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● *Original Contribution*

PREDICTION OF RENAL ALLOGRAFT ACUTE REJECTION USING A NOVEL NON-INVASIVE MODEL BASED ON ACOUSTIC RADIATION FORCE IMPULSE

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Abstract—Point shear wave elastography based on acoustic radiation force impulse is a novel technology used to quantify tissue stiffness by measuring shear wave speed. A total of 115 kidney transplantation recipients were consecutively enrolled in this prospective study. The patients were subdivided into two groups using 1 mo post-transplantation as the cutoff time for determining the development of acute rejection (AR). Shear wave speed was significantly higher in the AR group than in the non-AR group. We created a model called SEV, comprising shear wave speed, estimated glomerular filtration rate and kidney volume change, that could successfully discriminate patients with or without AR. The area under the receiver operating characteristic curve of SEV was 0.89, which was higher than values for other variables; it was even better in patients within 1 mo post-transplantation (0.954), but was lower than the estimated glomerular filtration rate in patients after 1 mo post-transplantation. Therefore, the SEV model may predict AR after renal transplantation with a high degree of accuracy, and it may be more useful in the early post-operative stage after renal transplantation. (E-mail: Wanyuanhe@126.com or he.wanyuan@zs-hospital.sh.cn) © **2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Acoustic radiation force impulse, Point shear wave elastography, Kidney transplantation, Acute rejection, Shear wave speed, Non-invasive.**

INTRODUCTION

Renal transplantation has emerged as a valuable therapeutic modality for the treatment of end-stage renal disease. However, acute rejection (AR) limits survival of both renal allografts and recipients (Ingulli 2010). The clinical findings in AR include an acute increase in serum creatinine level, with or without a decreased urine output. Unfortunately, however, acute rejection may be clinically asymptomatic (Goldberg et al. 2016).

Although the state-of-the-art standard for the diagnosis of renal allograft AR is renal biopsy, which is an invasive procedure with a low risk of bleeding and hematoma (Torres Munoz et al. 2011), non-invasive methods are still important for clinical decision making, especially for recipients during outpatient follow-up (McArthur et al. 2011). Ultrasound, as a non-invasive and convenient examination, has now been well accepted for the evaluation of renal allograft status. The resistive index (RI), an important index of Doppler ultrasound, reflects the hemodynamic status of a transplanted kidney and has been used in the early diagnosis of acute renal allograft rejection in initial Doppler studies (Rifkin et al. 1987; Rigsby et al. 1986). As early as 1992, it was reported that a high initial RI indicated that kidney allografts were dysfunctional or vulnerable to development of acute rejection in non-functioning grafts (Renowden et al. 1992; Saarinen et al. 1992). In the subsequent two decades, conflicting results were reported (Dupont et al. 2003; Mehrsai et al. 2009; Raiteri et al. 2005). It was also reported that an increased RI was observed in patients with stable renal allograft function (Kocabas et al. 2008). To date, the diagnostic value of the RI for

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AR is still controversial. In a recent clinical trial involving 321 renal allograft recipients, Naesens et al. (2013) found that the RI was not associated with the histologic features of renal allograft rejection at protocol-specified biopsy time points. Older recipient age was the strongest determinant of a higher RI. Biopsies performed at the time of the discovery of graft dysfunction revealed that both antibody-mediated rejection and tubular necrosis were associated with a higher RI compared with normal biopsy results (Naesens et al. 2013). Hence, it is important to develop a novel accurate, reliable and reproducible model for the non-invasive diagnosis of renal allograft AR.

Recently, a novel technology, acoustic radiation force impulse (ARFI), has been integrated into a conventional ultrasound instrument. Focused acoustic radiation force pushing pulses of short duration are used to generate shear waves within a region of interest (ROI), and the shear wave speed (SWS) propagating away from the pushing location is measured. The information can be reported as an average value within an ROI (a point measurement) (Shiina et al. 2015). There is a defined relationship between SWS and tissue stiffness. The stiffer the tissue, the higher is the SWS. Point shear wave elastography (p-SWE) quantification has been widely used for the detection of fibrosis in chronic liver disease because it is tolerable, accurate and reproducible (Friedrich-Rust et al. 2009; Sporea et al. 2013; Takahashi et al. 2010). In addition, Stock et al. (2010) described a significant correlation between SWS and renal allograft fibrosis and suggested that SWS may have potential for evaluating the grade of fibrosis in renal transplants. In 2011, Stock et al. further reported their experience that SWS is correlated with acute rejected kidney allografts. However, the number of patients enrolled in that study was quite small, with one drug toxicity case, five acute rejection cases and two acute tubular necrosis (ATN) cases. The sensitivity and specificity of the diagnosis of acute rejection in kidney allografts based on p-SWE are still unknown. In 2014, we reported a study in which the 102 patients (50 with stable renal function vs. 52 with dysfunction) enrolled underwent p-SWE examination. The results revealed that the sensitivity and specificity of SWS in the diagnosis of renal allograft dysfunction were 72.0% and 86.5% (cutoff value = 2.63), respectively. The latter values were better than those of RI, which were 62.0% and 69.2% (cutoff value = 0.63), respectively (He et al. 2014). However, we did not distinguish patients with AR from all patients with renal dysfunction. In addition, no diagnostic model was established in our previous study.

Therefore, in this study, we evaluated the application of p-SWE in the assessment of different types of pathologic renal allograft dysfunction and further established a novel, simple, non-invasive model for predicting AR.

METHODS

Patients

A total of 115 kidney transplant recipients were enrolled in this study from January 2011 to July 2014. Before renal biopsy was performed, all patients underwent ultrasound examination. This study protocol was approved by the ethics committee of Zhongshan Hospital, Fudan University. The procedures in this study complied with the 1975 Declaration of Helsinki and were performed after consents were received.

All patients were divided into one of two major groups based on the time post-transplantation, using 1 mo as a cut-off time. The normally functioning kidneys were used as controls at the corresponding period. The two major groups were subdivided into a total of five subgroups: (i) patients with stable (or normally functioning) kidneys who presented within 1 mo post-transplantation, (ii) patients with biopsy-proven AR who presented within 1 mo post-transplantation; (iii) patients with biopsy-proven ATN who presented within 1 mo post-transplantation; (iv) patients with stable kidneys who presented more than 1 mo post-transplantation; (v) patients with biopsy-proven AR who presented more than 1 mo post-transplantation (Supplementary Fig. 1, online only, available at http://dx.doi.org/10.1016/j.ultrasmedbio.2016.05.003).

Ultrasound examination and the principle of p-SWE

All patients in our study underwent conventional ultrasound examinations and assessment of renal allograft stiffness by two experienced ultrasound physicians using p-SWE; the physicians had at least 10 y of experience in clinical ultrasound examinations. The doctors were blinded to the patients' clinical and laboratory data. Ultrasound examinations were performed with a Siemens Acuson S2000 ultrasound machine using a 1- to 4-MHz curved array multifrequency transducer (4 C1) (Siemens, Munich, Germany). The study conditions were controlled. All patients were examined at 8–10 AM on an empty stomach without fluid infusion or caffeine intake. Patients were examined in the supine position. To calculate the volume of the transplanted kidney, we used the ellipsoid formula: volume (cm^3) = length (cm) × width (cm) × thickness (cm) × $\pi/6$. The three dimensions of the transplanted kidney were measured by B-mode ultrasound examination. Color Doppler ultrasound was used to evaluate the blood perfusion of the transplanted kidney. Gain and pulse repetition frequency were adjusted individually. The peak systolic velocity (PSV) and RI of three interlobar arteries (upper, mid- and lower poles) were obtained by pulsed-wave Doppler (Fig. 1a). Data are presented as the means of three readings. All patients were examined within 24 h