The purpose of this work is to use noninvasive low cost methods to characterize the vascular perfusion of tissues for diagnosis. Since the wide clinical use of arterial and venous plethysmography to diagnose arterial and venous obstructive diseases, there has been controversy about whether the primary volume changes in tissue were due to changes in the volume of the major arteries and veins or to changes in the volume of the microcirculation.

Tissue Pulsatility Imaging of Brain

Traditional methods of plethysmography measured volume changes in an entire body part, including both major vessels and micro-vessels. The introduction of photo-plethysmography, showing both pulsatile changes in skin reflectivity with the cardiac cycle and phasic changes in reflectivity with the respiratory cycle, supported the concept that the volume changes were, at least in part, volume changes in the arterioles and venules. We have extended the study of the volume changes in arterials and venules to deeper tissues using ultrasonic strain measurement methods.

Tissue can be considered a composite structure of cells, interstitium, matrix and microvessels. We consider the cells and matrix to be of constant volume over periods of a minute. The interstitium is an extravascular, extra-cellular space containing saline and is a space which may expand with edema over periods longer than a minute. The intravascular volume has three regions, venular at low pressure, capillary and arteriolar at high pressure. Images of tissue are comprised of “voxels,” small volumes resolved by the method.

In ultrasound imaging, voxels are nearly cubes, 1 mm on each dimension. Microvessels (arterioles, capillaries and venules) are too small to resolve in 1 mm voxels. In each voxel the spacing of microvessels is about 0.1 mm, so there are about 1000 capillaries in each voxel. About 1% of tissue volume is capillaries, 1% is arterioles and small arteries, and 3% is venules and small veins. About 5% of each imaging sample volume contains blood in the microcirculation. Normally the tissue pressure is below the venous pressure, leaving the veins fully inflated. However, in regions at an elevation above the heart (above the right atrium) the veins and venules are collapsed. Whenever the local tissue pressure is below the local venous pressure, the venules are inflated; when the tissue pressure exceeds the venous pressure, the venules collapse.

We are developing ultrasonic and optical methods to measure percent volume changes in tissue. These methods can be used to determine both whether the microvascular volume in tissue is normal, elevated (from tumor angiogenesis), or reduced (from ischemia). They can also be used to detect elevated interstitial tissue pressures by determining the local venous pressure at which the local tissue volume changes from deflated to inflated. Of particular interest are tissues at high pressures, such as arterial walls and atherosclerotic plaques on those walls.

Transmural pressure is the difference between intravascular pressure and the surrounding tissue pressure. A model made of balloons representing the microcirculation and columns of fluid representing the venous pressure, arterial pressure and interstitial pressure demonstrates the principle that the tissue composite does not have a linear volume change as the tissue pressure rises, but there are sudden changes. As the interstitial pressure exceeds the venous pressure, the veins and venules collapse, reducing the tissue volume by 3% suddenly. Then, the volume changes little with increases in pressure until the arterial pressure is reached. At those pressures, the volume of the tissue pulsates, as arterial pressure rises above and drops below the interstitial...
pressure. This latter effect is the cause of large pulsations under a blood pressure cuff, because the blood pressure cuff, of course, controls the interstitial pressure.

**Atherosclerotic Plaque Neovascularization**

Applying these principles to the microcirculation providing nourishment to the cells within an atherosclerotic plaque, we are conducting a study of the effect of Bernoulli pressure depression due to high intra-stenotic velocities on carotid plaque pulsatile strain.

The vasa vasorum are a network of tiny arteries and veins on the outer wall of major blood vessels which penetrate into the wall to supply oxygen and nutrition to the vascular wall and remove metabolic waste products. In addition, these vessels penetrate through the arterial wall and into neovessels in the atherosclerotic plaques to provide nutrients and oxygen to the abnormal cells forming the plaque. The blood in the intraplaque neovessels is squeezed out in systole and inflates the neovessels in diastole.

We are developing an ultrasound examination method that can be performed through the skin of the neck to measure the strain (deformation) of these plaques due to the filling and emptying of the neovessels as the arterial pressure rises and falls with the cardiac cycle. By determining the arterial pressure when the neovessels inflate, the pressure in the vasa vasorum can be determined; the inflation volume is equal to the neovascular volume. Atherosclerotic carotid artery plaques which have a large neovascular volume are vulnerable to rupture, causing a stroke. The ultrasonic measurement developed in this project will differentiate plaques vulnerable to rupture from those that are stable. In this study we will measure the plaque strain in patients to provide a distribution of normal and abnormal strain values in the people who have stenotic atherosclerotic carotid artery plaques.

We expect the plaque strain waveform to deviate from the artery diametric waveform if the stenosis causes an arterial pressure drop; the waveform strain will mimic the pressure drop waveform and will be expansion in the proximal region of the plaque and contraction in the distal region of
Brain imaging studies show that people have many infarcts in other regions of the brain such as those associated with decision making, language, perception and memory which might not cause recognizable symptoms and might be missed on conventional neurological examination.

**Figure 2**: Carotid Plaque Vascularity Theory—A vulnerable atherosclerotic plaque is expected have a pulsatile strain waveform with a sudden inflations component in the upper right. **MIDDLE RIGHT WAVEFORMS**: UPPER: measured arterial diameter pulsatile waveform, LOWER: measured tangential wall strain waveform.

**Figure 3**: Inverse Plaque Strain Waveform at different locations in the plaque compared to the diametric waveform (black). If vascularization is absent and shear strain is absent, then the inverse radial plaque strain waveform will match the diametric strain waveform according to theory. Deviations indicate either neovascularization or shear strain.

**Figure 4**: Reproducibility of Plaque Strain between cardiac cycles.

**Figure 5**: 1000 examinations for carotid stenosis yield 16 cases with severe carotid stenosis; 3 of those will have carotid embolic stroke in 2 years if untreated. This project is designed to differentiate those who will have embolic stroke from those who will not. Nearly half of strokes come from carotid artery plaques (3 in this example). Other causes of stroke (5 in this example) include hemorrhage into the brain, emboli from the heart and paradoxical emboli from the venous system through a Patent Foramen Ovale (PFO).
Among the factors that increase the risk of stroke are symptoms of Transient Ischemic Attack (TIA), also called “mini stroke.” These are symptoms of sudden loss of sensation or motor control on one side of the body. From brain imaging studies, infarcts in the motor or sensory cortices in the brain can be associated with those symptoms. However, brain imaging studies show that people have many infarcts in other regions of the brain—such as those associated with decision making, language, perception and memory—which might not cause recognizable symptoms and might be missed on conventional neurological examination. Such infarcts, if detected, might help to improve identification of people with embolizing carotid plaques or other sources of emboli. We are attempting to conceive of low cost methods of screening to identify these “silent infarcts” without brain imaging.

**Ultrasound Reading Center for Carotid Stenosis**

Currently, all patients with high blood velocity in a carotid stenosis are recommended for treatment with endarterectomy or stent. If left untreated only 20% of those cases will have stroke.

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