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## *Original Contribution*

# RENAL TRANSPLANT ELASTICITY ULTRASOUND IMAGING: CORRELATION BETWEEN NORMALIZED STRAIN AND RENAL CORTICAL FIBROSIS

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**Abstract—After transplantation, over a widely variable time course, the cortex of the transplanted kidney becomes stiffer as interstitial fibrosis develops and renal function declines. Elasticity ultrasound imaging (EUI) has been used to assess biomechanical properties of tissue that change in hardness as a result of pathologic damage. We prospectively assessed the hardness of the renal cortex in renal transplant allograft patients using a normalized ultrasound strain procedure measuring quasi-static deformation, which was correlated with the grade of renal cortical fibrosis. To determine cortical strain, we used 2-D speckle-tracking software (EchoInsight, Epsilon Imaging, Ann Arbor, MI, USA) to perform offline analysis of stored ultrasound loops capturing deformation of renal cortex and its adjacent soft tissue produced by pressure applied using the scanning transducer. Normalized strain is defined as the mean developed strain in the renal cortex divided by the overall mean strain measured in the soft tissues from the abdominal wall to pelvic muscles. Using the Banff scoring criteria for renal cortical fibrosis as the gold standard, we classified 20 renal transplant allograft biopsy tissue samples into two groups: group 1 (n = 10) with mild (<25%) renal cortical fibrosis and group 2 (n = 10) with moderate (26%–50%) renal cortical fibrosis. An unpaired two-tailed *t*-test was used to determine the statistical difference in strains between patients with mild and those with moderate renal cortical fibrosis. Receiver operating characteristic curve analysis was performed to assess the accuracy of developed strain and normalized strain in predicting moderate renal cortical fibrosis. The reference strain did not significantly differ between the two groups ($p = 0.10$). However, the developed renal cortical strain in group 1 with mild fibrosis was higher than that in group 2 with moderate fibrosis ($p = 0.025$). The normalized strain in group 1 was also higher than that in group 2 ($p = 0.0014$). The areas under receiver operating characteristic curves for developed strain and normalized strain were 0.78 and 0.95, respectively. The optimal cutoff for distinguishing moderate renal cortical fibrosis was −0.08 for developed strain (sensitivity = 0.50, specificity = 1.0) and 2.5 for normalized strain (sensitivity = 0.80, specificity = 1.0). In summary, renal cortex strain is strongly correlated with grade of renal cortical fibrosis. Normalized strain is superior to developed strain in distinguishing moderate from mild renal cortical fibrosis. We conclude that free-hand real-time strain EUI may be useful in assessing the progression of cortical fibrosis in renal transplant allografts. Further prospective study using this method is warranted. (E-mail: jig2001@med.cornell.edu)** **© 2013 World Federation for Ultrasound in Medicine & Biology.**

*Key Words:* **Elastography, Renal cortical fibrosis, Renal transplant, Ultrasound strain.**

## INTRODUCTION

In current practice, assessment of renal transplant dysfunction relies on the monitoring of biochemical laboratory tests and, if definitive diagnosis is needed, renal biopsy. However, routine laboratory tests such as serum creatinine are insensitive to loss of renal function (Hunsicker and Bennett 1995), and kidney biopsy is limited by its invasive nature and high cost (Schwarz et al. 2005). Therefore, improved non-invasive techniques to assess renal function and detect renal dysfunction early would be desirable. Elasticity ultrasound imaging (EUI) is an emerging non-invasive imaging

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technique for the assessment of internal organ and tissue biomechanical properties that may be useful in assessing pathologic changes that influence tissue mechanics (O'Donnell et al. 1993; Xu et al. 2012). In the kidney, EUI may provide information about the mechanical changes that accompany histologic changes useful for monitoring renal disease (Chaturvedi et al. 1998). Quasi-static ultrasound strain measurements of the renal cortex in renal transplant recipients may help detect and monitor tissue hardness changes in a chronic transplant allograft nephropathy (CTAN) (Weitzel et al. 2004). More recently, techniques such as acoustic radiation force impulse imaging (Stock et al. 2011; Syversveen et al. 2011, 2012), shear wave velocity imaging (Gennisson et al. 2010; Ozkan et al. 2013) and shear wave dispersion vibrometry (Amador et al. 2009) have been used to assess renal cortical mechanical changes in renal transplants. Work remains to establish and improve the reliability and accuracy of these techniques, taking into account the effects of renal anisotropy and boundary conditions (Gennisson et al. 2012; Rubin et al. 1988; Syversveen et al. 2011).

We chose to test and further evaluate the free-hand push method suggested in earlier work (Weitzel et al. 2004) because of (i) the locally isotropic renal cortical structure, wherein pathologic changes of interest develop relatively near the surface (transducer); (ii) the possibility of standardized data collection in the measurement by normalizing with a reference strain measurement from the acquired strain image; (iii) the availability of gold standard criteria for reference measurements using an accepted pathology scoring system for fibrosis in the transplant setting; and (iv) the simplicity of the measurement method, which would allow for broad clinical use if the method should prove useful.

In this study we sought to prospectively assess, using EUI, the relationship between the hardness of renal cortex, represented by mean developed renal cortical strain measurements and normalized strain measurements (developed renal cortical strain divided by imaged soft tissue strain), and the grade of renal cortical fibrosis by Banff criteria. The ultimate goal of this study was to assess the value of ultrasound strain imaging in monitoring the progression of renal cortical fibrosis in the allograft after transplantation.

## METHODS

*Patients*

We performed EUI on 20 patients (11 men and 9 women, age range 28–87 y, mean age 50 ± 16 y) who underwent transplanted kidney biopsy from March 2012 to August 2012. All patients were studied after providing written informed consent in this study. All color Doppler sonography and quasi-static elastography were conducted at the New York-Presbyterian Hospital, Weill Cornell Medical College, after obtaining approval from institutional review board of Weill Cornell Medical College. The study was compliant with the Health Insurance Portability and Accountability Act. Patients were eligible to participate if a referring nephrologist or transplant surgeon referred them for renal biopsy. The indications for renal biopsy were loss of renal function, suspicion of allograft rejection, or participation in protocol renal transplant biopsy. As a standard of care for patients having renal transplant in our institution, color Doppler sonography was routinely performed to screen for allograft vascular complications, for example, transplant renal artery stenosis, and non-vascular complications, such as hydronephrosis for an elevated serum creatinine.

Patients with hydronephrosis, large perinephric collections, immediate post-transplantation status (<7 d after the surgery), significant transplant renal artery stenosis and an existing intrarenal vascular abnormality (*e.g.,* arteriovenous fistula), which may be contraindications for renal biopsy and/or affect renal cortical strain measurement, were not enrolled in the study; in addition, patients who could not tolerate compression for any reason were excluded.

*Real-time ultrasound data acquisition*

Two investigators who had more than 20 y of experience in ultrasound scanning and were trained in free-hand compression performed the scans (one investigator scanned 15 cases, and the other scanned 5 cases).

Gentle but firm free-hand compression of a transplanted kidney was performed during standard renal transplant sonography before kidney biopsy, on the same day as the biopsy (n = 17) or <7 d before the biopsy (n = 3). Subjects were placed in the supine position. The transplanted kidney was imaged using either a General Electric (Logic E9, General Electric, Milwaukee, WI, USA) or Siemens (Sequoia 512, Siemens Medical Solution, Mountain View, CA, USA) scanner equipped with a multi-frequency 2- to 4-MHz curved linear array transducer. Transmission gel was placed on the anterior abdominal wall as standard acoustic coupling for ultrasound examination over the region where the transplanted kidney is located. The speckle reduction setting on the Logic E9 scanner was turned off while capturing real-time compression to increase the fidelity of speckle data acquisition. The speckle reduction feature performs an averaging function on the images, making the examination more pleasing to the eye, but may influence tracking and therefore was disabled as part of this protocol.

We used a transducer frequency range of 2–4 MHz to improve penetration of the ultrasound beam to the deep pelvis. The depth of gray-scale imaging ranged