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Transplant renal artery stenosis: Evaluation with contrast-enhanced ultrasound

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ABSTRACT

Objective: To assess the efficacy of contrast-enhanced ultrasound (CEUS) in depicting transplant renal artery stenosis (TRAS).
Materials and methods: Seventy-eight patients (56 men and 22 women; aged 36 ± 12.2 years) who were suspected of TRAS due to either Doppler ultrasound (DUS) abnormalities or difficult control of blood pressure and/or persistent deterioration of renal function were enrolled to perform CEUS. The reference standard for the TRAS diagnoses was computed tomography angiography (CTA). The diagnostic performance of DUS and CEUS parameters was assessed by the area under the receiver operating characteristic curve (AUC).
Results: TRAS was diagnosed in 32 out of 78 cases by CTA. The AUC, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of CEUS in predicting TRAS were 0.92, 92.3%, 87.5%, 95.7%, 93.3%, and 91.7%, respectively. CEUS rectified 13 (28.3%) false-positive cases on DUS, which were confirmed by CTA. Compared to DUS parameters, CEUS showed the highest AUC, statistically significant differences of AUC were found (P = 0.006–0.039), except for that of the PSV ratio in the main transplant renal artery to that in interlobar artery (PSV-ratio) (AUC: 0.92 versus 0.86, P = 0.422). However, CEUS showed a significantly higher specificity (95.7% versus 76.1%, P = 0.008) and the same sensitivity compared to PSV-ratio.
Conclusions: CEUS is superior to DUS in depicting TRAS. Moreover, our results suggest that CEUS might potentially be used as a noninvasive tool to spare many patients from unnecessary CTA.

1. Introduction

With improved outcome and graft longevity, secondary vascular complications such as transplant renal artery stenosis (TRAS) are well recognized. TRAS is not a rare disorder with angiographic incidence ranging from 5% to 10% and usually occurs during the first 2 years after transplantation [1,2]. Early detection of TRAS is of great importance because most stenoses can be treated with surgical or radiologic intervention and, if untreated, may progress to medically refractory hypertension, deteriorating renal function, and even renal graft loss [2,3].

Digital subtraction angiography (DSA) remains the gold standard for diagnosing TRAS after renal transplantation [4]. However, its application has been restricted owing to its invasive nature and reliance on nephrotoxic contrast media. Recent study has found that the rate of acute kidney injury following computed tomography angiography (CTA) is low in transplanted kidneys [5], thus CTA is a widely accepted reference standard to monitor arterial complications after renal transplantation [6]. MRA has been sufficiently proved in previous literature to be an accurate method for TRAS diagnosis [7], nevertheless, a tendency to overestimate stenosis is its drawback [8]. Furthermore, MRA may pose the patients at the risk of nephrogenic systemic fibrosis [9].

Doppler ultrasound (DUS) has become the primary imaging technique in the initial screening and follow-up of vascular complications due to its portable, inexpensive and noninvasive [10]. A variety of Doppler parameters have been assessed in screening for TRAS, such as peak systolic velocity (PSV), intrarenal resistance index (RI) and acceleration time [11–16]. However, the optimal

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diagnostic threshold PSV for TRAS is still controversial due to the wide disparity in different studies, which ranges from a PSV ≥1.5 m/s to 4.0 m/s [11,12,14]. Additionally, there is no agreement on a specific cut-off intrarenal RI value for TRAS diagnosis [12,13,15]. Finally, DUS is highly operator-dependent, and there may be technical difficulties in evaluating transplant renal vessels [2,17]. Thus, a noninvasive and accurate method is required for the early detection of TRAS.

Owing to the fact that the contrast agent's microbubbles are ideal intravascular tracers, recent studies have shown that the application of contrast enhanced ultrasound (CEUS) has greatly improved the performance of ultrasonography in vascular patency assessment [18,19]. Due to relatively superficial location of transplanted kidney, limited respiratory movement as well as non-nephrotoxic contrast agent, CEUS seem to be a potential and safe imaging modality to monitor the patency of transplant renal artery (TRA). However, to our knowledge, relatively few studies have described the diagnosis performance of CEUS for TRAS [20,21]. The purpose of this study was to evaluate the efficacy of CEUS in TRAS diagnosis.

2. Patients and methods

2.1. Patients

This retrospective study was approved by the institutional review board, and written informed consent was obtained from all patients. Between January 2010 and April 2016, 785 consecutive patients underwent renal transplantation because of chronic renal insufficiency at our institution. DUS was routinely performed after transplantation. CEUS examination was performed in 163 patients who were suspected of TRAS due to one or more of the following reasons [11–13,15,16]: (a) with a focal PSV ≥ 2.5 m/s in TRA; (b) RI < 0.50 at the interlobar artery; and (c) difficult control of blood pressure and/or persistent deterioration of renal function. Of these, 85 patients were excluded. Thus, 78 patients (56 male, 22 female; mean age 36 years ± 12.2, range 18–68 years) were enrolled in the final analysis (Fig. 1). Transplanted kidneys were obtained in 45 patients from deceased donors and 33 patients from living relative donors. Vascular anastomosis between the end of the TRA and the side of the external or common iliac artery was performed in 68 (87.2%) recipients. In the remaining 10 patients (12.8%), the end of the TRA was anastomosed with the end of the internal iliac artery. The interval between transplantation and CEUS ranged from 1 day to 30 months (mean, 128.9 days). Computed tomography angiography (CTA) were performed for all of the 78 patients, meanwhile, 17 patients underwent DSA for further interventional treatment. The interval between CEUS and CTA was all less than 2 weeks.

2.2. Ultrasound examination

All the US examinations were performed by two ultrasound physicians (F.S.P. and Y.L.Z.), each with more than 3 years of experience using CEUS in renal transplants.

DUS and CEUS were performed with Acuson Sequoia 512 system (Siemens Medical Solutions, Mountain View, CA, USA) equipped with a 1.0–4.0 MHz convex transducer or iU22 ultrasound system (Philips royal electronic corporation, the Netherlands) with a 2–5-MHz convex transducer. All DUS examinations were conducted to assess the iliac vessels, main donor renal artery as well as interlobar artery. Color Doppler was used to delineate the course of the entire TRA in order to select a good insonation angle for PSV assessment, especially in cases with curved TRA; it was also applied to search for turbulences in the main TRA and the primary branches by tissue vibration artifact. Once turbulence was detected, the color scale was upgraded until color aliasing was utmost eliminated before PSV measurement. Three measurements were made and averaged for all of the DUS parameters except for that of PSV in the turbulence, which was recorded as the highest value of the three measurements.

After the long-axis view of the TRA was identified on DUS, the CEUS mode was initiated. The focus was positioned at the bottom of the target artery. The Timer was activated at the beginning of the intravenous contrast agent injection. The CEUS was performed using contrast harmonic imaging at a low mechanical index. The contrast agent selected was SonoVue (Bracco Imaging, Milan, Italy), consisting of sulphur hexafluoride micro-bubbles stabilized by a phospholipid shell. A 1.2 ml SonoVue was injected in 5 s via a 20-gauge intravenous cannula (Venflon; Becton Dickinson, Helsingborg, Sweden) placed in the antecubital vein; this was followed by a flush of 5 ml of a 0.9% sodium chloride solution. The duration of contrast enhancement ranged from 4 to 6 min. For observation of the iliac and TRA, it was scanned along its course in the early phase within 30 s. SonoVue administration was repeated when deemed to be necessary. A minimum interval of 10 min and complete microbubble destruction was obtained by scanning the TRA at a high mechanical index. During CEUS, still images and cine loops were acquired and stored in the picture archiving and communication system for subsequent analysis.

2.3. CTA

A 64-slice CT (Aquillion 64; Toshiba Medical Systems, Tokyo, Japan) was used for all patients. Effective pitch was 0.175 or 0.225. The rotation time was 0.4–0.45 s. Breath-holding technique was used in all patients. A 60–75 ml dose of nonionic contrast medium (iopromide: 370 mg/dL) was injected at the rate of 4.0–5.0 ml/s into the antecubital vein followed by 40 ml of saline flush. Images were routinely reconstructed using a 0.5 mm slice thickness and 0.3 mm slice increment during the optimal phase. All the data were transferred to the workstation (Vitrea@2 version 3.7.0; vital images, Minnetonka, Minnesota, USA). CTA was reconstructed by various methods such as multiplanar reformations, maximum intensity projections, curved planar reformation, and volume rendering technique.

2.4. Image interpretation

Three DUS parameters, including PSV in the TRA (PSV-TRA), PSV-ratio (the ratio of the PSV in the TRA to that in interlobar artery), and RI in interlobar artery (RI-interlobar), were recorded.

The CEUS images were independently analyzed by two other staff radiologists (M.L. and J.L.), both of whom had more than 3 years of experience in transplanted renal CEUS. Both observers were blinded to the clinical history and previous DUS imaging. In cases where the results differed between the two authors, a final conclusion was decided by conference. If a stenosis was found, the location and quantitative measures of the degree of stenosis were recorded. The following measurements were made for each stenosis: minimum lumen diameter of the stenotic segment (A), diameter of the patent lumen in a normal post-stenotic segment adjacent to the stenosis (B), and/or diameter of the patent lumen in a normal pre-stenotic segment adjacent to the stenosis (C). The degree of stenosis was then calculated as $(1 - A/B) \times 100\%$ if the stenosis located at anastomosis, and $(1 - A/C) \times 100\%$ if the stenosis located at the main TRA. Combined with the experience of other authors [11–15], we classified the degree of stenosis on CEUS into two groups: non-TRAS, normal or <50%; TRAS, ≥50%.

The reference standards for TRAS diagnoses were CTA. The location and degree of stenosis were recorded by one radiologist (X.X.X), who was blinded to the results of DUS and CEUS. The cal-