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TECHNICAL NOTE

# Feasibility of applying ultrasound strain imaging to detect renal transplant chronic allograft nephropathy

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**Feasibility of applying ultrasound strain imaging to detect renal transplant chronic allograft nephropathy.** Chronic renal transplant fibrosis, often termed Chronic Allograft Nephropathy, may progress undetected. Since renal fibrosis may be accompanied by a change in measurable elastic tissue properties, ultrasound strain measurements may be useful in its detection. Ultrasound strain imaging was performed for two subjects with renal transplants; one with normal renal function and one with mild renal insufficiency and biopsy demonstrated fibrosis. Subjects underwent ultrasound examination with application of a controlled deformation using phase-sensitive, two-dimensional speckle tracking to evaluate internal tissue motion to measure tissue displacement and strain. Measurements over multiple beams for an equivalent deformational stress showed there was a threefold differences in renal cortical strain between the two subjects. These data suggest that ultrasound elasticity imaging may prove useful in measuring mechanical changes related to fibrosis within the transplant kidney.

While acute rejection is responsible for early renal transplant loss, chronic progressive fibrosis and vasculopathy, often termed chronic allograft nephropathy (CAN), is responsible for the preponderance of late graft loss [1, 2]. CAN often progresses undetected because sensitive laboratory markers do not exist [2]. Since the fibrosis associated with CAN may be accompanied by an increase in measurable elastic tissue properties such as shear or Young's modulus, elasticity imaging may provide a means of measuring renal fibrosis and diagnosing or monitoring CAN [3, 4]. While renal biopsy allows assessment of fibrosis, frequent renal biopsies are not practical for monitoring because of the risk and cost involved. The clinical situation is exacerbated by the fact that substantial renal parenchymal loss may occur before there is any change in functional measurements of renal function [5]. Since previous ex vivo studies have suggested that ultrasound elasticity imaging may be able to detect localized elastic changes within the kidney [3, 4], ultrasound elasticity imaging may offer a means to detect and monitor renal fibrosis. This may in turn allow monitoring of therapies aimed at mitigating CAN in the future.

Ultrasound strain imaging is performed by application of controlled deformation to the study object [6, 7] followed by phase-sensitive, two-dimensional speckle tracking and evaluation of internal tissue motion (i.e., measurement of displacement and strain components) [6, 8]. The process can be carried further to reconstruct the spatial distribution of elastic modulus in the imaging plane [9, 10]. The goal of this study was to see if ultrasound strain imaging could detect differences between the transplanted kidney renal cortical parenchymal hardness of a recipient with excellent kidney function and one with chronic rejection and poor kidney function.

## METHODS

### Subjects

After informed consent was obtained under the study protocol approved by our local investigational review board, two renal transplant recipients were studied. Subject 1 was a 38-year-old woman with end-stage renal disease (ESRD) secondary to diabetes and a cadaveric renal transplant $2^1/_2$ years prior to the study with no history of rejection and a serum creatinine of 0.8 mg/dL. Subject 2 was a 41-year-old woman with ESRD secondary to lupus nephritis and a cadaveric renal transplant 5 years prior to the ultrasound study. She had a history of prior acute rejection 4 years earlier. Because of rising creatinine, a renal biopsy was performed 1 month prior to the ultrasound study. Her creatinine at the time of the study was 1.4 mg/dL. Renal pathology showed marked chronic changes manifested by moderate to severe interstitial fibrosis and glomerular scarring. The interstitial fibrosis was somewhat stripe-like in some locations. Blood vessels in the biopsy were thickened secondary to fibroelastosis

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and hyalinosis. However, no cyclosporine arteriopathy was present.

### Data collection and processing

A 4 MHz convex array transducer was used with continuous freehand compression performed on the surface of the lower abdomen where the kidney is located while imaging the cross-section of the kidney and collecting ultrasound data frame by frame. Surface deformation was performed by the investigators using forces comparable to firm palpation used in the standard physical examination of the transplant kidney, but not sufficient to cause discomfort for the subject. For each kidney, longitudinal and transverse scans on the major and minor axis of the kidney were performed.

Data were subsequently processed using a phase-sensitive, two-dimensional speckle-tracking algorithm to determine displacement and strain estimates [6–8, 11]. Correlation-based algorithms were used to track internal displacements. Frame-to-frame lateral and axial displacements were estimated from the position of the maximum correlation coefficient, where a correlation kernel approximately equaling the speckle spot was used for optimal strain estimation. Frame-to-frame displacement error was also reduced using a weighted correlation sum and by filtering spatially adjacent correlation functions prior to displacement estimation [11]. Numerical derivatives of the displacement estimations yielded the strain estimates. Since the deformational stresses within the kidney are not known, a means of gauging equivalent strain between images was performed by normalizing the strain to the amount of deformation of the entire kidney achieved during the deformation imaging procedure. By determining the net deformation of the kidney as a whole during the deformation procedure, and dividing the deformation of each image kernel (approximately one speckle spot) by the average deformation of the entire kidney, the *relative* strain of any region of interest within the kidney can be determined. This *normalized strain* may be used to compare strains in regions of interest within a kidney, such as capsule, cortex, medulla, and collecting system. In addition, if the relative hardness of the cortex changes with fibrosis, then this normalized strain can be used to compare regions of interest between different kidneys even when different deformational stresses are applied between kidneys during ultrasound data collection. This normalization is robust if the cross-sectional area of the kidney is preserved during deformation.

## RESULTS

Figure 1 shows the transverse scans of the kidney of subject 1 (Fig. 1A) and subject 2 (Fig. 1B) at the beginning (top) and end (bottom) of the deformation imaging procedure. Inspection of the ultrasound showed no appreciable difference in degree of echogenicity or other sonographic qualities of the two kidneys. The strain was determined for regions of interest (ROI) in the near field renal cortex of each kidney indicated in Figure 1. The cross-sectional area was found to remain the same (within 1%) while the shape of the kidney changed due to deformation, indicating that the normalization procedure was robust for this clinical application.

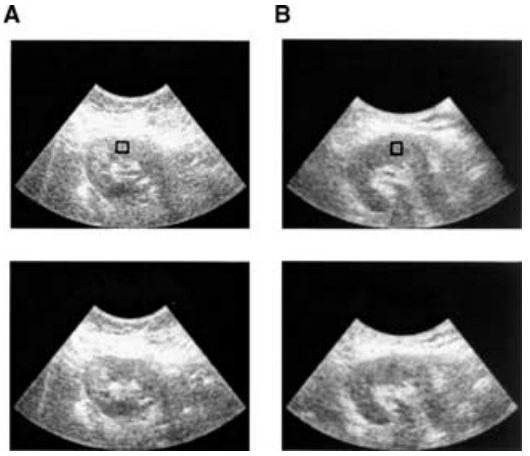


**Fig. 1. Ultrasonographic images.** (*A*) Transverse scans of the kidney of subject 1 before (top) and after (bottom) deformation. The imaging depth is set to be 9 cm. (*B*) Transverse scans of the kidney of subject 2 before (top) and after (bottom) deformation. The imaging depth is set to be 6 cm. Region of interest (ROI) is marked with a black box. Note that ROI is not exactly scaled.

Figure 2 shows the relative strain of the renal cortex of subjects 1 and 2. The ROI is mapped on the xy plane of Figure 2A with the relative strain along the z axis. The top brighter surface is for subject 2 and the bottom darker one is for subject 1. The averaged strain over 15 beams for the same ROI is shown in the two-dimensional Figure 2B. The solid (top) line is for subject 2 and the dashed (bottom) line is for subject 1. Note that the strain is normalized to the average strain magnitude developed in the kidney as a whole. These strain images showed subject 2 with approximately one third the average strain magnitude of subject 1, indicating that for an equivalent deformational stress, the renal cortex of subject 1 deformed three times as much as the cortex of the transplant kidney subject 2. In addition, note the relatively small standard deviation of the strain estimate, represented by error bars in Figure 2B, compared with the relatively large difference in strain measurements between the two kidneys. The difference between the two subjects exceeds the measurement error, suggesting that strain measurements may be a sensitive and precise measure. These imaging results are consistent with the pathology findings of marked fibrosis in the transplant of subject 2 having significantly harder (less deformable) renal cortex resulting in lower strain.

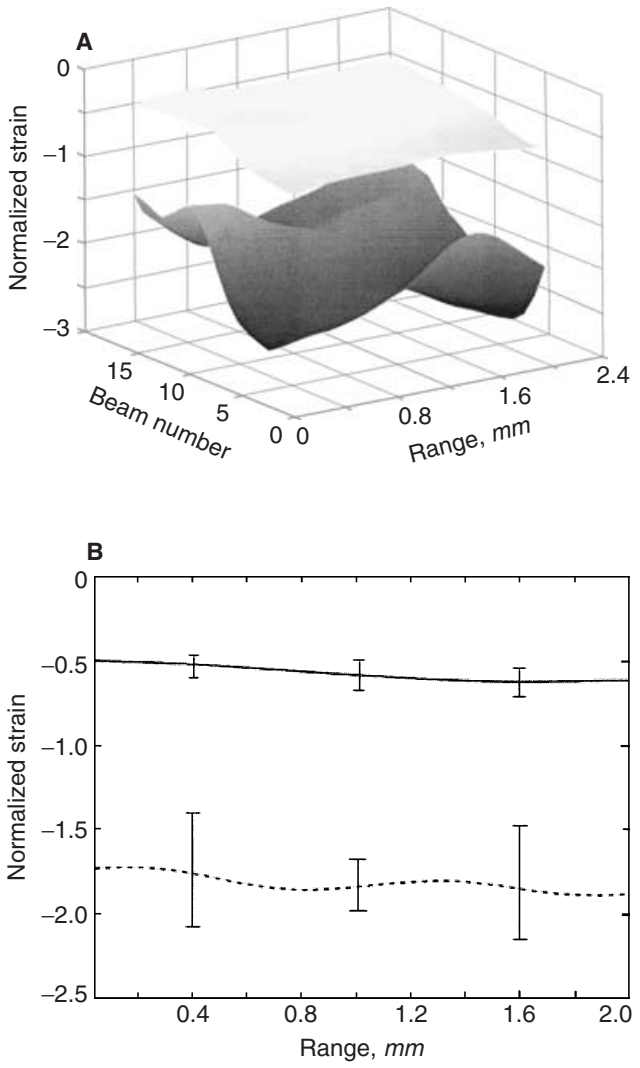


**Fig. 2. Strain over the range of interest (ROI) of the cortex.** (*A*) The top surface is for subject 2 and the bottom for subject 1. (*B*) Averaged strain over 15 beams for the same ROI. The solid line is for subject 2 and the dotted line is for subject 1. Left, middle, and right error bars indicate standard deviation of measurements in the near, mid, and far field, respectively. The difference between the two subjects exceeds the measurement error.

## DISCUSSION

Renal cortical elasticity is expected to change with tissue damage and resulting scar formation from a variety of causes. The transplanted kidney often undergoes changes secondary to inflammation and edema with acute rejection, and resulting scarring and fibrosis developing from either acute rejection or from multiple factors in CAN. Since conventional laboratory markers such as serum creatinine levels are not sensitive for detecting CAN in early stages, the process often progresses until extensive fibrosis is present. Currently, definitive diagnosis requires obtaining tissue by invasive renal biopsy, which is not practical for routine surveillance. Subject 2 exemplifies the potential utility of elasticity imaging since a creatinine of 1.4 mg/dL may not be considered severely impaired kidney function and sonographic appearance of the cortex was not visually distinguishable from subject 1 with a creatinine of 0.8 mg/dL. Yet biopsy findings from subject 2 indicated extensive fibrosis. While it would have been preferable to have biopsy data on subject 1, none was available. In addition, the relationship between elastic properties and pathologic data needs to be better defined. We will soon begin a study to systematically compare measured ultrasound strain with quantified fibrosis scores based on pathology specimens to better determine the relationship between renal cortical fibrosis and ultrasound strain measurements. However, the goal of this study was to test the feasibility of ultrasound elasticity imaging to detect changes in elasticity that may be associated with fibrosis in the in vivo renal transplant and these results do suggest that differences in renal cortical strain may be measurable using this technique.

There are many factors that must be rigorously investigated to determine if this technique will prove to be diagnostically useful. The method of compression during ultrasound data acquisition is an important consideration. We initially tried an external harness to hold the ultrasound transducer and apply a controlled deformation. Unlike previous phantom experiments, we found the speckle decorrelation from out-of-plane motion too great to calculate meaningful strain images. In this study, we found that careful manual compression allows for visual inspection of the image during compression with adjustment of the compression angle to maintain in-plane motion during compression and results in superior speckle tracking. Clearly, operator dependence and data quality feedback to the operator will need to be explored as important variables during future evaluation of this technique.

Future work is planned to compare the quantified strain image or reconstructed Young's modulus to the degree of fibrosis in subjects to determine if elasticity imaging can be used to reliably estimate the degree of renal fibrosis. In addition, the influence of factors such as acute rejection and edema on strain measurements must be explored. Other factors unrelated to the degree of cortical fibrosis, such as hydronephrosis, or hardening of the renal capsule or cyclosporin toxicity may influence the mechanical properties of the kidney as a whole and confound the strain measurements or necessitate different normalization techniques or other means of image standardization. Nonetheless, these data do suggest that ultrasound elasticity imaging may prove useful in measuring mechanical changes related to fibrosis within the transplant kidney. More data are needed and studies are ongoing in transplant recipients to evaluate this technique.

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