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● *Original Contribution*

COMPARISON OF ULTRASOUND CORTICOMEDULLARY STRAIN WITH DOPPLER PARAMETERS IN ASSESSMENT OF RENAL ALLOGRAFT INTERSTITIAL FIBROSIS/TUBULAR ATROPHY

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Abstract—To compare the capability of ultrasound strain and Doppler parameters in the assessment of renal allograft interstitial fibrosis/tubular atrophy (IF/TA), we prospectively measured ultrasound corticomedullary strain (strain) and intra-renal artery Doppler end-diastolic velocity (EDV), peak systolic velocity (PSV) and resistive index (RI) in 45 renal transplant recipients before their kidney biopsies. We used 2-D speckle tracking to estimate strain, the deformation ratio of renal cortex to medulla produced by external compression using the ultrasound transducer. We also measured Doppler EDV, PSV and RI at the renal allograft inter-lobar artery. Using the Banff scoring system for renal allograft IF/TA, 45 patients were divided into the following groups: group 1 with ≤5% (n = 12) cortical IF/TA; group 2 with 6%–25% (n = 12); group 3 with 26%–50% (n = 11); and group 4 with >50% (n = 10). We performed receiver operating characteristic curve analysis to test the accuracy of these ultrasound parameters and duration of transplantation in determining >26% cortical IF/TA. In our results, strain was statistically significant in all paired groups (all $p < 0.005$) and inversely correlated with the grade of cortical IF/TA ($p < 0.001$). However, the difference in PSV and EDV was significant only between high-grade (>26%, including 26%–50% and >50%) and low-grade (≤25%, including <5% and 6%–25%) cortical IF/TA ($p < 0.001$). RI did not significantly differ in any paired group (all $p > 0.05$). The areas under the receiver operating characteristic curve for strain, EDV, PSV, RI and duration of transplantation in determining >26% cortical IF/TA were 0.99, 0.94, 0.88, 0.52 and 0.92, respectively. Our results suggest that corticomedullary strain seems to be superior to Doppler parameters and duration of transplantation in assessment of renal allograft cortical IF/TA. (E-mail: jig2001@med.cornell.edu) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Doppler velocity, Renal cortical interstitial fibrosis/tubular atrophy, Renal transplant, Ultrasound strain.**

INTRODUCTION

Renal allograft interstitial fibrosis/tubular atrophy (IF/TA) is a pathophysiologic consequence of the kidney's response to injuries of various etiologies (Chapman et al. 2005; Hewitson 2009). Renal allograft IF/TA is also a leading cause of renal allograft loss in renal transplant recipients. Immunologic and non-immunologic injuries that include acute and chronic rejection, hypoperfusion, ischemia–reperfusion injury, calcineurin toxicity, infection and recurrent disease (*e.g.*, lupus nephritis) are among the many factors contributing to IF/TA. The development of IF/TA is often insidious and may result from subclinical rejection undetected by changes in serum creatinine in what appears to be a well-functioning allograft (Fletcher et al. 2009), as biochemical markers (*e.g.*, serum creatinine) are not sensitive enough to detect early stages of renal IF/TA (Hunsicker and Bennett 1995).

Although kidney biopsy is considered the gold standard in the diagnosis and staging of IF/TA, its invasive nature, high cost and sampling error limit its application as a frequently repeatable method for monitoring renal allograft (Lukenda et al. 2014; Schwarz et al. 2005). Recently developed elasticity imaging methods

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including shear wave velocity imaging (Gennisson et al. 2010, 2012; Grenier et al. 2012; Syversveen et al. 2011, 2012), transient elastography (Lukenda et al. 2014; Sommerer et al. 2013), real-time elastography (Orlacchio et al. 2014) and magnetic resonance elastography (Lee et al. 2012) have shown promise in providing non-invasive means of measuring renal cortical hardness resulting from pathologic damage. Questions about the reliability of using ultrasound shear wave elastography to monitor renal transplants have been raised because the renal cortex is a highly anisotropic structure, which influences the reproducibility of measuring shear wave propagation in renal cortices in both ultrasound elastography (Gennisson et al. 2012) and magnetic resonance elastography (Lee et al. 2012) studies. Transient elastography is 1-D sampling without real-time imaging guidance. Our previous work suggested that freehand ultrasound elasticity imaging (UEI) using speckle tracking can be used to analyze tissue deformation under an external compression to assess renal cortical hardness related to cortical IF/TA (Gao et al. 2013; Weitzel et al. 2004).

Another non-invasive imaging technique that has been used after renal transplantation is color Doppler sonography. The relationship between the renal allograft arterial resistance index (RI) and early allograft function has been studied (Ozkan et al. 2013). However, the RI does not seem to reliably correspond to renal transplant dysfunction in IF/TA (Stock et al. 2011). Interestingly, a close relationship between renal transplant dysfunction and decreases in intra-renal Doppler velocities, including end-diastolic velocity (EDV) and peak systolic velocity (PSV), has been suggested (Gao et al. 2011; Krumme 2006).

Given recent reports on the correlation between renal ultrasound elasticity and RI (Ozkan et al. 2013) and the relationship between ischemia and renal IF/TA on magnetic resonance elastography (Warner et al. 2011), we hypothesized that a decrease in intra-renal blood flow measured with EDV and PSV, an increase in cortical hardness estimated with corticomedullary strain, or both, may be of clinical importance in detecting IF/TA. We therefore conducted this study to compare the capability of corticomedullary strain and intra-renal Doppler parameters in determining the degree of cortical IF/TA in renal transplant recipients.

METHODS

Patients

We performed color Doppler sonography and freehand UEI on 45 patients (26 men and 19 women, age range: 24–76 y, mean age: 52 ± 16 y) who underwent transplanted kidney biopsy from March 2012 to June 2014. All patients were enrolled after providing written informed consent in this study approved by the institutional review board. A nephrologist or transplant surgeon referred them for renal transplant sonography and kidney biopsy (for cause and per protocol) as the standard of care for renal recipients with decreased allograft function or suspicion of rejection.

The exclusion criteria for the study were: hydronephrosis, large perinephric collections, significant transplant renal artery stenosis and existing intra-renal vascular abnormality (arteriovenous fistulae), which may be contraindications for kidney biopsy and/or affect renal cortical strain measurement. Patients with significant arrhythmia, severe aortic valve stenosis or insufficiency and abdominal aorta aneurysm that may affect Doppler velocity in the intra-renal artery were likewise not enrolled in the study.

Doppler parameters and real-time ultrasound data acquisition

The subject was placed in the supine position. The transplanted kidney was imaged using a 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 lower abdominal wall as standard acoustic coupling for ultrasound examination over the region where the transplanted kidney is located.

We initiated the study with the conventional transplanted kidney ultrasound examination, including assessment of size and echotexture of the allograft on gray-scale image, delineation of the renal allograft arteries with color Doppler imaging and sampling of Doppler flow velocities with spectral Doppler. Spectral Doppler velocities of the inter-lobar artery were measured at the site where kidney biopsy tissue samples were taken. Doppler angle correction (sound beam being parallel to flow direction if possible, at least <30°) and 3 mm Doppler gate were standard settings throughout the study. Color and spectral Doppler settings (*e.g.*, pulse repetition frequency, scale, gain, and filter) were adjusted depending on the flow velocity in the vessels imaged. Velocity spectra with maximum amplitude without aliasing displaying four or five cardiac cycles were recorded with shallow breathing. Doppler parameters including EDV, PSV and RI were manually measured with electronic calipers and software built into the scanner. Mean EDV (V2, Fig. 1a, b) was calculated by averaging three measurements of the minimum velocity in diastole. Mean PSV (V1, Fig. 1a, b) was calculated by averaging three measurements of the maximal velocity in systole. The mean RI was the average of three RIs calculated with the equation RI = (PSV−EDV)/PSV. Special care was taken in ultrasound data acquisition. Inter-lobar artery Doppler