Asian Journal of Urology (2015) 2, 142–150

HOSTED BY

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

REVIEW

Evaluation of kidney allograft status using novel ultrasonic technologies

Cheng Yang [a,1], Mushuang Hu [a,1], Tongyu Zhu [a], Wanyuan He [b,*]

[a] *Department of Urology, Zhongshan Hospital, Fudan University, Shanghai Key Laboratory of Organ Transplantation, Shanghai, China*
[b] *Department of Ultrasound, Zhongshan Hospital, Fudan University, Shanghai Institute of Imaging Medicine, Shanghai, China*

Received 26 June 2015; accepted 29 June 2015
Available online 6 July 2015

KEYWORDS
Ultrasound;
Acoustic radiation force impulse;
Contrast-enhanced ultrasonography;
Kidney transplantation;
Non-invasive

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

* Corresponding author.
E-mail addresses: he.wanyuan@zs-hospital.sh.cn, wanyuanhe@126.com (W. He).
Peer review under responsibility of Shanghai Medical Association and SMMU.
[1] These authors contributed equally to this study.

http://dx.doi.org/10.1016/j.ajur.2015.06.008

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

Table 1 AFRI studies.

Design	Method	Result	Conclusion	Ref.
Prospective/18 Tx recipients	ARFI (15 measurements)	There was a positive moderate correlation between mean ARFI values and the grade of fibrosis, as well as between the mean ARFI values and the BANFF category.	Only severe fibrosis can be accurately diagnosed by elastography. ARFI values overlap between early fibrosis groups.	[8]
Prospective/30 Tx recipients	SWV of the renal cortex	SWV did not differ significantly in transplants with and without fibrosis. The mean intraobserver coefficient of variation was 22% for observer 1 and 24% for observer 2. Interobserver agreement, expressed as the intra-class correlation coefficient, was 0.31.	The results do not support the use of ARFI quantification to assess low-grade fibrosis in renal transplants. ARFI quantification has high intra- and interobserver variations in renal transplants.	[9]
Prospective/8 Tx recipients	ARFI (15 measurements)	There was an increase of more than 15% in the mean ARFI values in acute rejection. There was no increase in mean ARFI values among other pathologies and no increase in mean RI values in any histological type.	ARFI measurement shows promise as a complementary non-invasive parameter in the follow-up diagnosis of renal allograft rejection.	[10]
Prospective/102 Tx recipients	ARFI (5 measurements)	SWV was more significantly negatively correlated with eGFR than RI. The sensitivity and specificity of quantitative ultrasound in the diagnosis of renal allograft dysfunction were 72.0% and 86.5% (cutoff value 2.625), respectively. The coefficient of variation for repeat SWV measurements of the middle part of the transplanted kidney was 8.64%, with good interobserver agreement.	ARFI is more accurate than RI in diagnosing renal allograft function and has good stability and repeatability.	[11]
327 healthy volunteers and 64 CKD patients	Evaluation of influencing factors and measurement reproducibility in healthy volunteers. Analysis of correlations between SWV and laboratory tests in CKD patients.	The SWV of healthy volunteers was correlated with age, differed between men and women, and was not affected by height, weight, body mass index, waistline, kidney dimension or the depth for SWV measurement. Inter- and intraobserver agreement, expressed as intra-class coefficient correlations, were 0.64 and 0.6, respectively. In CKD patients, SWV was correlated with eGFR, urea nitrogen, and creatinine.	The SWV of healthy volunteers is correlated with age, differed between genders, and was not affected by height, weight, body mass index, waistline, kidney dimension or the depth of SWV measurement. In CKD patients, SWV is correlated with eGFR, urea nitrogen, and creatinine.	[12]
91 healthy volunteers	ARFI (5 measurements)	In univariate analysis, age, sex and measurement depth were significantly correlated with kidney SWV, whereas body mass index, kidney length and renal parenchyma thickness were not. In multivariate analysis, only age and sex were significantly correlated with kidney SWV.	Kidney SWV is influenced mainly by age and sex and less by measurement depth.	[13]

(*continued on next page*)

Table 1 (*continued*)

Design	Method	Result	Conclusion	Ref.
31 Tx recipients	SWV measurements performed in the cortex with controlled compression weight of 22, 275, 490, 975, 2040 and 2990 g.	SWV significantly differed by repeat measures and also by pairwise comparisons. There was no difference in SWV performed with any of the applied transducer forces between grafts with various degrees of fibrosis.	SWV in kidney transplants depends on the applied transducer force and does not differ in grafts with different grades of fibrosis. ARFI quantification cannot detect renal allograft fibrosis.	[14]

ARFI, acoustic radiation force impulse; CEUS, contrast-enhanced ultrasonography; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RI, resistive index; SWV, shear wave velocity; Tx, transplant.

age-related effect on SWV results within a limited pediatric population. The conclusion drawn by Goertz et al. [20] did not entirely agree with the experimental results of Nightingale et al. [22], who estimated mean Young's modulus values of between 3.8 and 5.6 kPa, 11.7 kPa and 14.0 kPa for fat, fibroadenoma and skin, respectively. Given that the formula for body mass index (BMI) calculation contains only height and body weight and that no index of body type or tissue proportion was considered, these findings indicated somewhat that two patients with the same BMI yet with very different fat and muscle ratios should have the same SVW. An explanation for such a conclusion could be the limited subject distribution. More research on the matter with broad subject distribution might provide a satisfactory answer. While debate continues over the influences of surface tissue and target depth, most researchers agree that transplanted kidneys are usually located in the iliac fossa. This knowledge ensures a relatively consistent anatomic position and small target depth. Because of the superficial and consistent locations of transplanted kidneys, the possible influences of tissue depth and type are relatively lower among kidney allografts, compared to normal kidneys.

3. CEUS

3.1. The mechanisms of CEUS technology

CEUS employs microbubble contrast agents and complementary harmonic pulse sequences to demonstrate parenchymal perfusion, detecting microvascular blood flow in real time without affecting renal function [23]. CEUS enables the dynamic assessment and quantification of microvascularization up to capillary perfusion.

3.2. Evaluation of kidney allograft status

As a novel ultrasonography diagnostic method, CEUS has been reported to be promising for the assessment of renal allograft dysfunction [24,25]. Its parameters include rising time (RT), time to peak (TTP) and the delta-time among ROIs (ΔRT and ΔTTP). In a pilot study in renal allograft patients in 2006, the Schwenger group demonstrated the diagnostic value of CEUS in diagnosing chronic allograft nephropathy (CAN). The determination of renal blood flow by CEUS demonstrated significantly higher sensitivity, specificity and overall accuracy compared with the RI for the detection of chronic allograft nephropathy, and CEUS was the most significant test for the detection of CAN, compared with all of the other conventional parameters [26]. Benozzi et al. [27] later found that, in addition to CAN, some CEUS-derived parameters were able to distinguish ATN and AR episodes, including reduced peak enhancement, TTP, cortical to medullary ratio of regional blood flow and cortical to medullary ratio of mean transit time.

Delayed graft function (DGF) could also be distinguished by CEUS. Grzelak et al. [28] assessed graft perfusion in the early period after kidney transplantation (72—120 h) in 63 kidney allograft recipients; 35 had good early graft function (EGF), and 28 had DGF. In patients with DGF, a delay in the inflow of the contrast medium was observed, as well as significant differences in the time of inflow to the ROIs between the two groups. Schwenger et al. [29] recently discovered in a study that consists of 69 kidney transplant recipients that renal blood flow, estimated by CEUS 1 week post-transplantation, is significantly correlated with kidney function after 1 year, suggesting a prognostic value of CEUS soon after kidney transplantation. The renal blood flow assessed through CEUS resembled a significant correlation with donor age but not recipient age, and was associated with vascular fibrosis and intimal thickening of the engraftment biopsies from their study, implying the ability of CEUS to reveal information on kidney allograft perfusion independent of recipient vascular compliance. Fernandez et al. [30] concluded, after a retrospective analysis of five patients who underwent emergency transplantectomy, with the cases later proving to be acute cortical necrosis, that CEUS could show the typical peripheral rim sign in cases of cortical necrosis, allowing for the reliable and rapid diagnosis of this condition and earlier decisions for nephrectomy, obviating the need for further imaging studies or biopsy.

Recently, our research group enrolled 57 renal transplant recipients in a prospective study. CEUS examinations were performed before renal allograft biopsy. The biopsy results proved 23 cases of AR, 10 cases of ATN, and 24 cases with normal evolution (stable). In addition to the findings of the CEUS parameters among these groups, we further

Table 2 CEUS studies.

Design	Method	Result	Conclusion	Ref.
Prospective/57 Tx recipients	CEUS parameters were RT, TTP and the delta-time among regions of interest (ΔRT and ΔTTP).	In the AR group, RT and TTP of the interlobar artery and the medulla (RTi, RTm, TTPi and TTPm) and ΔRT and ΔTTP between the medulla and the cortex (ΔRTm-c and ΔTTPm-c) were significantly higher, compared to the stable group. RTm, TTPm, ΔRTm-c and ΔTTPm-c were higher, compared to the ATN group. ΔRTm-c and eGFR were independent predictors.	CEUS parameters are reliable markers for differentiating the perfusion status of transplanted kidneys. The new simple index $P = -0.587 + 0.286 \times \Delta RTm\text{-}c - 0.028 \times eGFR$; New Index $= e^P/(1 + e^P)$ has better AUROCs than eGFR, and individual CEUS parameters can easily predict AR with a high degree of accuracy.	[24]
26 Tx recipients	CEUS and conventional color Doppler ultrasonography	Renal blood flow estimated by CEUS was highly significantly related to creatinine. Determination of renal blood flow by CEUS reached higher sensitivity (91% *vs.* 82%), specificity (82% *vs.* 64%) and accuracy (85% *vs.* 73%) for the diagnosis of chronic allograft nephropathy, compared to conventional color Doppler ultrasound.	Perfusion parameters derived from CEUS significantly improve the early detection of chronic allograft nephropathy. It is a feasible method for evaluating microvascular perfusion in renal allograft recipients.	[26]
39 Tx recipients	CEUS and US examinations at 5 (T0), 15 (T1), and 30 (T2) days after Tx	An increased RI occurred in the ATN and AR groups, as well as reduced PEAK and RBF. RATIO-RBV and RATIO-MTT were lower than normal among ATN cases, while TTP was higher than normal in AR. MTT (T0) was significantly related to creatinine at T2.	CEUS parameters distinguish ATN from AR, which adds prognostic information.	[27]
63 Tx recipients in the early post-transplantation period (7—120 h)	Time-intensity curves compared with hemodynamic flow parameters typically assessed in post-operative graft diagnostics	There was a delay in the inflow of the contrast medium observed in patients with DGF and different time of inflow to the regions of interest between the AR and ATN groups. A significantly longer inflow time of the contrast medium to the cortex and renal pyramids was observed in patients with AR compared to ATN recipients.	CEUS might be a valuable diagnostic tool for the determination of the cause of DGF.	[28]
Prospective/68 Tx recipients 1 week after Tx	CEUS and color Doppler ultrasonography	RBF estimated by CEUS 1 week post-transplantation was significantly correlated with kidney function after 1 year. Determination of RBF by CEUS revealed a significant correlation with donor age but not with recipient age, whereas the conventional color Doppler ultrasonography resistive index was significantly correlated with recipient age ($r = 0.54$; $p < 0.001$) but not donor age. Furthermore RBF was associated with vascular fibrosis and intimal thickening of the engraftment biopsies.	CEUS reveals information regarding kidney allograft perfusion independent of recipient vascular compliance.	[29]

(*continued on next page*)

Table 2 (*continued*)

Design	Method	Result	Conclusion	Ref.
5 Tx recipients/ emergency transplantectomy with cortical necrosis	B-mode, color Doppler and then CEUS. Renal transplant vascularization was evaluated.	Color Doppler ultrasound showed decreased renal parenchymal vascularization and difficulty in finding the spectral waveforms with resistive indices greater than 0.7 in four of five patients. CEUS showed enhancement of the main arteries and medullary pyramids but with an unenhanced peripheral cortical continuous band viewed in all phases. Pathologic assessment showed violet kidneys macroscopically with hemorrhagic foci in the outer cortical area that drew a well-defined band; these findings agreed with the CEUS findings.	CEUS can show the typical peripheral rim sign in cases of cortical necrosis, thus allowing for the reliable and rapid diagnosis of this condition, and it could obviate the need for further imaging studies or biopsy, allowing an earlier decision of nephrectomy.	[30]
97 Tx recipients	Tc-DTPA and CEUS after surgery.	Tc-DTPA detected nine perfusion defects of varying sizes. CEUS detected all of these defects plus 14 further defects (0.2% −17% of total renal volume) not detected on DTPA ($p < 0.0001$). Retrospective clinical correlation showed ligated polar arteries in eight of these 14 cases.	CEUS detects perfusion defects seen and not seen on Tc-DTPA. 3 D CEUS is useful in the quantification of perfusion defects.	[35]

AR, acute rejection; ARFI, acoustic radiation force impulse; ATN, acute tubular necrosis; AUROCs, area under the roc curves; CEUS, contrast-enhanced ultrasonography; DGF, delayed graft function; DRT, the delta-RT among regions of interest; DTTP, the delta-TTP among regions of interest; eGFR, estimated glomerular filtration rate; MTT, mean transit time; PEAK, peak enhancement; RATIO, cortical to medullary ratio of these indices; RBF, renal blood flow; RBV, regional blood volume; RI, resistive index; RT, rising time; Tc-DTPA, Tc-diethylene-triamine-pentaacetate; TTP, time to peak; Tx, transplant; US, ultrasound.

established the following novel simple index to distinguish AR: $P = -0.587 + 0.286 \times \Delta$RTm-c (medulla to cortex) $- 0.028 \times$ eGFR; New Index $= e^P/(1 + e^P)$. This index could easily predict AR with a high degree of accuracy [24] (Table 2) (Fig. 1).

3.3. Advantages and limitations of CEUS

Like all ultrasonic examinations, CEUS is believed to be safe and simple, with wide tolerance and no proven nephrotoxicity. The contrast medium can be safely injected in patients with renal failure because there is no renal excretion of the contrast agent [31], making CEUS a top choice for patients with suspected renal allograft dysfunction. US contrast agents are known to be very safe, with very low anaphylactic reaction rates (1:7000 patients, 0.014%) that are much lower than the comparable anaphylactic reaction rate with CT agents (0.035%—0.095%) [23].

However, CEUS, like other ultrasonic techniques for diagnosis, is restricted by lesion location. Obesity and bowel gas interposition are interfering factors or even contraindications. While the use of CEUS is highly promising in kidney allograft recipients, experience remains limited in a clinical setting.

4. Comparison between ARFI and CEUS with other non-invasive diagnostic methods

4.1. Comparison between ARFI and CEUS with other ultrasonic indicators

Real-time color Doppler ultrasound provides parameters including the RI and pulsatility index (PI). The RI reflects the vascular status of a transplanted kidney, and it has been used in the early diagnosis of acute renal allograft rejection in initial Doppler studies. It has been reported that during the early post-transplantation period, RI and PI were correlated with long-term allograft function and could potentially be used as prognostic factors to aid in risk stratification for future transplant dysfunction [2]. An RI value greater than 0.8 was shown to be predictive of death and poor long-term prognosis for the renal allograft [32]. However, it was also reported that an increased RI was observed in patients with stable renal allograft function [33]. It has been accepted that RI has a lack of sensitivity and specificity for the diagnosis of renal allograft function, except in acute rejection, because it varies with different factors, such as age and blood flow velocity [34]. A higher RI level indicates a dysfunctional allograft kidney, but it does not differentiate AR from ATN, which are two important

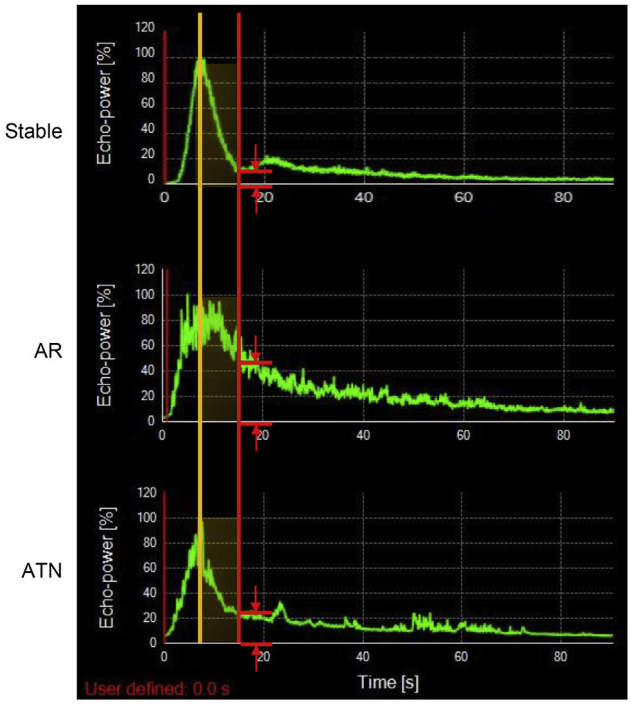

Figure 1 The time-intensity curve (TIC) of CEUS in kidney allografts with different status. Adequate perfusion in the kidney grafts was observed in the stable group but not in the AR or ATN groups. In a stable kidney graft, the TIC had a positively skewed distribution with a smooth curve. It rose rapidly and then reached a peak, followed by an increase in contrast agents in the renal cortex. After a rapid decrease, it slowly increased when the contrast agent moved from the cortex to the medulla. Finally, it decreased after reaching a second peak. In AR and ATN kidneys, the TIC was coarse, particularly in the AR kidney, with apparent ups and downs. In addition, the ascending and descending rates of TIC were slow, compared with those instable kidney grafts. The solid yellow line indicates the peak time point in the stable kidney, and the solid red line indicates the resolution time of contrast agent in the cortex. The period between the yellow and red lines reflects the metabolism of contrast agent in the cortex. Compared to the stable group, the echo-power in the AR and ATN groups was much higher at the time when the contrast agent was excreted from the cortex. AR, acute rejection; ATN, acute tubular necrosis. This is a modified figure that came originally from our published article (Ref. [24]).

and common causes of allograft kidney dysfunction during the early post-transplantation stage. This fact reduces the clinical value of RI because the therapeutic strategies for the two diseases are different. As mentioned above, ARFI and CEUS parameters have shown higher sensitivity and specificity for the diagnosis of kidney allograft dysfunction, compared to conventional ultrasound parameters.

4.2. Comparison between ARFI and CEUS and other non-ultrasonic diagnostic methods

Nuclear medicine: Tc-DTPA is a common post-transplant renogram examination performed to assess perfusion. It provides some functional information, but overall, it is a lengthy, immobile and costly examination method with low spatial resolution that uses ionizing radiation [35]. A recent study by Stenberg et al. [35] compared the detection of post-surgical perfusion defects in kidney transplants between 3-dimensional CEUS and Tc99m-DTPA. They found that Tc-DTPA detected nine perfusion defects of varying sizes. CEUS, however, detected all of these defects plus 14 further defects not detected by DTPA. This finding likely occurred because CEUS detected perfusion defects seen with Tc-DTPA, as well as further perfusion defects not seen on Tc-DTPA, possibly due to increased spatial and temporal resolution and multiple scanning angles.

Computerized tomography (CT): With regard to the kidney, CEUS can obviate the need for CT. The greatest advantage of ARFI and CEUS is their lack of nephrotoxicity caused by CT contrast agents, affording kidney recipients with impaired renal function a simple method of evaluation [36]. In addition, it is estimated that 1.5%—2% of all cancers might be attributable to radiation from CT examinations. Neither ARFI nor CEUS exposes a patient to radiation as CT does, making it significantly safer even among special patient populations.

Functional magnetic resonance imaging (MRI): Functional MRI contributes to multilateral, noninvasive, *in vivo* assessment of kidney function. Two promising functional MRI techniques for assessing kidney function are diffusion-weighted (DW) MRI and blood oxygen level-dependent (BOLD) MRI [37]. DW MRI is based on the thermally induced Brownian motion of water molecules in tissue, and it does not require a contrast medium. Kaul et al. [38] found that apparent diffusion coefficient (ADC) values decreased significantly when rejection occurred, and this decrease was correlated with the degree of rejection on kidney biopsies. However, the reduction in ADC was also observed in kidney allografts with ATN in animal models [39]. Park et al. [40] revealed that DW MRI at 3T could demonstrate the early functional state of renal allografts, but it might also be limited in characterizing the cause of early renal allograft dysfunction. In contrast, CEUS is able to distinguish more of the possible causes of kidney allograft function impairment due to its display of blood flow (such as thrombosis), making it a more ideal choice as a non-invasive method for allograft function assessment, in the hope of replacing renal biopsy.

BOLD MRI utilizes deoxygenated hemoglobin as an endogenous marker of tissue oxygenation. Xiao et al. [41] reported that decreased R2 values of the cortex and medulla and the R2 ratio of M/C suggested AR in renal allografts. Although this tool represents a major addition to our armamentarium of methodologies to investigate the role of hypoxia in the pathogenesis of acute kidney injury and progressive chronic kidney disease, numerous technical limitations have confounded the interpretation of data derived from this approach. Attempts using BOLD MRI have been undertaken to assess acute and chronic rejection, as well as ATN, but the experimental results and conclusions have lacked agreement [42].

Several other MR-based non-invasive technologies, including arterial spin labeling MRI [43], diffusion-tensor MRI [44] and ferumoxytol-enhanced MRA [45] have also been reported to have potential in kidney allograft function evaluation. However, until now, there have been no

comparison studies between ARFI or CEUS and these new MRI technologies.

5. Perspectives and conclusions

ARFI and CEUS are both considered promising because they share features, including safety, convenience and efficiency, and they are non-invasive, have low costs and do not require hospitalization. It is also possible that better evaluation of kidney allograft function lies in a formula containing multiple ultrasonic and clinical indicators.

Ultrasonic examinations can be performed in the outpatient department, making them a top choice for economical kidney allograft assessment. They are highly convenient and efficient, requiring an average of 2—5 min for a trained physician to evaluate a single patient through ARFI. Clinical application of ultrasonic renal allograft function evaluation also avoids the potential risks and complications of renal biopsies, lessening the concern among patients during both routine post-operative evaluations and the confirmation of suspected allograft injury. To achieve an agreeable conclusion despite possible interfering factors, more research with a much larger sample size is required, as well as a standard for ensuring proper interobserver agreement. With a unified diagnostic standard and controlled environment, minimal interference during evaluation can be achieved. The current value of ARFI and CEUS in kidney allograft function assessment remains experimental, yet these technologies have a hopeful future.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by the Science and Technology Commission of Shanghai Municipality (13ZR1406400, 15411964900 to Wanyuan He) and the National Natural Science Foundation of China (81270833 to Tongyu Zhu; 81400752 to Cheng Yang).

References

[1] Torres Munoz A, Valdez-Ortiz R, Gonzalez-Parra C, Espinoza-Davila E, Morales-Buenrostro LE, Correa-Rotter R. Percutaneous renal biopsy of native kidneys: efficiency, safety and risk factors associated with major complications. Arch Med Sci 2011;7:823—31.

[2] McArthur C, Geddes CC, Baxter GM. Early measurement of pulsatility and resistive indexes: correlation with long-term renal transplant function. Radiology 2011;259:278—85.

[3] Goya C, Hamidi C, Hattapoglu S, Cetincakmak MG, Teke M, Degirmenci MS, et al. Use of acoustic radiation force impulse elastography to diagnose acute pancreatitis at hospital admission: comparison with sonography and computed tomography. J Ultrasound Med 2014;33:1453—60.

[4] Park MK, Jo J, Kwon H, Cho JH, Oh JY, Noh MH, et al. Usefulness of acoustic radiation force impulse elastography in the differential diagnosis of benign and malignant solid pancreatic lesions. Ultrasonography 2014;33:26—33.

[5] Wu YM, Xu N, Hu JY, Xu XF, Wu WX, Gao SX, et al. A simple noninvasive index to predict significant liver fibrosis in patients with advanced schistosomiasis japonica. Parasitol Int 2013;62:283—8.

[6] Ozkan F, Menzilcioglu MS, Duymus M, Yildiz S, Avcu S. Acoustic radiation force impulse elastography for evaluating renal parenchymal stiffness in children. Pediatr Radiol 2015;45:461.

[7] Takahashi H, Ono N, Eguchi Y, Eguchi T, Kitajima Y, Kawaguchi Y, et al. Evaluation of acoustic radiation force impulse elastography for fibrosis staging of chronic liver disease: a pilot study. Liver Int 2010;30:538—45.

[8] Stock KF, Klein BS, Vo Cong MT, Sarkar O, Romisch M, Regenbogen C, et al. ARFI-based tissue elasticity quantification in comparison to histology for the diagnosis of renal transplant fibrosis. Clin Hemorheol Microcirc 2010;46:139—48.

[9] Syversveen T, Brabrand K, Midtvedt K, Strom EH, Hartmann A, Jakobsen JA, et al. Assessment of renal allograft fibrosis by acoustic radiation force impulse quantification—a pilot study. Transpl Int 2011;24:100—5.

[10] Stock KF, Klein BS, Cong MT, Regenbogen C, Kemmner S, Buttner M, et al. ARFI-based tissue elasticity quantification and kidney graft dysfunction: first clinical experiences. Clin Hemorheol Microcirc 2011;49:527—35.

[11] He WY, Jin YJ, Wang WP, Li CL, Ji ZB, Yang C. Tissue elasticity quantification by acoustic radiation force impulse for the assessment of renal allograft function. Ultrasound Med Biol 2014;40:322—9.

[12] Guo LH, Xu HX, Fu HJ, Peng A, Zhang YF, Liu LN. Acoustic radiation force impulse imaging for noninvasive evaluation of renal parenchyma elasticity: preliminary findings. PLoS One 2013;8:e68925.

[13] Bota S, Bob F, Sporea I, Sirli R, Popescu A. Factors that influence kidney shear wave speed assessed by acoustic radiation force impulse elastography in patients without kidney pathology. Ultrasound Med Biol 2015;41:1—6.

[14] Syversveen T, Midtvedt K, Berstad AE, Brabrand K, Strom EH, Abildgaard A. Tissue elasticity estimated by acoustic radiation force impulse quantification depends on the applied transducer force: an experimental study in kidney transplant patients. Eur Radiol 2012;22:2130—7.

[15] Tozaki M, Isobe S, Fukuma E. Preliminary study of ultrasonographic tissue quantification of the breast using the acoustic radiation force impulse (ARFI) technology. Eur J Radiol 2011;80:e182—7.

[16] Kaminuma C, Tsushima Y, Matsumoto N, Kurabayashi T, Taketomi-Takahashi A, Endo K. Reliable measurement procedure of virtual touch tissue quantification with acoustic radiation force impulse imaging. J Ultrasound Med 2011;30:745—51.

[17] Yamanaka N, Kaminuma C, Taketomi-Takahashi A, Tsushima Y. Reliable measurement by virtual touch tissue quantification with acoustic radiation force impulse imaging: phantom study. J Ultrasound Med 2012;31:1239—44.

[18] Potthoff A, Attia D, Pischke S, Kirschner J, Mederacke I, Wedemeyer H, et al. Influence of different frequencies and insertion depths on the diagnostic accuracy of liver elastography by acoustic radiation force impulse imaging (ARFI). Eur J Radiol 2013;82:1207—12.

[19] Asano K, Ogata A, Tanaka K, Ide Y, Sankoda A, Kawakita C, et al. Acoustic radiation force impulse elastography of the kidneys: is shear wave velocity affected by tissue fibrosis or renal blood flow? J Ultrasound Med 2014;33:793—801.

[20] Goertz RS, Amann K, Heide R, Bernatik T, Neurath MF, Strobel D. An abdominal and thyroid status with acoustic radiation force impulse elastometry—a feasibility study: acoustic radiation force impulse elastometry of human organs. Eur J Radiol 2011;80:e226—30.

[21] Lee MJ, Kim MJ, Han KH, Yoon CS. Age-related changes in liver, kidney, and spleen stiffness in healthy children measured with acoustic radiation force impulse imaging. Eur J Radiol 2013;82:e290—4.
[22] Nightingale K, McAleavey S, Trahey G. Shear-wave generation using acoustic radiation force: in vivo and ex vivo results. Ultrasound Med Biol 2003;29:1715—23.
[23] Cokkinos DD, Antypa EG, Skilakaki M, Kriketou D, Tavernaraki E, Piperopoulos PN. Contrast enhanced ultrasound of the kidneys: what is it capable of? BioMed Res Int 2013;2013:595873.
[24] Jin Y, Yang C, Wu S, Zhou S, Ji Z, Zhu T, et al. A novel simple noninvasive index to predict renal transplant acute rejection by contrast-enhanced ultrasonography. Transplantation 2015; 99:636—49.
[25] Harvey CJ, Sidhu PS, Bachmann Nielsen M. Contrast-enhanced ultrasound in renal transplants: applications and future directions. Ultraschall Med 2013;34:319—21.
[26] Schwenger V, Korosoglou G, Hinkel UP, Morath C, Hansen A, Sommerer C, et al. Real-time contrast-enhanced sonography of renal transplant recipients predicts chronic allograft nephropathy. Am J Transplant 2006;6:609—15.
[27] Benozzi L, Cappelli G, Granito M, Davoli D, Favali D, Montecchi MG. Contrast-enhanced sonography in early kidney graft dysfunction. Transplant Proc 2009;41:1214—5.
[28] Grzelak P, Szymczyk K, Strzelczyk J, Kurnatowska I, Sapieha M, Nowicki M, et al. Perfusion of kidney graft pyramids and cortex in contrast-enhanced ultrasonography in the determination of the cause of delayed graft function. Ann Transplant Q Pol Transplant Soc 2011;16:48—53.
[29] Schwenger V, Hankel V, Seckinger J, Macher-Goppinger S, Morath C, Zeisbrich M, et al. Contrast-enhanced ultrasonography in the early period after kidney transplantation predicts long-term allograft function. Transplant Proc 2014;46:3352—7.
[30] Fernandez CP, Ripolles T, Martinez MJ, Blay J, Pallardo L, Gavela E. Diagnosis of acute cortical necrosis in renal transplantation by contrast-enhanced ultrasound: a preliminary experience. Ultraschall Med 2013;34:340—4.
[31] Wilson SR, Burns PN. Microbubble-enhanced US in body imaging: what role? Radiology 2010;257:24—39.
[32] Perrella RR, Duerinckx AJ, Tessler FN, Danovitch GM, Wilkinson A, Gonzalez S, et al. Evaluation of renal transplant dysfunction by duplex Doppler sonography: a prospective study and review of the literature. Am J Kidney Dis 1990;15: 544—50.
[33] Kocabas B, Aktas A, Aras M, Isiklar I, Gencoglu A. Renal scintigraphy findings in allograft recipients with increased resistance index on Doppler sonography. Transplant Proc 2008; 40:100—3.
[34] Schwenger V, Keller T, Hofmann N, Hoffmann O, Sommerer C, Nahm AM, et al. Color Doppler indices of renal allografts depend on vascular stiffness of the transplant recipients. Am J Transplant 2006;6:2721—4.
[35] Stenberg B, Chandler C, Wyrley-Birch H, Elliott ST. Postoperative 3-dimensional contrast-enhanced ultrasound (CEUS) versus Tc99m-DTPA in the detection of post-surgical perfusion defects in kidney transplants — preliminary findings. 2014;35: 273—8.
[36] McArthur C, Baxter GM. Current and potential renal applications of contrast-enhanced ultrasound. Clin Radiol 2012;67: 909—22.
[37] Inoue T, Kozawa E, Okada H, Inukai K, Watanabe S, Kikuta T, et al. Noninvasive evaluation of kidney hypoxia and fibrosis using magnetic resonance imaging. J Am Soc Nephrol 2011;22: 1429—34.
[38] Kaul A, Sharma RK, Gupta RK, Lal H, Jaisuresh, Yadav A, et al. Assessment of allograft function using diffusion-weighted magnetic resonance imaging in kidney transplant patients. Saudi J Kidney Dis Transplant 2014;25:1143—7.
[39] Yang D, Ye Q, Williams DS, Hitchens TK, Ho C. Normal and transplanted rat kidneys: diffusion MR imaging at 7 T. Radiology 2004;231:702—9.
[40] Park SY, Kim CK, Park BK, Kim SJ, Lee S, Huh W. Assessment of early renal allograft dysfunction with blood oxygenation level-dependent MRI and diffusion-weighted imaging. Eur J Radiol 2014;83:2114—21.
[41] Xiao W, Xu J, Wang Q, Xu Y, Zhang M. Functional evaluation of transplanted kidneys in normal function and acute rejection using BOLD MR imaging. Eur J Radiol 2012;81:838—45.
[42] Neugarten J, Golestaneh L. Blood oxygenation level-dependent MRI for assessment of renal oxygenation. Int J Nephrol Renovasc Dis 2014;7:421—35.
[43] Heusch P, Wittsack HJ, Blondin D, Ljimani A, Nguyen-Quang M, Martirosian P, et al. Functional evaluation of transplanted kidneys using arterial spin labeling MRI. J Magn Reson Imaging 2014;40:84—9.
[44] Lanzman RS, Ljimani A, Pentang G, Zgoura P, Zenginli H, Kropil P, et al. Kidney transplant: functional assessment with diffusion-tensor MR imaging at 3T. Radiology 2013;266: 218—25.
[45] Bashir MR, Jaffe TA, Brennan TV, Patel UD, Ellis MJ. Renal transplant imaging using magnetic resonance angiography with a nonnephrotoxic contrast agent. Transplantation 2013; 96:91—6.