Corticomedullary Strain Ratio

A Quantitative Marker for Assessment of Renal Allograft Cortical Fibrosis

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Objectives—To quantitatively assess the correlation between the corticomedullary strain ratio and cortical fibrosis in renal transplants.

Methods—Using quasistatic ultrasound elasticity imaging, we prospectively assessed the corticomedullary strain ratio in renal allografts of 33 patients who underwent renal transplant sonography and biopsy. Based on Banff score criteria for renal cortical fibrosis, 33 allografts were divided into 2 groups: group 1 (n = 19), with mild (<25%) fibrosis; and group 2 (n = 14), with moderate (>26%) fibrosis. We used 2-dimensional speckle-tracking software to perform offline analysis of cortical and medullary strain induced by external compression by the ultrasound transducer. We then calculated the corticomedullary strain ratio (cortical normalized strain/medullary normalized strain; normalized strain = developed strain/applied strain [deformation from the abdominal wall to the pelvic muscles]). An unpaired 2-tailed *t* test was used to determine differences in normalized strain and the strain ratio between the groups. Receiver operating characteristic curve analysis was performed to determine the best strain ratio cutoff value for identifying moderate fibrosis.

Results—Normalized strain differed between the cortex and medulla (mean ± SD: group 1, 4.58 ± 2.02 versus 2.58 ± 1.38; $P = .002$; group 2, 1.71 ± 0.42 versus 2.60 ± 0.87; $P = .0011$). The strain ratio in group 1 was higher than in group 2 (2.06 ± 1.33 versus 0.70 ± 0.20; $P = .0007$). The area under the receiver operating characteristic curve was 0.964. The sensitivity and specificity of a strain ratio cutoff value of 0.975 for determining moderate fibrosis were 92.9% and 94.7%, respectively.

Conclusions—Strain values vary in different compartments of the kidney. The corticomedullary strain ratio on ultrasound elasticity imaging decreases with increasing renal cortical fibrosis, which makes it potentially useful as a noninvasive quantitative marker for monitoring the progression of fibrosis in renal transplants.

Key Words—chronic allograft nephropathy; corticomedullary ratio; renal transplant; speckle tracking; ultrasound elasticity imaging

Changes in the renal corticomedullary relation have been associated with renal parenchymal damage and renal insufficiency secondary to a variety of etiologies.[1] In renal transplants, changes in the corticomedullary relation may be associated with acute rejection[2] and gradually developing renal cortical fibrosis in chronic allograft nephropathy, the most prevalent cause of chronic allograft dysfunction in the first post-transplant decade and late graft loss.[3]

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Abbreviations
GFR, glomerular filtration rate

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At least 3 factors may affect the accuracy of evaluating the corticomedullary relation in transplanted kidneys on conventional grayscale sonography, which makes evaluation of the corticomedullary relation challenging.[4] First, cortical echogenicity may vary due to anisotropy, a property associated with the orientation of the microstructure of the kidney to the direction of the ultrasound beam.[5] Therefore, an echogenic appearance in the renal cortex on a grayscale image does not necessarily indicate chronic allograft nephropathy. Second, a transplanted kidney is superficially located in the lower abdomen, deep to the abdominal wall. The absence of adjacent organs makes it difficult to compare the echogenicity against a control (such as the liver). Third, evaluating renal echogenicity on grayscale sonography is strongly observer dependent. The interpretation of cortical and medullary echogenicity on grayscale images may vary from one observer to another. Moreover, grayscale settings (transducer frequency for imaging, total gain, dynamic range, and harmonic imaging) and the sound beam angle to the cortex for acquiring images may also differ between operators, and no application standards exist. Finally, the corticomedullary relation may change due to factors not associated with renal disease, such as hydration and diuresis, as well as rarer factors, such as denervation.[2]

Another imaging modality that has been used for evaluating renal corticomedullary differentiation is magnetic resonance imaging. The loss of corticomedullary differentiation has been observed in acute and chronic renal failure on magnetic resonance elasticity imaging.[6–8] However, relatively high cost, problems with some implanted metal devices, and claustrophobia limit the utility of magnetic resonance imaging in longitudinally monitoring renal transplant patients.

Recently, ultrasound elasticity imaging has been used to measure the hardness of the kidney as an indicator of renal cortical fibrosis, which develops after renal transplantation. However, standards for machine design, image acquisition, and diagnostic criteria for this technique remain lacking, and correlations with cortical fibrosis between various studies have been inconsistent. Some researchers have demonstrated a close correlation between transient elastography,[9] acoustic radiation force impulse imaging,[10] and shear wave speed imaging[11] and the grade of renal cortical fibrosis, whereas another study showed a poor correlation between these parameters.[12] To date, there has been insubstantial work on assessing tissue elasticity in different compartments of the kidney.[11] To our knowledge, there exists no published literature measuring strain values in different compartments of transplanted kidneys with quasistatic ultrasound elasticity imaging.

Given references on imaging internal strain for detecting renal scars before any detectable change in kidney function[13] and applying ultrasound elasticity imaging for examining the hardness of transplanted kidneys in 2 cases,[14] we hypothesized that with the use of ultrasound elasticity imaging, the ratio of renal cortical to medullary strain can be determined, and that this ratio could correlate with the grade of renal cortical fibrosis. Results may aid in quantitatively monitoring the progression of fibrosis after renal transplants.

Materials and Methods

Patients

Patients were prospectively enrolled between March 2012 and December 2012 as part of a study that was approved by the Institutional Review Board of Weill Cornell Medical College, and written informed consent was obtained from all patients. The study was compliant with the Health Insurance Portability and Accountability Act.

Inclusion criteria included the following: (1) The renal medullary compartment was definable by distinguishing medullary pyramids as hypoechoic areas between the columns laterally on a grayscale image (Figure 1). (2) The thickness of the renal cortex was greater than 4 mm. Strain was measured using coupled regions of interest, represented by the colored boxes connected by the dashed line in Figure 1. The motion of each box was calculated and applied by speckle-tracking software (EchoInsight; Epsilon Imaging, Ann Arbor, MI) and represented motion of the underlying tissue. The gradient of displacement within each region of interest determined the strain (deformation) of the tissue within each region. For measurement protocol standardization, a strain region of 4 mm was used in the cortex of each patient, as shown in Figure 1. This size was selected because this thickness of the cortex and medulla permitted inclusion of all of our cases, including those with thin (maximal thickness, 4 mm) cortices and other cases with small (maximal anteroposterior dimension, 4 mm) medullas. (3) Both regions of interest in the cortex and medullary pyramids were measured axially along the direction of the compression to avoid lateral decorrelation while performing speckle tracking. Exclusion criteria included transplant renal artery stenosis, arteriovenous fistulas, hydronephrosis, and large perinephric collections.

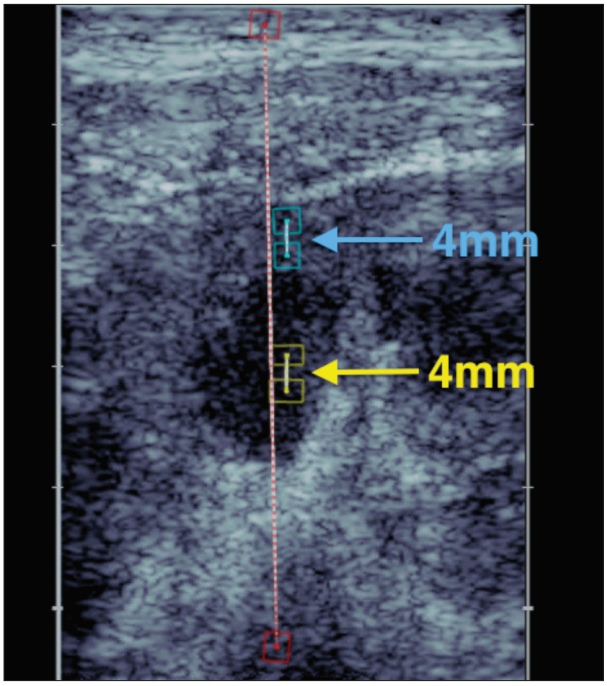
All patients underwent ultrasound elasticity imaging of their transplanted kidneys and renal biopsy at Weill Cornell Medical College. A nephrologist or transplant surgeon requested sonography for assessing vascular and nonvascular renal transplant complications (eg, renal artery

stenosis and hydronephrosis) as the standard of care for renal transplant patients. The main indications for requiring sonographically guided renal transplant biopsy included an elevated serum creatinine value or a low glomerular filtration rate (GFR) value, suspicion of allograft rejection, and participation in protocols requiring transplant biopsy. Trained nephrologists performed all kidney biopsies under real-time sonographic guidance.

Real-time Ultrasound Image Acquisition

Grayscale image loops used for ultrasound elasticity imaging were acquired as part of standard renal transplant color Doppler sonography on the same day as and before the renal biopsy. A 4C1 curved linear array or 6L3 linear array transducer with multiple frequencies of 2 to 4 or 4 to 6 MHz (Acuson Sequoia 512; Siemens Medical Solutions, Mountain View, CA) was used for renal transplant sonography and ultrasound elasticity imaging.

Figure 1. Longitudinal grayscale sonogram of a transplanted kidney (zoomed image). The renal cortex (blue arrow) is the peripheral portion of the kidney. The medullary pyramids (yellow arrow) are located between the cortex and collecting system anteroposteriorly and between the columns laterally. Quasistatic ultrasound elasticity imaging was performed to measure strain in different compartments of the renal allograft. We used 2-dimensional speckle-tracking software to analyze deformation in the cortex within a 4-mm region of interest between the renal capsule to the medulla (blue dotted line). Similarly, medullary strain was measured within a 4-mm region of interest centered within the medullary pyramid (yellow dotted line). Red dotted line indicates applied strain.



Each patient was placed in the supine position and underwent a conventional sonographic examination, including grayscale, color flow, and spectral Doppler analysis. Ultrasound elasticity imaging was then conducted. Deformation in the kidney during real-time grayscale imaging was recorded at a high frame rate (33–47 Hz), a single transmit focus, and a depth of 10 to 13 cm from the abdominal wall to the pelvic muscles. A gentle and constant push by the transducer with a subsequent quick release was performed over the transplanted kidney, and the scanning investigators attempted to keep the kidney in plane during compression. The pushing force was similar to deep palpation during a physical examination, while ensuring that each patient did not feel discomfort or pain during the compression. Compression was conducted in both sagittal and transverse views of the transplanted kidneys. Ultrasound data capture continued throughout compression and release to record prepush and postpush reference images for postprocedure data processing and speckle tracking.[15] All compression loops were stored in the institutional picture archiving and communication system for further offline analysis.

Kidney Biopsy

We adapted the same standard criteria for both kidney biopsy and biopsy tissue sample pathologic interpretations in this study as in our previous work.[16]

Renal Strain Measurements With 2-Dimensional Speckle Tracking

To measure strain in the kidney, we first transferred Digital Imaging Communications in Medicine–format images from deidentified grayscale compression loops from the picture archiving and communication system to a personal computer for offline processing. We then used the EchoInsight 2-dimensional speckle-tracking software to analyze the deformation in the renal cortex and medulla induced by external compression.

For this study, regional strain measurements were done using connected dual regions of interest, as shown by the blue and yellow graphics in Figures 1 and 2. The movement of each region of the tethered pair through image loops was calculated from tissue motion estimates produced by speckle tracking. The strain (Figures 2 and 3) represents the tissue deformation between the region of interest pair (ie, strain along the connecting line of the region of interest tether). In this study, cortical strain was the deformation along a 4-mm axial distance between the renal capsule and medulla (Figure 1), and medullary strain was the deformation within a 4-mm anteroposterior

dimension in the center of the pyramids (Figure 1). We used the loops recorded along the long axis of the kidney, as the sound beam was parallel to the main pyramid axis.[11] Special attention was paid to measuring strain approximately along the sound beam (ie, perpendicular to the transducer face) and consequently along the compressional direction. This process served to maximize the strain signal by measuring in the direction of maximum deformation. Furthermore, speckle tracking was optimized by largely constraining tissue motion to along the beam because along-beam (axial) resolution was finer than across-beam (lateral) resolution for the images used in this study. The finer axial resolution provides better tracking accuracy and noise robustness along the beam compared to tracking across the beam.[15]

Figure 2. Strain analysis recorded from a patient in group 1. The cortical peak strain (cyan), medullary peak strain (yellow), and applied peak strain (red) measured –0.19, –0.1, and –0.05, respectively. In this case, the cortical normalized strain was higher than the medullary normalized strain (3.8 versus 2), with a corticomedullary strain ratio of 1.9. The kidney biopsy reported that the allograft had 10% renal cortical fibrosis based on Banff criteria.

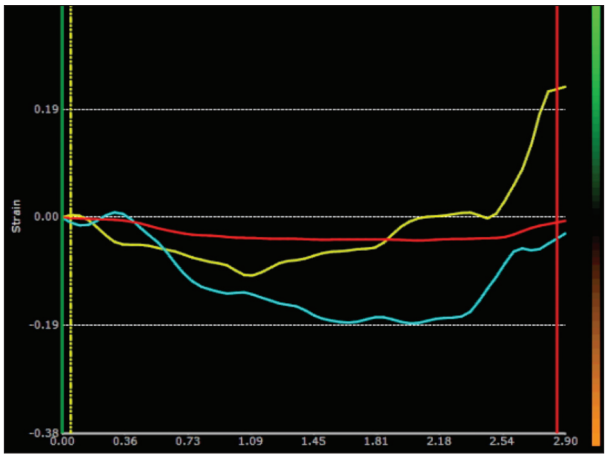
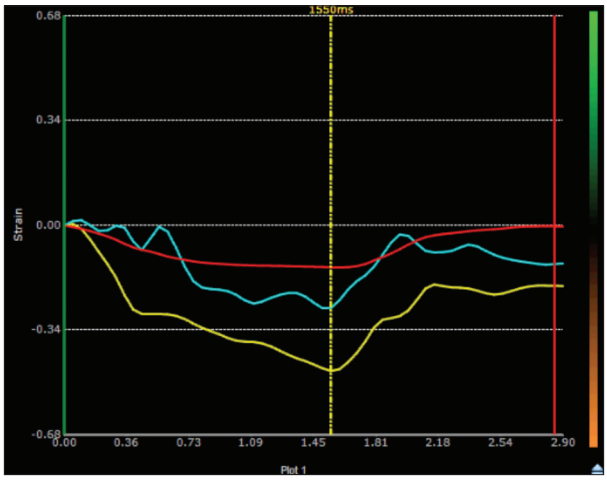


Figure 3. Strain analysis recorded from a patient in group 2. The cortical peak strain (cyan), medullary peak strain (yellow), and applied peak strain (red) measured as –0.27, –0.47, and –0.14, respectively. In this case, the cortical normalized strain was significantly lower than the medullary normalized strain (1.9 versus 3.4), with a corticomedullary strain ratio of 0.56. The kidney biopsy reported 50% renal cortical fibrosis.



Region of interest placement within the renal cortex and medulla was based on the consensus opinion of 2 investigators (J.G., with 28 years of ultrasound experience, and K.J., with 11 years of abdominal imaging experience). A single operator (J.G.) performed all strain measurements. Cortical and medullary developed strain values were calculated by averaging 3 strain measurements in the cortex and medulla, respectively. Applied strain was calculated as the deformation produced between the anterior abdominal wall and the pelvic muscles under compression in each case.

Finally, the corticomedullary strain ratio was calculated for each of the 33 cases as follows: the strain ratio of the cortex to the medulla was defined as the ratio of the strain in each region of interest measured during the same compression examination. The cortical (medullary) normalized strain was defined as developed strain in the cortex (medulla)/applied strain. Specifically, the corticomedullary strain ratio was defined as cortical normalized strain/medullary normalized strain.

Statistical Analysis

All parameters, including cortical and medullary normalized strain and the corticomedullary strain ratio, were expressed as mean ± standard deviation. An unpaired 2-tailed *t* test was used to determine the difference in normalized strain and the strain ratio between group 1 (mild fibrosis) and group 2 (moderate fibrosis) as well as normalized strain between the cortex and medulla in each group. $P < .05$ was considered statistically significant. Receiver operating characteristic curve analysis was performed to determine the best strain ratio cutoff value for identifying moderate fibrosis.

Results

A total of 33 patients (19 men and 14 women; age range, 24–75 years; mean age, 52 ± 11 years) were recruited. Demographics are shown in Table 1. Significant differences were found in the duration of transplantation ($P = .0163$) and GFR ($P = .00004$) between the groups (Table 1). There was no significant difference in serum creatinine between the groups ($P = .1691$).

The normalized strain values differed in the different compartments of the kidney in both groups. In group 1 with mild renal cortical fibrosis, the strain in the cortex was higher than that in the medulla. In group 2 with moderate fibrosis, the strain in the cortex was lower than that in the medulla in all but 1 case. Furthermore, the corticomedullary strain ratio was significantly higher in group 1 than group 2 ($P = .0007$). Notably, the difference in cortical normalized strain between the groups was significant ($P = 00001$). However, the difference in the medullary normalized strain between the groups was not ($P = .8416$; Table 2).

The receiver operating characteristic curve for the corticomedullary strain ratio as a predictor of moderate renal cortical fibrosis is displayed in Figure 4. The area under curve was 0.964. The best strain ratio cutoff value for identifying moderate fibrosis was 0.975, with 92.9% sensitivity and 94.7% specificity.

Discussion

In this article, we have introduced a technique for measuring the hardness of renal compartments with ultrasound strain imaging. To the best of our knowledge, this study was the first to apply the corticomedullary strain ratio as a quantitative marker for assessing the grade of cortical fibrosis in renal transplants.

Renal cortical fibrosis is a direct consequence of the kidney's response to multiple forms of injury. Renal scarring results in a progressive loss of renal function, ultimately leading to end-stage renal failure.[17] The corticomedullary relation represents the association between changes in the relative compliance or hardness of the cortex and medulla, and changes in the corticomedullary relation possibly reflect the development of progressive fibrosis in the cortex of the transplanted kidney.

Given that the kidney is a complex, highly compartmentalized, and anisotropic organ, ultrasound techniques may produce a large variation in measurements of backscatter intensity[5] and shear wave propagation speed,[11] which might be problematic in evaluating renal corticomedullary differentiation based on echogenicity or shear wave velocity alone. However, measuring renal strain via a robust speckle-tracking technique, which analyzes the internal tissue deformation produced by external compression, may have advantages over other methods.

Our results suggest that renal transplant ultrasound elasticity imaging can assess biomechanical properties of renal tissues that correlate with microstructural and pathologic damage in the kidney. In other words, when the tissue in a renal compartment is softer, its strain is higher, whereas when tissue in the renal compartment is harder, its strain is lower. In our results, the strain values differed between the renal cortex and medulla. The corticomedullary strain ratio was greater than 1 in mild renal cortical fibrosis (cortex softer than medulla), whereas it was less than 1 in moderate fibrosis (cortex harder than medulla). With 0.975 as the cutoff value, the sensitivity and specificity of the strain ratio for distinguishing moderate from mild fibrosis were 92.9% and 94.7%, respectively. Not only are the strain measurements and strain ratio in renal transplants related

Table 1. Clinical Information and Renal Cortical Fibrosis Grades for 33 Renal Allografts

Characteristic	Group 1 (n = 19) (<25% Fibrosis)	Group 2 (n = 14) (>26% Fibrosis)	*P*
Age, y	50 ± 17	55 ± 11	.1482
Male/female, n	8/11	11/3	
Transplantation, mo	26 ± 29	77 ± 39	.0163
Living/deceased donors, n	12/7	4/10	
GFR, mL/min/1.73 m^2	46.4 ± 15.4	24.1 ± 10.5	.00004
Creatinine, mg/dL	2.11 ± 2.54	3.12 ± 1.09	.1691

Data are presented as mean ± SD where applicable.

Table 2. Strain and Corticomedullary Strain Ratio Values for 33 Renal Allografts

Parameter	Group 1 (n = 19) (<25% Fibrosis)	Group 2 (n = 14) (>26% Fibrosis)	*P*
Cortical normalized strain	4.58 ± 2.02	1.71 ± 0.42	.00001
Medullary normalized strain	2.58 ± 1.38	2.60 ± 0.87	.8416
Corticomedullary strain ratio	2.06 ± 1.33	0.70 ± 0.20	.0007
P, cortex/medulla	.002	.0011	

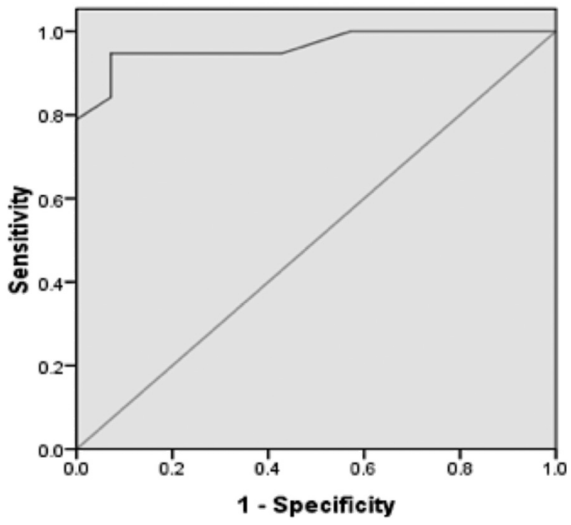
Data are presented as mean ± SD.

to the variable microstructure in different compartments of the kidney, but they also reflect the consequences of renal cortical fibrosis.

Generally, the glomeruli are spherical, and proximal and distal tubules are convoluted and relatively anisotropic compared to the medulla[18]; thus, the renal cortex has a structure that results in softer and higher cortical strain than the medulla on ultrasound elasticity imaging. Conversely, the medulla is composed of predominantly radially oriented tubes perpendicular to the capsule. In addition, the orientation of the loops of Henle and vasa recta makes the medullary pyramids spatially heterogeneous and anisotropic tissue.[1] Therefore, the strain in the heterogeneous medulla may be lower than in the homogeneous cortex. The finding that the strain value differs in each particular compartment of the kidney suggests that special attention should be paid to choosing a correct region of interest for accurately measuring strain in that particular anatomic location.

Even though the mechanisms are yet to be fully understood, the strain in the cortex was remarkably decreased in group 2, with moderate fibrosis, and there was a significant difference in cortical normalized strain between groups 1 and 2. One can clearly note that there is a close relationship between the value of renal cortical strain and the degree of fibrosis. The higher the grade of fibrosis, the less deformation produced under compression, and the lower the measured cortical strain. In other words, changes in the biomechanical properties of the renal cortex appear to be strongly related to the development of fibrotic tissue, as measured by ultrasound elasticity imaging and displayed on strain analysis curves (Figures 2 and 3).

Figure 4. Receiver operating characteristic curve for the corticomedullary strain ratio as a predictor of moderate renal cortical fibrosis. The area under curve was 0.964. The best strain ratio cutoff value for identifying moderate fibrosis was 0.975, with 92.9% sensitivity and 94.7% specificity.



Finally, it seemed that the changes in cortical and medullary normalized strain values were not proportional in chronic allograft nephropathy (Table 2). Although the difference in cortical normalized strain between the groups was significant ($P < .001$), the difference in medullary normalized strain was not ($P = .8416$). We hypothesize that chronic rejection–related lesions are more common and more prominently affect the mechanical changes in the cortex in proportion to the pathologic changes in chronic allograft nephropathy, which predominately take place in the renal cortex.[19] Therefore, a decrease in strain resulting from moderate scarring and varyingly oriented fibrotic tissues predominantly affected the renal cortex. It is interesting to note that the medulla does not appear to change with fibrosis. This aspect makes it possible to use the medulla to normalize future strain measurements, which would overcome a big criticism that normalization will change from patient to patient: eg, obese, thin, and those with fluid present. If it is possible to normalize cortical measurements to the medulla, these problems are avoided. Furthermore, there was a statistically significant difference in the GFR between the groups, with the GFR being significantly lower in group 2.

Limitations of this study included the small number of enrolled patients. All strain values in different compartments of the kidney were measured in an allograft with either mild or moderate renal cortical fibrosis, but kidneys without fibrosis or with severe fibrosis were absent. In addition, pathologic complexities (eg, coexisting acute rejection, substantial glomerular inflammation, and arteriolosclerosis) and immunosuppression therapy may contribute to the hardness of the transplanted kidney in addition to renal cortical fibrosis, and these factors will need to be investigated further. Finally, interobserver and intraobserver variation could not be tested because a single operator performed most of the transducer palpations (1 performed 27 and another performed 6) during a single event. For all of these reasons, reproducibility of the data needs further investigation.

In conclusion, we have quantitatively demonstrated that strain values vary in different compartments of the transplanted kidney. There is a close correlation between the cortical normalized strain and strain ratio and the grade of renal cortical fibrosis. Ultimately, the corticomedullary strain ratio on ultrasound elasticity imaging has the potential to be used as a noninvasive quantitative marker for monitoring the progression of cortical fibrosis in renal transplants.

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