Chapter 10 : Conclusions

10.1 Summary

This dissertation described diagnostic ultrasound methods for characterization of carotid atherosclerosis. Carotid characterization is important because of carotid plaque's role in stroke. Vulnerable carotid plaques generate emboli that cause cerebral ischemia. The purpose of *in vivo* ultrasonic characterization is to determine which plaques are likely to cause future events.

In the literature review, the imaging techniques that have been applied to this problem are examined. A number of modalities have tried to associate features of composition, ulceration, hemodynamic stress, inflammation, morphology, or the vasa vasorum with vascular vulnerability. By examining the theory of solid-body mechanics, it was hypothesized that the quantity that summarizes the combined effect of all the previously studied features is strain, a measure of the material deformation.

Noise due to out-of-plane motion, image decorrelation, discretization, and limited image frequency content make it difficult to robustly quantify plaque strain *in vivo*. A number of techniques were described to improve the robustness of the strain images. A Bayesian regularization technique was described that greatly improves the robustness of the tracked images. This regularization technique was parameterized by the amount of expected strain. An unbiased subsample displacement interpolation method that reduces bias errors, especially in the lateral direction, was explored. Furthermore, strain calculation was improved around the

discontinuity that can occur at the wall-lumen boundary by detecting and accounting for this discontinuity. The quality of the strain images were kept high by using a dynamic incremental frame skip, while an algorithm was presented to still obtain the incremental strain at equal time steps. A multi-level motion tracking framework further improved algorithm robustness. Tracking lower frequency image content with large matching-blocks reduced peaking-hopping errors. Search region reduction over levels also decreased peak-hopping errors. Inter-level scaling of the matching block improved overall tracking quality. In prior strain imaging work, obtaining all components of the strain tensor proved difficult because of the lower resolution in the lateral direction. Because of the algorithmic methods employed, effective quantification of all components of the 2D strain tensor was achieved. It was shown how the strain tensor can be represented with an elliptical glyph. New quantities derived from the strain tensor that have been used in other contexts as material failure criteria were proposed as indices of plaque vulnerability.

Five case studies were examined that demonstrated strain image features and how they correspond to different conditions associated with plaque vulnerability. A hypoechoic plaque, associated with soft, weak materials, exhibited high strain. High strain was also observed in a region where a plaque protruded into the lumen. In the third case, high strain was observed local to a post-stenotic region with turbulent flow. A large of amount of longitudinal deformation at the base of a plaque was also observed, which possibly may be attributed to the shape of the plaque or vasa vasorum. Finally, a plaque that had many abrupt transitions between calcified and soft areas was presented high strain in these transition regions.

Ex vivo plaque characterization methods were also explored with high-frequency quantitative ultrasound. Most quantitative methods require spectral information, and calculation

of a characteristic local power spectrum requires a window of relatively homogenous tissue. Since plaque is relatively small and heterogeneous, high transmit frequencies are desirable. Techniques for using a commercial high-frequency system to create 3D integrated backscatter coefficient images with the reference phantom method were developed. Experimental techniques for estimating the acoustic properties of the reference phantom were improved and adjusted from the low-frequency techniques.

Finally, transcranial Doppler ultrasound (TCD) was performed with the aim of detecting micro-emboli to validate strain image derived metrics of vulnerability. While microemboli were successfully detected, general confidence in the results was compromised by challenges such as motion artifacts. A number of approaches to improve the quality of TCD data were discussed.

10.2 Future Work

With a larger cohort of subject data, various measures of ischemic burden, such as TCD microembolic signals, can be used in the future to validate the hypothesis that carotid plaque strain is correlated with risk of adverse ischemic events. Not all subjects that receive carotid endarterectomy (CEA) have had previous ischemic events, and those that are classified as symptomatic as opposed to asymptomatic should be considered higher risk. Neural MRI data can be used to quantify atrophy and ischemic regions. Strain results can also be compared to neuropsychological assessments that index executive function and activation, visio-spatial ability, language and lexical retrieval, and memory and learning. It remains to be seen how effective ultrasound strain imaging is at differentiating high-risk plaque, and which strain metric or combination of metrics are the most effective.

Preliminary work has found that it is feasible to create closely spaced (50 μm), serial, longitudinal histopathological slides of an *in vitro* plaque. If these slides can be registered

against each other to create a 3D volume, the histopathological images can be registered against the high-frequency plaque volume. If the histopathological slides are segmented by composition, the correspondence between quantitative ultrasound image values and tissue types can be quantified. Also, a fully sampled 3D ultrasound volume may be used to determine the histopathological slices that correspond to the 2D *in vivo* ultrasound images.