have higher resolution than other modalities, which is important for such small tissue volumes.

Intravascular optical coherence tomography (OCT) is a catheter based method that provides limited penetration, but very high resolution, on the order of 10 μm axially and 20 μm laterally [83]. Sensitivity and specificity rates for composition classification range from 71% and 79% to 97% and 98% [83]. Lipid and necrotic core have low optical attenuation, while fibrous and calcified tissue have higher attenuation [84].

Time-resolved fluorescence spectroscopy (TRFS) is another optical technique that is used in conjunction with intravascular ultrasound (IVUS) [85, 86]. Anatomical guidance is provided by IVUS which is registered with the TRFS signal. TRFS detects auto-fluorescence from elastic, collagen, lipids, and by-products of inflammatory processes to characterize the local biochemical composition.

A method that focuses on collagen content is polarization-sensitive OCT (PSOCT) [87]. Many different types of collagen fibers, primarily Type I and Type III, provide the majority of tensile strength and elasticity in healthy arteries [88]. While smooth muscle cells migrate from

the media to intima in order to increase extracellular collagen during atherosclerosis, MMPs cause proteolysis of the collagen and apoptosis of intimal smooth muscle cells resulting in a net loss of collagen content [89]. In addition to high resolution plaque microstructure from OCT, PSOCT measures tissue bi-refringence. This behavior manifests itself as changes in back-reflected intensity when polarized light passes through anisotropic material such as organized collagen or smooth muscle cell actin-myosin in atherosclerotic plaque [87].

Laser speckle is generally considered a source of noise in optical imaging, but the time-dependent characteristics of the speckle are targeted in laser speckle imaging (LSI) [87]. Speckle will change because of Brownian motion of suspended particles in the tissue. The motility of particles depends on the viscoelastic properties of the medium, which is related to plaque vulnerability. Images related to local viscoelastic properties are made by quantifying the speckle decorrelation time constant.

Raman spectroscopy is a method that measures the weak scattered signal from a laser light that shifts in frequency due to interactions with characteristic molecular vibrations and rotations [90]. Spectra provide a chemical footprint of biochemical composition. Recent developments in optical fiber technology and small diameter probes with sufficient filtering capabilities enable real-time *in vivo* acquisition [91]. The sensitivity and specificity rates for determining carotid and femoral plaque composition were found to be 79% and 85%, respectively [91]. Near-infrared (NIR) spectroscopy is similar to Raman spectroscopy, but investigates the absorbance at wavelengths from 400 to 2400 nm [92]. The defining characteristics of tissue components in these situations can be determined empirically by applying a histology-based training set on principal component analysis or other methods to components of the spectra [93].

Finally, OCT elastography can generate strain images of vascular tissue [94]. Unlike MRI

strain imaging but similar to ultrasound strain imaging, discussed later, OCT elastography is essentially a deformable image registration problem [94, 95, 96]. Again, a clear advantage of OCT is the resolution for profiling these small inhomogeneous tissues. In fact, the precision of OCT is so high that deformation in the skin due to pressure waves in the audible range has been imaged [97]. While resolution is more ideal than other modalities, depth of penetration may limit application to coronary plaques and preclude carotid plaques. On the other hand, if behavior proximal to the lumen proves to be the area of diagnostic interest, the depth of penetration would be sufficient.

2.2.3 Plaque characterization with diagnostic ultrasound

2.2.3.1 B-Mode intensity and textural features

Vulnerability assessment with ultrasound focuses on many of the same parameters examined using other modalities such as MRI. Stenosis is currently assessed with Doppler velocity measurements, along with color-flow and B-mode imaging. After measuring peak systolic velocity, end-diastolic velocity, and pre and post-stenotic ratios, a percent stenosis can be implied based on these measurements [98, 99, 100]. Many radiologists also try to access the plaque through visual inspection of the B-mode images. Echolucent plaque are considered more vulnerable because lipid and hemorrhage are often echolucent. [101, 27, 102, 31, 103, 104] In contrast, homogeneous calcification is thought to cause plaque stabilization [105]. While calcified tissue is usually echogenic, fibrous plaque can also be echolucent. Additionally, shadowing and other effects can make echogenicity difficult to interpret. Nonetheless, echogenicity has been the most commonly tested and most widely used metric of vulnerability. Ultrasound echogenicity is assessed via direct visual examination of B-mode images. Some authors prefer to use the Gray-Weale scale for echogenicity which stratifies echogenicity into

five types ranging from echolucent to calcified with shadowing [106]. A slight improvement to visual examination are computer-assisted gray-scale median (GSM) measurements [107, 108, 109]. These results are semi-quantitative since they rely on the settings and properties of the ultrasound scanning device. Plaque intensities are normalized to intraluminal blood and adventitia. When the definition of thresholds and regions of interest is forced and quantitative intensity measurements are made, objectivity is increased [110]. Additionally, the quality of B-mode images have recently been improved with angular compounding [111].

More sophisticated analysis of B-mode properties focuses on factors other than local intensity, broadly termed 'texture analysis'. Texture analysis has the aim of differentiating tissue composition and properties [112, 113, 114, 115, 116]. Texture analysis examines statistical parameters of the intensity, Fourier spectrum, Wavelet Transform, or other quantities in a local area, and statistical techniques are applied to empirically determine which parameters may differentiate tissue composition.

Morphologically, the appearance of ulceration is also associated with vulnerability [27]. Ulcerations are irregularities on the plaque surface. In a study monitoring patients over 6.2 years on 1,091 plaques, it was found that these irregularities or ulcerations increased stroke risk with a 2.7:1 hazard ratio [117]. Resolution and two dimensional imaging limitations with *in vivo* ultrasound make it difficult to consistently evaluate ulceration. It is more difficult to detect ulceration for plaques with increased stenosis. By comparing with results from histology, it was found that for plaque with >50% stenosis, the sensitivity for direct ulceration detection was only 41% [102]. However, the use of microbubble contrast agents improve surface definition by increasing contrast at the lumen border where it may otherwise be compromised by partial-volume effects [118].

Neoangiogenesis in large plaques also plays a role similar to ulceration as mechanical stress concentrators. Unlike surface ulcerations, neoangiogenesis compromises the tissue at a deeper level, making large ruptures more likely. These tiny vessels were previously undetectable with ultrasound, and they may now be visible when contrast agents are applied [119, 120]. Harmonic imaging of microbubbles allows visualization the vasa vasorum in atherosclerotic rabbit models [121]. In the future, ultrasound molecular imaging of atherosclerosis may be performed by targeting markers for neoangiogenesis or inflammation with microbubbles, acoustically active nanoparticles, or micro-particles like echogenic liposomes [120].

2.2.3.2 Radiofrequency signal based characterization

Quantitative ultrasound tissue characterization attempt to improve on simple B-mode texture analysis by removing system dependent features from an image to isolate tissue characteristics in the image [122]. These images attempt to show tissue properties that influence ultrasound propagation and scattering while removing effects such as the geometry and material makeup of the transducer or electronics of the imaging machine. This removes the burden of accounting for system effects from the observer and allows calculation at a precision equal to the precision of digitization instead of being limited to the dynamic range of the human eye. There are many aspects of ultrasound propagation and scattering, and the parameter to be measured and displayed can be chosen to elucidate a single aspect of the physics of acoustic propagation, such as the attenuation coefficient or effective scatterer size or density, or a combination of multiple aspects. Determining the most appropriate parameters depends on the ability to generate accurate and precise estimates of the parameter and on the amount of correlation between the parameter and the tissue state of interest. A parameter is most desireable if there is high contrast between healthy and diseased tissue states, the parameter can be estimated with a high signal-to-

noise ratio, and an image of the parameter has sufficient resolution to distinguish the structures present.

Various tissue characterization parameters have been utilized for plaque examination, including backscattered spectral slope, midband fit, intercept, minimum and maximum powers and their frequencies in the resulting spectra, along with the integrated backscatter, and attenuation slope parameters [123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134]. For example, lipid infiltrated and calcified tissue have a higher attenuation than fibrous plaque [135, 136, 137]. Also, integrated backscatter increases in magnitude from thrombic to lipidic to fibrous to calcified atherosclerotic plaques [133, 138, 127]. Additional parameters can be obtained through high frequency texture analysis [116] or simple integrated backscatter calculations [128, 134]. However, the quantities obtained in these methods is dependent on the machine and acquisition settings [135, 139]. Volcano Corporation has released a clinically available IVUS tissue characterization system they call Virtual Histology [140]. Their system measures local spectral parameters that have been statistically classified into tissue types to label tissue areas. S. Lori Bridal performed high-frequency plaque characterization with some of the most rigorous attention towards quantitative parameter estimation. Early work examined normal and atherosclerotic aorta *in vitro* [141, 125, 136]. Different quantities were examined: apparent integrated backscatter, attenuation slope, and attenuation at 37.5 MHz [125]. Integrated backscatter was highest for calcified regions and was significantly higher for collagen-lipidic and lipidic regions relative to normal media and dense collagen [136]. In following work on excised carotid plaques, Bridal suggested that discriminant analysis which incorporates multiple parameters, integrated backscatter, frequency dependence of backscatter, integrated attenuation and slope of attenuation, may be a more effective classifier than any single parameter [126].

Most of the ultrasonic tissue characterization methods on atherosclerotic plaque have used the method introduced by Lizzi to account for system characteristics [122]. In this method, a flat reflector, often made of acrylic or steel, is placed at various distances in front of the transducer, and the returned signal is recorded. The estimated power spectra is used to normalize the spectra obtained from the region of interest in tissue.

While this is an improvement, there are still inaccuracies inherent to the system approximation. The measurement is made in water, which does not exhibit scattering throughout the beam path as would generally occur *in vivo*, and water does not have the same attenuation properties as tissue. Furthermore, it relies on good alignment between the transducer and reflector, which is increasingly difficult at higher frequencies. Reference phantom based methods have been developed that ameliorate many of these inadequacies [142]. In this method, the signal from a reference phantom with well characterized properties is used in the spectral normalization instead of that of a flat reflector. The reference phantom method has been attempted at low frequencies on carotid plaques [143, 127], but has yet to be evaluated at higher frequencies. At lower frequencies, the small volume and heterogeneity of the tissue makes spectral estimation difficult.

2.2.3.3 Acoustic radiation force impulse (ARFI) imaging

An emerging ultrasound imaging technology is acoustic radiation force impulse (ARFI) imaging [144]. In this technique, a high-intensity acoustic impulse of short duration (0.03-1 ms) generates localized displacements in the tissue, which is is tracked with diagnostic pulse-echo signals following the pushing pulse [145]. The magnitude and time course of the displacement reflects the local mechanical environment. Preliminary results by Allen et. al. using an clinical external ultrasound transducers indicate that the magnitude of the ARFI displacement can be

used to differentiate plaque composition [145].

2.2.3.4 Strain imaging

2.2.3.4.1 Motivation

The interaction of morphology, composition, and pulse pressures can lead to high stress states, but the instability depends on mechanical system configuration as a whole [146, 147, 148, 149, 150, 151, 152]. P.D. Richardson performed seminal work examining this hypothesis, and he points out that rupture is a result of structural mechanics, fluid mechanics, plaque morphology, plaque micromechanical material properties, and MMPs [153, 154]. For example, large lipid pools can cause mechanical stresses, but these stresses are much more significant when the pool is closer to the lumen [110, 155]. D.L. Tang has created 2D and 3D fluid-structure interaction (FSI) based finite element analysis using MRI and IVUS based morphology and composition information [156, 157]. From this model, vulnerability is graded according to a computational plaque stress index based on the maximum principal stress [158]. Tang's research has shown that plaque wall stress was 126% higher in 5 ruptured plaques compared to 7 non-ruptured plaques for 12 patients that underwent CEA in one study and was found to have an 85% agreement rate with histopathological analysis in a second study [159, 160]. These studies also verify that markers traditionally considered for vulnerability such as morphology and composition also increase local stress/strain [152]. Similarily, Kock et al. found that MRI derived FSI models of carotid plaque showed elevated first principal stresses at areas of notorious risk [161]. These FEA studies are not limited to IVUS and MRI microstructure inputs; an OCT microstructure and composition derived model has shown stress extrema at locations known for rupture [162]. In a sophisticated FEA model derived from 3D IVUS coronary images, Yang et al. found that "cyclic bending, anisotropic material properties, pulsating pressure, plaque

structure, and axial stretch may affect critical stress/strain values in coronary plaques from 40% to 400% or more, depending on morphology, location, and contributing factors" [157]. Trivedi reached similar conclusions in an MR imaging-based computational analysis of 5 symptomatic and 5 asymptomatic patients: principal shear stress was higher in symptomatic plaques than in asymptomatic plaques [163]. Ohayon et al. used a FEA model generated from IVUS images taken during a coronary angioplasty procedure [164]. Morphology from an unloaded vessel state was obtained by injecting ATP, which caused a brief atrioventricular block. Locations of peak circumferential tensile stress were compared to locations of plaque rupture cause by the angioplasty, and they were found to correspond. In another case study, high shear stress was associated with the rupture and ulceration of a carotid artery plaque on an individual that had received serial MRI imaging. Computational fluid dynamics based on MRI structure and composition identified the location of high shear stress with the location of the ulcer [165]. Ulceration has been observed to be more common proximal to stenosis and more common for fatty plaques [46].

Inflammation may be part of a positive feedback process where mechanical tearing would stimulate a necrotic response that catabolizes the extracellular matrix, leading to further mechanical weakness at the site [166, 167, 168, 169, 170, 114, 35]. This is supported by a recent study comparing gene expression in calcified areas, often associated with stability, when compared to non-calcified areas. It was found that gene expression of factors that promote interleukin 8 and monocyte chemoattractant protein 1, associated with inflammation and thereby vulnerability, were higher in non-calcified areas [171]. Lee et al. performed a mechanical finite element analysis simulation using the morphology of 12 unruptured human coronary lesions and assumed appropriate mechanical material properties for the tissue components. When comparing

images of immunoreactive MMP-1, they found that high stress regions had twice the MMP-1 expression as low stress regions [172]. Elevated levels of highly sensitive C-reactive protein, another inflammation marker, correlates with increased intima-media thickness [173]. These high stress states may also lead to fatigue failure [174, 175, 176].

Stress-stretch curves ([177] Fig. 6) were created by Holzapfel during a tensile test on diseased intima sectioned from cadaver iliac arteries. As the graphs progresses from the origin, the stretch and stress is increased on the tissue until the tissue fractures at the curve's termination. The point in the curve farthest from the origin defines the stretch at which failure occurs, ultimate tensile stretch λ_{ult}, and the stress at which failure occurs, ultimate tensile stress, σ_{ult}.

Many of the atherosclerosis diagnostic imaging techniques discussed focus on imaging of plaque composition, which determines the elastic modulus. While the distribution of material properties certainly affects stress and strain state, the sensitivity of stress and strain at the site of rupture in a diseased artery can be low. In a computational analysis, it was found that +/- 50% variation in elastic modulus leads to less than a 10% change in stress at the site of rupture [178]. In contrast, strain imaging has the potential to directly image the feature of interest.

Recently, ultrasonic strain imaging techniques have been applied to imaging of the carotid arteries. Strain imaging creates an *in vivo* map of strain, a feature directly related to tissue stretch or contraction, drawn on the abscissa in the mechanical tests in [177]. Vulnerable plaques have a higher extensibility and a lower ultimate stress [35, 177]. Therefore, strain imaging directly measures a parameter that determines how close a plaque is to failure [160]. This contrasts with other characterization methods that focus on parameters like composition, which may affect strain in a secondary manner and may be system dependent. Strain imaging directly measures the effect of multiple stress concentrators including composition, ulceration,

morphology, neovascularization, and hemodynamics.

2.2.3.4.2 IVUS strain imaging

Most of the initial arterial strain imaging studies were performed with IVUS by de Korte [179, 180, 181, 182]. IVUS imaging differs from external ultrasound transducers in its insonification routine-- IVUS transducers are placed in a small catheter and a set of A-lines are emitted radially as the transducer is mechanically rotated or electronically steered. The high frequencies in IVUS, from 20 MHz to 60 MHz, provide higher resolution images but lower penetration, and it is more common to find it applied to coronary arteries. Shapo et al. reported IVUS strain measurements *in vivo* where strain was induced with an angioplasty balloon [183]. De Korte reported on strain measurements with IVUS on tissue-mimicking phantoms by performing one-dimensional correlation with peak interpolation [179]. Adaptive and iterative estimation of local scaling factors has been added to simple one-dimensional cross-correlation techniques [184]. Two dimensional correlation windows were utilized by Shapo et al. [183] and Ryan and Foster [185], with phase sensitive analysis and phase insensitive analysis performed by the former and latter. Maurice et al. applied his motion tracking algorithm, the Lagrangian speckle model estimator (LSME) [186]. Instead of block-matching techniques, Wan et al. applied an optical flow method to estimate tissue motion [187]. Liang et al. applied a Levenberg-Marquardt nonlinear minimization technique to a cubic B-spline model of displacement governed by a cost function that contained terms for intensity fidelity, a sum of squared difference, and strain smoothness, a sum of strain gradients [188].

The feasibility of *in vivo* application was examined on 12 patients undergoing angioplasty, and it was found that strain in calcified material (0.20% +/- 0.07) was smaller than non-calcified tissue (0.51% +/- 0.20) [189]. During that study, it was revealed that catheter movement due to

cardiac motion and blood flow impede strain estimation, so strain estimation was gated to points in late diastole. Catheter movement with blood flow can make it difficult to determine the orientation of the transducer and to differentiate between catheter and artery movement, although movement compensation schemes have been described [190, 191]. In the technique described by Shapo et al., motion is constrained with the angioplasty balloon, but strains are also measured relative to an artery's geometric center that is calculated from segmentation of the lumen [183]. Schaar et al. described the effectiveness of what they termed palpography, an elastogram that only investigates the first 450 μm at the lumen boundary since this is where rupture may occur [192]. Comparison of mean strain values and histology revealed higher strain colocalized with fatty areas and areas with increased concentration of macrophages [193]. In a study of 54 cross sections validated by histology, palpography was found to have a sensitivity of 88% and a specificity of 89% [194]. In a study of an atherosclerotic Yucatan mini-pigs, it was found that mean strain correlated with tissue type and localized high strain values correlated with indicators of inflammation, macrophages [195]. The nature of IVUS acquisition results in 2D images of the vessel cross-section, but catheter pullback methods can be performed to generate a 3D profile of plaques that are typically spatially variant [196]. In the 2004 study by Schaar et al., it was found the that number of deformable plaque locations had a negative correlation with the stability of angina and a positive correlation with the level of C-reactive protein, a marker of inflammation [196].

2.2.3.4.3 Thermal strain imaging

A slightly different approach is thermal strain imaging, which has recently been examined as a method for characterizing plaque composition [197, 198]. Strain in the ultrasound signal is a result of the tissue's coefficient of thermal expansion and the change in sound speed that occurs

with temperature. Temperature changes on the order of 1º C can be detected [197]. The temperature change is induced by microwave radiation or ultrasound energy absorption. In the study by Kim et al., ultrasound signal motion tracking with a high frequency (50 MHz) transducer was employed to monitor ultrasound induced thermal expansion on *in vitro* tissue [198]. Yet, it remains to be seen how this technique can be applied *in vivo* where tissue movement, from both bulk motion and mechanical strain, is significant [199].

The thermal strain effect was used to estimate the spatio-temporal temperature changes that occur with another plaque characterization imaging technique, photoacoustic imaging [200]. During intravascular photoacoustic imaging (IVPA), tissue is irradiated with a sub-ablation threshold laser at 20 Hz [201]. Optical absorption of the laser energy results in thermoelastic expansion of the tissue and subsequent generation of acoustic waves. The acoustic waves are detected with an IVUS transducer, and a spatial map of optical absorption reconstructed. This method allows for imaging at optical resolutions but with a depth of penetration that is closer to ultrasound. By exciting tissue with multiple wavelengths in the 680 - 900 nm range, the absorption properties across a spectrum can be used to differentiate fibrous and lipid plaque components [202].

2.2.3.4.4 External transducer strain imaging

Recently, strain imaging with external ultrasound imaging using linear array transducers has been attempted. While the resolution of external ultrasound is much lower, it is noninvasive and appropriate for general stroke risk screening purposes.

The first plaque strain characterization based on an external clinical transducer, a 7.0 MHz Acuson linear array, was reported by Meairs and Hennerici in 1999 [45]. 4D *in vivo* characterization was performed on carotid artery plaques of 23 asymptomatic and 22

symptomatic patients by scanning the linear array with an ECG gated stepper motor. The motion estimator was a hierarchical algorithm applied to Laplacian filtered images that minimized a sum-of-squared differences cost function with the Gauss-Newton method. They found that even though no significant differences in echogenicity or surface structure between symptomatic and asymptomatic cases could be found, symptomatic plaques demonstrated inherent plaque movement relative to asymptomatic plaques. Meairs evaluated two parameters: maximal surface velocity (MSV) and maximal discrepant surface velocity (MDSV). They found that MSV, which is termed local displacement in other literature that does not account the inter-frame time period, did not have significant differences between symptomatic and asymptomatic cases. In contract, MDSV, which is termed local strain in other literature, did show a statistically significant difference between symptomatic and asymptomatic patients.

Later, Bang et al. implemented a motion tracking algorithm similar to what is found in the elastography literature [203, 204], though they appeared to be unaware of that body of literature [205, 206]. That is, a 2D cross correlation is calculated between small windows of tissue at frames contiguous in time for different translations of the window. The local displacement is assumed to correspond to the translation with highest correlation. The precision of the correlation function can be improved with interpolation of the correlation matrix. Their images appeared to be quite noisy, and the fidelity of their method can not be determined because there was no rigorous validation. However, they commented on a few challenges that exist in the image analysis. First, the selection of optimal correlation window size is required for good performance. Second, a low framerate results in significant out-of-plane motion that diminishes tracking performance.

Kanai et al. performed regional plaque displacement tracking in images acquired along the

longitudinal plane using a phase tracking method previously used in cardiac strain applications [207, 208, 209]. This method was reported to have a precision of approximately 0.5 μm observed with a rubber plate in a water tank [207].

Recent efforts working towards noninvasive strain estimation come from The University of Montreal and Montreal Hospital, Quebec. They refer to their motion tracking algorithm as the Lagrangian speckle model estimator (LSME) [210, 211]. The algorithm is similar to the approach taken by Meairs and Hennerici; i.e. the local motion is formulated as a non-linear minimization problem where the cost function is a sum of squared difference in intensity. The optimization algorithm utilized in this case is the Levenberg-Marquardt method instead of the Gauss-Newton method, and this motion model is a full affine transform instead of a simple translation. The translation portion of the problem is determined from the peak of the 2D cross-correlation, while determination of the parameters of the linear transformation (scaling, rotation, and shearing) matrix is treated as a nonlinear optimization problem. In order for the model to incorporate decorrelation noise in their model, they have tried adding brightness offset and contrast parameters to the affine model [212]. They have also used an optical flow approach [213]. Unlike other methods where strains are calculated from the displacement slope of adjacent tracking points, strains are calculated from components of the linear transformation matrix of a single tracking point. Their method was applied to 16 subjects without carotid atherosclerosis binned into four age categories, [40-49], [50-59], [60-69], and [70-79] years old. While they were able to obtain reproducibility between left and right carotid and scanning from two independent radiologists, a statistically significant difference was not observed across age groups [214].

The de Korte group from the Netherlands, whose efforts were previously focused on IVUS

strain imaging, as described earlier, have recently forayed into the non-invasive strain imaging area [215]. A 2-D cross-correlation motion tracking technique was applied to a cylindrical phantom and some *in vivo* test cases have been reported. A challenge noted in transverse images of the vessel mimicking phantom were the refraction artifact that occurs in this configuration. The speed of sound change coupled with the curvature of the artery's inner wall redirects propagation of the ultrasound beam. Observed motion distal to the lumen-artery interface can then actually be due to movement of the lumen-artery interface instead of local tissue, or the refracted signal may not return to the transducer, which makes motion tracking a challenge.

Recently, Shi et al. from our laboratory presented preliminary results from diagnostic characterization of carotid endarterectory patients with strain imaging [216]. A hierarchical 2D cross-correlation method was used for motion tracking. The results indicated that the estimated axial strain values correlated with calcified and non-calcified B-Mode presentation and that strain indices may differentiate symptomatic and asymptomatic cases.

2.2.3.4.5 Angular compounding

Quality in ultrasound strain images can potentially be improved with angular compounding [217]. Angular compounding is achieved by electronically steering the ultrasound beam with appropriate time delays applied to transducer array elements during the transmit phase. For B-Mode images, angular compounding provides a different view of tissue speckle, which in can be averaged to improve image quality. In strain imaging, a different realization of tissue scattering is again made available, but the observation of the strain tensor is also obtained in a different coordinate system. This is advantageous since ultrasound image resolution in inherently highly anisotropic; resolution is inherently high along the axis of beam propagation, but low lateral to the beam propagation direction. As a result, the quality of displacement estimates in the beam

(axial) direction are better than that along the lateral direction. Angular compounding has the potential to improve image quality with an averaging effect, but also provides axial quality motion tracking when the beam is steered to that obtained in the lateral direction when the beam is not steered.

Preliminary work on applying angular compounding to strain images on transverse images of a hollow cylinder phantom have been performed by Hansen et al. [218]. However, a number of complications exist that have to be addressed before angular compounding of strain images of extensive carotid atherosclerosis *in vivo* would improve image quality.

First, there are practical limitations to the maximum angle that can be steered with linear array transducer technology. Grating lobe artifacts, which signifantly decrease image quality, will appear if the spacing between array elements are not small enough for a given excitation frequency and steering angle. As a consequence, steering angles on current high frequency linear array transducers are limited to approximately +/- 15º. Hansen et al. worked around this limitation to some extent by low pass filtering the signal at higher angles with a cutoff frequency corresponding to the frequency when grating lobes occur. This allowed them to steer up to +/- 45º without significant artifacts, but the removal of high frequency content decreases the advantage of tracking along the beam direction.

Secondly, the combination of multiple images may introduce more noise than signal in the composite image. The noise may be introduced by multiple factors. Averaging strains with a simple arithmetic mean of axial and lateral components may decrease quality in areas that were previously calculated with only the lateral component. Artifacts, due to refraction of the pulse at the curved arterial borders [215], may be compounded [218]. The manner by which the strain components are calculated and extracted from the strain tensor also plays a role. Additional

noise is introduced if an approach is taken such as the one proposed in Hansen et al., where the strain matrix is rotated to a particular orientation, and components are averaged at that orientation. This is because the orientation may not be the same in all compounded images. For example, if the prinicipal components (eigenvalues of the strain matrix) are averaged, they do not necessarily correspond to the same coordinate system orientation (eigenvectors of the strain matrix). It is natural to try to extract 'radial' and 'circumferential' components of the strain tensor when dealing with a transverse view of an artery, because these correspond to the direction of the principal components for a simple cylinder. However, determination of the radial and circumferential directions introduce additional noise since the center of the lumen is used as a reference [218] or the local curvature at the lumen-artery interface [68] must be determined for each image. Furthermore, radial and circumferential directions are not very meaningful when dealing with the structure of a complex plaque as opposed to a healthy artery. Most importantly, it remains to be determined if the registration and displacement compensation techniques are effective for the significant motion that occurs *in vivo*.

Even though strain imaging holds much promise in the detection of vulnerable plaque, its success depends on the ability to measure strain accurately, with a large dynamic range, and with minimal noise. The research presented in this dissertation focuses on the development of improved strain imaging algorithms and techniques and applies them to the diagnosis of stroke risk due to carotid plaque disruption.

2.3 References

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