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High-resolution Ultrasound Speckle Tracking May Detect Vascular Mechanical Wall Changes in Peripheral Artery Bypass Vein Grafts

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Abstract

We report the use of high-resolution, phase-sensitive ultrasound speckle tracking to measure the local vessel-wall strain in two subjects with artery-vein bypass grafts. In addition, we combined this technique with a free-hand pressure equalization procedure to elucidate the non-linear effects of blood pressure on vessel wall compliance. While conventional ultrasound imaging can be used to elucidate the mechanical properties of tissues within the body, it is constrained by comparatively lower resolution and inferential, rather than direct measurements of strain and by the small strain normally produced under physiologic pressure in highly nonlinear structures such as arteries. One of our subjects was examined both before and after developing stenosis 3 months post-surgery. The strain values for this individual were found to be significantly lower indicating a stiffer vessel wall at the stenotic region than at a non-stenotic region under both physiologic and equalized pressure. These results suggest the possibility of noninvasive detection of the neointimal hyperplasia preceding anastomotic stenosis.

INTRODUCTION

Ultrasound elasticity imaging is a novel imaging technique that has the potential to accurately and non-invasively measure the mechanical properties of structures within the body that may change with various disease processes.¹ To fully characterize tissue stiffness, ultrasound strain measurements must be made over a wide dynamic range to accurately elucidate the linear and nonlinear mechanical properties of subsurface structures. Some structures, such as blood vessels, are highly nonlinear, and the nonlinear characteristics of the arterial wall can be clearly demonstrated using ultrasound elasticity imaging.¹ With advanced computational algorithms, the “feel” of subsurface structures detected by ultrasound speckle tracking is translated into a visual representation of the structure’s hardness.^{2,3} Since local nonlinear elasticity imaging offers the potential for direct, high-resolution measurements of arterial mechanical properties, it may be helpful in early detection of diseases where local mechanical properties are altered, such as peripheral vascular disease bypass grafts.

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Peripheral arterial disease is common, affecting 12 million people in the United States alone.^{4–6} Of these, approximately 10% will need an intervention for limb salvage. Although peripheral artery bypass surgery can prevent limb amputation, arterial occlusive disease often progresses after bypass surgery, leading to clinically significant stenosis or occlusion. While duplex ultrasound examination can identify stenosis, the underlying disease process of neointimal hyperplasia within the vessel wall progresses undetected prior to the development of stenosis. Since neointimal hyperplasia results in a stiffer vessel wall, conventional ultrasound imaging of parameters such as vessel diameter change with pulse pressure may indicate compliance changes of the vessel wall. However, conventional ultrasound makes inferential measurements of strain based on the diameter change of the vessel, and does not measure vessel-wall strain directly. The ultrasound elasticity measurements performed in this study using phase-sensitive speckle tracking allow direct measurement of wall strain with unprecedented resolution.

Another factor limiting the success of other methods is that arteries normally distended under physiologic pressure produce only small strain. Because the normal vessel wall is a highly non-linear elastic medium, measurements require a wide dynamic strain range for accurate characterization.¹ Elastic nonlinearities can be determined over a large strain dynamic range by applying a lumen pressure equalization technique previously developed and tested in a brachial artery application.^{1,7,8} This technique incorporates high-resolution, phase-sensitive speckle tracking, which offers the potential for sub-micron precision.^{1,9} We therefore applied high-resolution non-linear elasticity imaging to the bypass grafts of two subjects to test the feasibility of using this method to detect sub-clinical neointimal hyperplasia.

METHODS

Ultrasound Methods

Local, non-linear, high-resolution ultrasound elasticity imaging was performed using a linear array ultrasound transducer (iU22, Philips, Bothell, WA), with continuous freehand compression on the surface of the leg to briefly close the bypass artery-vein graft while imaging the artery and vein graft and collecting ultrasound data frame by frame. The applied external force produces internal pressure comparable to that generated in measuring a subject's blood pressure. The artery and vein graft pulsate maximally when the applied external pressure equals the diastolic pressure, and the vessel collapses completely when the applied pressure is greater than the systolic pressure. This method was confirmed in a previous study with pressure readings when the artery was compressed by a blood pressure cuff.¹ The pulse pressure of each subject was recorded by measuring blood pressure before and after the ultrasound scan. Real-time data were obtained using the radio frequency (RF) ultrasound signal containing speckle information used to accurately track the motion of structures within the object imaged.^{10,11} High frame rates (up to 500Hz) for transverse intramural strain and PWV measurements were collected during compression and stored and processed off-line as described below.

The first step in elasticity imaging is to estimate the motion between two (not necessarily adjacent) frames. Frame-to-frame displacements are estimated using a two-dimensional correlation-based phase-sensitive speckle-tracking technique.² This particular technique combines the ability of correlation-based algorithms to track relatively large internal displacements with the precision of phase-sensitive methods. First, frame-to-frame lateral and axial displacements are estimated from the position of the maximum correlation coefficient, where a correlation kernel approximately equaling the speckle spot is used for optimal strain estimation. Figure 1 illustrates the displacement “lag” from one frame to the next calculated using the underlying RF signal. The axial displacement estimate is then further refined by determining the zero-crossing position of the phase of the analytic signal correlation. Frame-to-frame displacement error is also reduced using a weighted correlation sum and by filtering

spatially adjacent correlation functions prior to displacement estimation.² Motion is tracked in two dimensions (Fig. 1) within the ultrasound field of view and axial strain is measured along the axis of the ultrasound beam where resolution is highest. Out-of-plane motion is minimized by the operator during data collection and assessed by examining the correlation between frames during image processing. The quality of an elasticity image is dependent on the signal-to-noise ratio (SNR), which is closely related to strain-induced decorrelation.^{2,12–15} That is, if tracking is performed between two frames with significant (more than several percent) internal strain, the resulting displacement and, therefore, strain estimates will have significant errors. To overcome this limitation, we have developed a method that allows us to use a combination of high frame rates when motion is large and processing non-adjacent frames when motion is small to increase the correlation between images while improving SNR in both displacement and strain estimates which allows increased accuracy in elasticity imaging.^{1–3, 9,16}

Clinical Subjects

As an initial clinical test of the potential utility of nonlinear elasticity measurements applied to peripheral artery-vein bypass grafts, pressure-equalized ultrasonic speckle-tracking estimates of intramural strain were performed on two human subjects under a study protocol approved by our local investigational review board. Subject 1 was an 81-year-old man who had a right femoral to popliteal artery *in situ* vein bypass 3 years previously. He had done well clinically, was asymptomatic and had no stenosis on follow-up ultrasound examinations. Transverse and longitudinal ultrasound scanning was performed on the vein side of the anastomosis under physiologic conditions and while compressing to a pressure equaling diastolic pressure. PWV measurements were also taken in the same area where the transverse scan was performed for intramural strain using the same probe rotated by 90 degrees. A previously validated, optimized elastic modulus reconstruction procedure from strain and PWV measurements⁹ was applied to the subject's strain data.

Subject 2 was a 78-year-old man who also had a femoral to popliteal artery *in situ* vein bypass and was examined twice using our experimental procedure: The first scan was performed at one month post-surgery and the second scan at four months post-surgery. The second scan was performed to obtain follow up elasticity data after this subject developed a stenosis three months post-surgery at the artery-vein graft anastomosis, which was treated successfully with angioplasty with good clinical and angiographic response. Transverse scanning was performed on the vein side of the anastomosis during both examinations under physiologic conditions and pressure equalization as described above.¹

RESULTS

In Subject 1, the pulse pressure induced intramural strain was 15% under physiologic pressure of 120/76 mmHg. After pressure equalization the strain increased to 65%. From the B-scan and correlation images the inner radius of the artery (lumen radius) was determined to be 2.3 mm under physiologic pressure and 2.0 mm after pressure equalization. The longitudinal scan data from the same region showed that PWV was 4.3 m/s under physiologic pressure and 1.7 m/s after pressure equalization. Using the elastic modulus reconstruction procedure previously described,^{8,9} the elastic moduli with and without compression were fit to a straight line with a slope was 3.1. The undistended vein elastic modulus was estimated to be 7.2 kPa. With only two measurement points with and without compression, the elastic property of the vein was fully characterized, demonstrating the feasibility of determining the undistended elastic modulus.⁹

Figure 2 shows the longitudinal scan of Subject 2 taken 4 months post-surgery (a) and transverse scans taken at 3 weeks and 4 months post-surgery (b and c, respectively), with

percent strain measurements of the vessel wall overlaid with the color map. This subject developed a stenosis proximally within the vein graft near the artery-vein graft anastomosis sometime between these two measurements, and the stenosis was treated successfully with angioplasty 3 months post-surgery with good clinical and angiographic response. However, the lesion showed some luminal narrowing at the follow-up exam at 4 months post-surgery (Fig. 1c). Prior to developing a luminal narrowing the proximal anastomosis exhibited a pulse pressure normalized induced intramural strain of $0.7 \pm 0.4\%$ under physiologic pressure and a pressure-equalized strain of $2.6 \pm 1.3\%$, compared with a mid-graft vein segment exhibiting a physiologic strain of $2.3 \pm 1.5\%$ and a pressure-equalized strain of $9.5 \pm 2.7\%$. Of note, the strain values at the stenotic region are significantly lower than at the normal region in this subject, and substantially lower than the strain values in the subject with no stenosis. Upon re-examination at 4 months Subject 2 continued to exhibit persistent low pressure-normalized proximal anastomosis strain compared with higher strain values seen in the more compliant mid-vein graft region of his bypass graft.

Since neointimal hyperplasia develops in the vascular wall prior to luminal narrowing, the low strain values of the stiffer proximal anastomosis preceded development of the clinical stenosis. Successful angioplasty increases the luminal diameter, but the mechanical stiffness of the diseased anastomosis remains elevated, as was seen in this subject post-angioplasty. For contextual reference, the strain of the diseased arterial anastomosis is in the same range as that observed in arteries of subjects with known vascular disease.¹ Furthermore, the non-diseased, more compliant vein-graft region in this subject exhibited strain measurements approximately four times greater than the diseased anastomosis segment.

DISCUSSION

High-resolution elasticity imaging using phase-sensitive speckle tracking with pressure equalization to elicit the highly non-linear vessel-wall properties may be of particular use in peripheral arterial disease. Anastomotic stenosis due to neointimal hyperplasia may occur in up to 20–30% of grafts within two years.^{17,18} While conventional duplex velocity and grey-scale measurements potentially allow detection of the stenosis, grafts still fail such that assisted primary patency may be only 70–80% at 5 years.¹⁹ Diagnostic strategies aimed at early detection of neointimal hyperplasia may allow for modification of medical and surgical treatment strategies aimed at altering the underlying disease process.

Previous attempts at non-invasive vascular elasticity imaging include vessel-wall motion estimation^{20–23} and pulse-wave velocity measurement.^{24,25} Within limits, these measurements have correlated with clinical events, including stroke²⁶ and claudication symptoms²¹ in non-ESRD (end-stage renal disease) patients and adverse cardiovascular events in patients with ESRD,^{27,28} as well as length of time on dialysis.²² However, current imaging modalities and non-invasive methods of compliance measurement are limited in that they rely on imprecise motion estimation or indirect assessments of vessel-wall motion. This feasibility study demonstrates the possibility of developing non-invasive means to directly measure vessel-wall deformations with high spatial resolution.

Another factor limiting the success of previously used methods is that arteries normally distended under physiologic pressure produce only small strain. The normal vessel wall, however, is a highly non-linear elastic medium.^{1,8,29} This implies that the artery in the physiologic region produces only a fraction of the strain in the low-preload region for the same pressure differential. By lowering preload, it may be much easier to differentiate diseased from normal vessel wall.¹ Vessel pathologies are often associated with decreased compliance.^{27,30} At low preload the difference in radial strain between normal and diseased arteries is much larger than at high preload. In previous reports on vessel elasticity over a wide range of

differential pressures across the wall,^{31,32} compliance was inferred from geometric changes such as artery diameter and lumen cross-section based on a numerical model (Langewouters' model).³³ However, the precision of phase-sensitive speckle tracking used in this study offers the possibility of detecting subtle underlying structural changes within the vascular wall with unprecedented resolution, precision and accuracy.

CONCLUSION

In a subject with an artery-vein bypass graft, high-resolution ultrasound elasticity imaging with speckle tracking revealed much lower values of arterial compliance in a region of proximal anastomosis compared to a mid-vein region, both before and after development of stenosis. The difference in values of strain in normal and diseased tissue was also greatly magnified by application of freehand compression to the area imaged in both stenotic and non-stenotic subjects. The addition of the techniques of ultrasound phase sensitive speckle tracking and pressure equalization may improve the early detection of diseases such as peripheral vascular disease, characterized by changes in the mechanical properties of tissue.

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Correlation Tracking

Fig. 1.

High-resolution ultrasound elasticity imaging can accurately estimate strain using a two-dimensional correlation-based speckle-tracking technique. Displacement from one frame to a succeeding frame produces a lag in the radio-frequency signature. Two-dimensional axial and lateral lag is estimated from the position of the maximum correlation coefficient. The size of the correlation kernel is approximately the same as that of the speckle spot.

Fig. 2.

Longitudinal (a) and transverse scan (b and c) images of Subject 2. The longitudinal scan was taken 4 months post-surgery and the transverse scans of the vein graft were taken at 3 weeks and 4 months post-surgery (b and c, respectively). The transverse images are overlaid with a color map depicting percent strain measurements of the vessel wall, and the mean and standard deviation of the strain measurements are tabulated below.