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REVIEW

Evaluation of kidney allograft status using novel ultrasonic technologies

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Abstract Early diagnosis of kidney allograft injury contributes to proper decisions regarding treatment strategy and promotes the long-term survival of both the recipients and the allografts. Although biopsy remains the gold standard, non-invasive methods of kidney allograft evaluation are required for clinical practice. Recently, novel ultrasonic technologies have been applied in the evaluation and diagnosis of kidney allograft status, including tissue elasticity quantification using acoustic radiation force impulse (ARFI) and contrast-enhanced ultrasonography (CEUS). In this review, we discuss current opinions on the application of ARFI and CEUS for evaluating kidney allograft function and their possible influencing factors, advantages and limitations. We also compare these two technologies with other non-invasive diagnostic methods, including nuclear medicine and radiology. While the role of novel non-invasive ultrasonic technologies in the assessment of kidney allografts requires further investigation, the use of such technologies remains highly promising.

1. Introduction

Renal transplantation is considered the best treatment for patients with end-stage renal dysfunction. Kidney allograft dysfunction and malfunction none the less remain major threats to the long-term survival of the graft and the recipient. Early diagnosis of allograft injury enables proper treatment to prevent further damage to the transplanted

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kidney. However, it is often difficult to differentiate the cause of kidney allograft injury. Although biopsy remains the gold standard for the diagnosis of kidney allograft dysfunction, it carries the risks and complications of any invasive examination, including hemorrhage, hematuria, perirenal hematoma and arteriovenous fistula [1]. In addition, renal allograft biopsies require adequate routine laboratory test results (routine blood and coagulation tests) prior to the operation, as well as a significant period of strict bed rest and monitoring. The patient is also required to be hospitalized and treated with additional care.

Given the inconvenience and potential risks inherent in allograft biopsies, non-invasive methods are important for clinical decision-making, particularly during outpatient follow-up of recipients [2]. Ultrasound (US), an economical and non-invasive technique, plays an important role in the assessment of renal allograft function. Recently, in addition to routine B-mode ultrasound, attempts to evaluate kidney allograft function through novel ultrasonic technologies have shown promise. Acoustic radiation force impulse (ARFI) has been integrated into a conventional ultrasound instrument. ARFI quantification estimates tissue stiffness by measuring shear wave velocity (SWV) in a region of interest (ROI). This technology has been used for the detection of inflammation [3], tumors [4] and fibrosis [5] due to its advantages of safety, accuracy and reproducibility. Another novel ultrasonic technology, contrast-enhanced ultrasonography (CEUS), uses microbubble contrast agents and complementary harmonic pulse sequences to demonstrate blood perfusion. The first attempts using these novel ultrasonic technologies to diagnose kidney allograft function have shown promise.

2. ARFI

2.1. The mechanisms of ARFI technology

ARFI technology quantifies tissue elasticity through the SWV (m/s) within an ROI [6]. Shear waves are created by a short-duration, high-intensity acoustic pulse. SWV has been documented to be correlated strongly with grade of fibrosis [7]; the stiffer the tissue is, the higher the shear wave velocity is.

2.2. Evaluation of kidney allograft status

In 2010, the first study by Stock et al. [8] of renal allograft fibrosis using ARFI reported a significant, positive, moderate correlation between mean SWV values and the grade of fibrosis in renal allografts, as well as the BANFF category. However, the next pilot study by Syversveen et al. [9] showed interfering factors and opposite results, and this study did not support the use of ARFI quantification to assess low-grade fibrosis in renal transplants. In 2011, the first clinical experience with ARFI-based tissue elasticity quantification for the examination of kidney allograft dysfunction was reported by Stock's group. The mean ARFI values showed an average increase of more than 15% in five acute rejected kidneys, whereas no increase was observed in the other three dysfunctional kidneys, including two cases of acute tubular necrosis (ATN) and one case of drug-related toxicity [10].

Our recent study compared the diagnostic efficacy of SWV and resistive index (RI) in an expanded sample. Fifty-two patients with stable renal function and 50 patients with acute rejection (AR) were enrolled. Our results indicated that the mean SWV was more significantly negatively correlated with estimated glomerular filtration rate (eGFR). The sensitivity and specificity of SWV in the diagnosis of renal allograft dysfunction were 72.0% and 86.5% (cutoff value = 2.625), respectively, and were better than those of RI, which were 62.0% and 69.2% (cutoff value = 0.625) [11], respectively.

The results from our and other groups revealed good inter- and intraobserver agreement in both kidney allografts [11] and native kidneys [12]. However, Syversveen et al. [9] raised concerns regarding the intra- and interobserver agreement in renal allograft ARFI evaluation. Their group found no significant difference in median SWV between patients without and with renal allograft fibrosis, as well as low intra- and interobserver agreement rates. It is difficult to ascertain the reason for these results. However, because of the limited number of enrolled subjects and less detailed descriptions of observer training, one must question the different conclusions drawn. Given the importance of inter- and intraobserver agreement in any type of ultrasonic examination, attention is certainly warranted. However, studies with larger samples are needed to confirm any conclusion, and these studies preferably should use experienced doctors who have participated in standard training and have proved to be qualified in ARFI performance (Table 1).

2.3. Possible factors influencing ARFI examinations

Recent studies have reported various factors that could interfere with measurement using ARFI. Such factors have included target depth [13], applied transducer force [14,15], medium between target and probe [16], probe machines and examiner differences [17,18], and diminution of organ blood flow [19]. Syversveen et al. [9] found that SWV measurements were dependent on the applied transducer force and that SWV measurements were not different in kidney allografts with different grades of fibrosis. The experiment was scientifically credible, yet part of the conclusion contrasted with the well-known relationship between SWV measurements and organ fibrosis. Through a phantom study, Yamanaka et al. [17] discovered that targets with deep ROI shad slightly lower SWV values than superficial targets. This conclusion is consistent with the results reported by Kaminuma et al. [16]. Because patients possess different tissue thickness and therefore organ depth, further research in larger samples is needed to investigate and prove the effects of each suspected factor on ARFI values.

Regarding factors known to not affect ARFI values, the study from our group proved that kidney volume did not affect SWV and RI measurements or eGFR [11]. Goertz et al. [20] reported that age, sex, height, weight, BMI and kidney volume did not affect SWV measurements. Lee et al. [21], however, discovered an age-related increase in SWV in the kidneys of children younger than 5 years old, suggesting an