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Original contribution

Assessment of transplant renal artery stenosis with diffusion-weighted imaging: A preliminary study☆

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ABSTRACT

Objective: To characterize capillary perfusion and tissue diffusion changes in transplant renal artery stenosis (TRAS) with diffusion-weighted imaging (DWI).

Materials & methods: We retrospectively identified 30 patients with non-contrast enhanced magnetic resonance angiography-proven TRAS. Another 20 kidney transplant recipients without TRAS were prospectively recruited to serve as control group. DWI parameters were compared among various groups with one-way analysis of variance and post hoc Tukey test. Additionally, DWI parameters were compared in 7 severe TRAS patients before and after successful angioplasty using paired Student *t*-test. Receiver-operating characteristic (ROC) curves were generated to evaluate the diagnostic performance of various DWI parameters.

Results: All DWI parameters of renal cortex and medulla were not statistically different between normal allografts and allografts with mild TRAS. Nonetheless, cortical total apparent diffusion coefficient (ADC_T) of allografts with moderate TRAS was significantly decreased compared with normal allografts. All cortical and medullary DWI parameters were significantly reduced in severe TRAS compared with normal allografts. ROC curve analysis indicated ADC_T could identify severe TRAS with 93.8% sensitivity, 82.4% specificity and an area under the curve of 0.930. ADC_T increased significantly after successful angioplasty while it showed no significant change in a patient with unsuccessful angioplasty.

Conclusion: DWI is a robust technique that revealed no tissue diffusion and perfusion impairment in mild TRAS. ADC_T has good sensitivity and specificity for identifying patients with severe TRAS. DWI is potentially an alternative radiologic biomarker for assessing microstructural and perfusion alterations in TRAS. DWI is useful in detecting renal functional recovery following successful angioplasty.

1. Introduction

Transplant renal artery stenosis (TRAS) is an underestimated but potentially curable vascular complication following kidney transplantation [1]. The reported prevalence of TRAS varied from 1% to 23% [2,3]. It frequently arises in proximity to surgical anastomosis, suggesting that mechanical trauma to the recipient or donor vessel is the most likely etiology [3]. Clinically, TRAS often presents with recalcitrant hypertension and/or allograft functional impairment.

Ultrasonography is commonly employed as the first-line modality to screen and diagnose TRAS. Nevertheless, this technique has been demonstrated to be low-yield and operator-dependent in TRAS, especially for detecting mild to moderate TRAS [4]. Contrast-enhanced computed tomography (CTA) and magnetic resonance angiography (MRA) are highly valuable in detecting TRAS. However, concerns of ionizing radiation deter the widespread use of CTA. Although gadolinium could be

Abbreviations: ADC_T, total apparent diffusion coefficient; D, true diffusion; DSA, digital subtraction angiography; DWI, diffusion-weighted imaging; eGFR, estimated glomerular filtration rate; Fp, perfusion fraction; IVIM, intravoxel incoherent motion; NC-MRA, non-contrast magnetic resonance angiography; ROC, receiver-operating characteristic curve; ROI, region of interest; TRAS, transplant renal artery stenosis

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used in patients with mild to moderate renal functional impairment, recent studies have raised concerns regarding gadolinium deposition in the human brain [5]. On the contrary, non-contrast enhanced magnetic resonance angiography (NC-MRA) has been demonstrated to possess potential advantages of ionizing-free, high accuracy and excellent applicability [6,7].

The tissue diffusion and perfusion characteristics of varying degrees of TRAS remain elusive. In the native kidneys with renal artery stenosis, a variety of functional imaging techniques have been employed to assess hemodynamic alterations induced by renal artery stenosis, such as arterial spin labeling [8], intravoxel incoherent motion (IVIM) diffusion-weighted imaging (DWI) [9] and dynamic contrast-enhancement [10]. Nevertheless, etiopathogenesis and treatment response between renal artery stenosis of the native kidneys and TRAS are completely different. To our knowledge, tissue diffusion and perfusion evaluation using MR functional imaging techniques has not been performed in TRAS yet. IVIM-DWI is a powerful technique that is capable of evaluating both capillary perfusion and true tissue diffusion by applying a biexponential model to magnetic resonance signal intensity decay [11]. IVIM is able to determine non-perfusion-based molecular diffusion (pure molecular diffusion, D), perfusion-based molecular diffusion (D^*) as well as perfusion fraction (Fp) separately. By concurrently applying NC-MRA and DWI, the morphological, diffusion and perfusion characteristics of TRAS can be simultaneously determined, which may potentially provide complementary information for optimal patient management.

In this retrospective cross-sectional study, the authors analyzed DWI data from allografts with varying degrees of TRAS to explore the association of tissue diffusion and capillary perfusion characteristics with TRAS severity. Moreover, DWI parameters before and after TRAS balloon angioplasty in a subset of severe TRAS patients were also compared to ascertain whether DWI parameter changes are associated with successfulness of balloon angioplasty.

2. Materials and methods

2.1. Patients

During June 2014 and January 2016, a total of 187 patients referred by the treating nephrologists for suspected TRAS underwent MR examinations, of which we identified 30 patients with NC-MRA–proven TRAS. Main indications for radiologic referral included increased velocity detected by ultrasonography, de novo onset of post-operative hypertension or worsening of preexisting hypertension, or unexplained renal allograft dysfunction with apparently no other causes. The control group consisted of 20 prospectively recruited kidney transplant recipients with normal renal function who also underwent MR examinations with negative NC-MRA findings. The present study was approved by local ethic committee and informed consents were gathered from all participated patients.

2.2. Non-contrast enhanced magnetic resonance angiography

All the patients were instructed to fast for at least 4 h before MR examinations. Patients were scanned in the supine position using a clinical 3-T imager (Discovery MR750, General Electric, Milwaukee, WI, USA) with a 32-element torso coil. T2- weighted images of the allograft were routinely acquired. For NC-MRA, a 3D respiration-gated inflow inversion recovery steady state free precision sequence was employed to assess transplant renal artery lucency. The related imaging parameters were as follows: field of view 36 × 34.4 cm, flip angle 45°, matrix 192 × 288, slice thickness 2 mm, TR 4 ms, TE 2 ms, TI 220 ms.

The percentage of luminal area reduction was calculated on the source images using vendor-supplied software (Functool, GE, Milwaukee, WI, USA). The narrowest diameter of the stenotic area and the diameter of normal caliber transplant artery were measured and the area calculated as previously reported [12] by an experienced abdominal radiologist (YJ.L, > 15 years of experience with abdominal radiology). Stenosis degree was reported as mild (10–40% stenosis), moderate (40–70% stenosis) and severe (≥70% stenosis).

2.3. Digital subtraction angiography

Thirteen of the 16 patients with severe TRAS underwent digital subtraction angiography (DSA) which was performed by an experienced interventional radiologist (S.D.H) with a DSA Unit (Axiom Artis dTA; Siemens, Forchheim, Germany). The narrowest point in the TRAS was measured followed by angioplasty using balloon expansion. The stenosis percentage was calculated as: 1-the area with stenosis/area of normal vessel located on the proximal side of stenosis within 1 cm.

2.4. Intravoxel incoherent motion diffusion-weighted imaging

We routinely perform DWI on patients with TRAS to determine the presence of ischemic/infarction areas. A single-shot echo planar imaging sequence with a range of 11 b values (0, 10, 30, 50, 70, 100, 150, 200, 400, 800, 1000s/mm^2) was acquired using respiration-triggered technique and following parameters: axial plane, field of view 38 × 30.4 cm, matrix 256 × 128, slice thickness 6 mm, number of slices 15; TR 2857 ms, TE 87.2 ms, number of excitations 2. The scanning time was approximately 4–6 min, depending on patient breathing rhythm. MR examinations were routinely repeated in the presence of motion artifacts that severely distorted image quality to ensure that acquired images were interpretable.

DWI raw data was transferred to a vendor-supplied workstation (ADW4.4, GE, Milwaukee, WI, USA) where a software programme (MADC, Functool, GE, Milwaukee, WI, USA) was used to analyze DWI parameters. The contributions of true diffusion (D) and microvascular perfusion fraction (Fp) were generated by fitting a biexponential model: $S_b/S_0 = (1 - Fp).exp\ (-bD) + Fp.exp\ (-b\ [D^* + D])$, where S_b represented the signal intensity at a given b value, S_0 was the signal intensity for b = 0 s/mm^2 and D^* was the pseudo-diffusion coefficient representing incoherent microcirculation within the voxel [13]. In line with previous studies [13,14], a constrained segmented fitting algorithm was employed. Briefly, initial D value was estimated using a reduced set of b values > 200 s/mm^2 and subsequently, the resulting D was taken as a fix parameter to fit the missing parameters D^* and Fp. The total apparent diffusion coefficient (ADC_T) was calculated by fitting all 11 b values using a mono-exponential model according to the following equation: $S_b/S_0 = \exp\ (-b{\cdot}ADC_T)$.

Regions of interests (ROIs) were manually placed in both the cortex and medulla on each of the 3 slices near the central hilum on the b = 0 s/mm^2 image by two authors (DH.S., 11 years of experience with abdominal radiology; YJ.L., > 15 years of experience with abdominal radiology) independently. A total of 3 large cortical ROIs that covered the entire cortex and 9 small medullary ROIs that measured roughly 15–30 mm^2 each were drawn for each allograft, and the readings of cortical ROIs and medullary ROIs were averaged for subsequent analyses. Slices with signal intensity inhomogeneities or cysts were excluded when delineating ROIs.

2.5. Statistical analyses

Statistical analysis was performed using commercially available SPSS 22.0 software (IBM, Armonk, NY). Results were presented as mean ± standard deviations for measurement data or ratio for enumeration data. Intraclass correlation coefficients were calculated to test the reproducibility of DWI parameters. DWI parameters among normal controls and mild, moderate and severe TRAS were compared using one-way analysis of variance with post hoc Tukey test. DWI parameters before and after angioplasty were compared with paired Student *t*-test. Enumeration data was analyzed by Chi-square test. Receiver-operating

Table 1
Clinical characteristics of patients with TRAS and normal controls.

	Normal control (N = 20)	Mild TRAS (N = 7)	Moderate TRAS (N = 7)	Severe TRAS (N = 16)	P value (ANOVA)
Age (years)	33.9 ± 7.9	36.9 ± 8.7	37.9 ± 6.8	38.7 ± 11.3	0.72
Male:female	16:4	5:2	6:1	15:1	0.53
Body mass index (kg/m^2)	20.5 ± 2.6	20.6 ± 3.4	22.5 ± 2.7	21.6 ± 2.8	0.35
Median time interval from transplant to TRAS detection (months) (range)	/	9 (5–32)	21 (6–66)	5 (1–42)	/
eGFR (ml/min/1.73m^2)	73.7 ± 17.8	73.4 ± 23.9	48.6 ± 18.7*	51.6 ± 25.9*	0.006
Systolic blood pressure (mmHg)	135 ± 5	144. ± 27	143 ± 6	144 ± 11	0.079
Diastolic blood pressure (mmHg)	78 ± 10	82 ± 10	79 ± 5	84 ± 8	0.225
Immunosuppressive regimens					
Pre + MMF + FK506 (%)	85	71.4	71.4	75	0.80
Other (%)	15	28.6	28.6	25	
No. of antihypertensives	0.7 ± 0.5	1.9 ± 1.6*	2.0 ± 1.2**	2.5 ± 0.8***	< 0.001

Abbreviations: ANOVA = one-way analysis of variance; eGFR = estimated glomerular filtration rate; FK506, tacrolimus; MMF, mycophenolate mofetil; Pre, prednisone; TRAS = transplant renal artery stenosis. *, ** and *** denote P < 0.05, < 0.01 and < 0.001 respectively compared with normal controls.

characteristic (ROC) curves were generated to determine the optimal threshold of various DWI parameters for differentiating moderate and/or severe TRAS from patients with mild or no TRAS. A P value of < 0.05 was deemed statistically significant.

3. Results

3.1. Patients' demographics and clinical parameters

Patient demographics and clinical parameters were summarized in Table 1. No significant differences were observed among various groups with regard to patients' age, gender, body mass index, blood pressure and immunosuppressive regimens. Nonetheless, the number of antihypertensive usage was significantly higher in TRAS patients than normal controls. However, estimated glomerular filtration rate (eGFR) were much lower in patients with moderate and severe TRAS than that of normal controls (48.6 ± 18.7 ml/min/1.73m^2 vs 73.7 ± 17.8 ml/min/1.73m^2, P = 0.044; 51.6 ± 25.9 ml/min/1.73m^2 vs 73.7 ± 17.8 ml/min/1.73m^2, P = 0.02 respectively).

3.2. DWI of renal allografts with TRAS and normal allografts

NC-MRA identified 30 TRAS, including 7 mild TRAS, 7 moderate and 16 severe TRAS. Thirteen patients with severe TRAS underwent DSA and balloon angioplasty at our hospital, of which 8 patients were re-examined with DWI and NC-MRA post-angioplasty. The other 3 patients chose to receive angioplasty at local hospitals and were lost to follow-up. Although these 13 cases were corroborated as severe TRAS by DSA, NC-MRA overestimated stenotic degree when DSA was considered the gold standard (87% ± 7.6% vs 79% ± 6.4%, P = 0.00).

The intraclass correlation coefficients of cortical ADC_T, D and Fp were 0.96, 0.90 and 0.83 respectively; the intraclass correlation coefficients of medullary ADC_T, D and Fp were 0.92, 0.83 and 0.78 respectively. Then DWI parameters calculated by 2 raters were averaged and used for further analysis.

DWI parameters were compared between various groups of TRAS and normal control (Table 2, Supplementary Figure). All DWI parameters of renal cortex and medulla were not statistically different between normal allografts and allografts with mild TRAS (all P > 0.05). Nonetheless, cortical ADC_T of allografts with moderate TRAS was significantly decreased compared with normal allografts ($1.99 \pm 0.17 \times 10^{-3}$ mm^2/s vs $2.22 \pm 0.08 \times 10^{-3}$ mm^2/s, P = 0.004). Moreover, all cortical and medullary DWI parameters were significantly reduced in allografts with severe TRAS as compared with normal allografts.

For TRAS patients with distinct degrees of severity, cortical ADC_T tended to be decreased in patients with moderate TRAS (P = 0.08) and more prominently in patients with severe TRAS as compared with allografts with mild TRAS. Except for medullary ADC_T that is significantly decreased in moderate TRAS as compared to mild TRAS ($1.91 \pm 0.20 \times 10^{-3}$ mm^2/s vs $2.17 \pm 0.24 \times 10^{-3}$ mm^2/s, P = 0.03), other DWI parameters showed no significant differences. Compared with moderate TRAS, cortical Fp was decreased in severe TRAS (P = 0.02).

ROC curve analysis (Table 3) indicated that all DWI parameters were able to differentiate moderate and/or severe TRAS from normal and mild TRAS. For differentiating no less than moderate TRAS from normal and mild TRAS, cortical ADC_T had the largest area under the curve (AUC = 0.953, 95% confidence interval 0.853–0.993) with good sensitivity (0.870) and excellent specificity (0.926). For specifically identifying severe TRAS, cortical ADC_T had 93.8% sensitivity, 82.4% specificity and an AUC of 0.930.

3.3. Comparison of DWI parameters of allografts with severe TRAS before and after balloon angioplasty

Balloon angioplasty were successful in 7 patients as indicated by post-angioplasty stenotic degree < 40% (i.e., no more than mild stenosis after angioplasty) and increased post-operative eGFR and/or decreased blood pressure (Table 4). Angioplasty in another patient was unsuccessful (i.e. still severe TRAS) due to technical difficulty. This patient remained hypertensive after angioplasty (Table 4). DWI was re-performed with a median of 47 days (interquartile range: 5.5–65.3 days) after angioplasty. For patients with successful angioplasty, cortical and medullary ADC_T, and cortical Fp increased significantly after angioplasty (Table 4). On the contrary, ADC_T showed no improvement in the unsuccessful case after angioplasty (Fig. 1). These data indicated that increased ADC_T could potentially be used to indicate the successfulness of angioplasty.

4. Discussion

In addition to morphologic evaluation of TRAS severity, determination of allograft tissue diffusion and capillary perfusion alterations in TRAS would probably afford insights into the underlying pathophysiology in TRAS. Nevertheless, previous studies regarding this topic were scarce and no clinical studies have been implemented to study TRAS tissue diffusion and perfusion changes yet. This study aimed to explore whether DWI parameter changes could be potentially exploited for radiologic functional interrogation in TRAS.

Interestingly, responses to percutaneous transluminal renal angioplasty between TRAS and renal artery stenosis of the native kidneys are completely different. It is being increasingly recognized that only a small subset of patients with renal artery stenosis of the native kidneys

Table 2
Comparison of IVIM-DWI parameter among normal control and various TRAS groups.

	Normal (N = 20)	Mild TRAS (N = 7)	Moderate TRAS (N = 7)	Severe TRAS (N = 16)	P value (ANOVA)	Post hoc Tukey test					
						P_{12}	P_{13}	P_{14}	P_{23}	P_{24}	P_{34}
Cortical ADC_T ($\times 10^{-3}$ mm^2/s)	2.22 ± 0.08	2.18 ± 0.16	1.99 ± 0.17	1.83 ± 0.19	< **0.001**	0.94	**0.004**	< **0.001**	0.08	< **0.001**	0.08
Medullary ADC_T ($\times 10^{-3}$ mm^2/s)	2.09 ± 0.12	2.17 ± 0.24	1.91 ± 0.20	1.76 ± 0.18	< **0.001**	0.74	0.09	< **0.001**	**0.04**	< **0.001**	0.24
Cortical D ($\times 10^{-3}$ mm^2/s)	1.62 ± 0.07	1.61 ± 0.09	1.56 ± 0.10	1.43 ± 0.15	< **0.001**	0.99	0.67	< **0.001**	0.86	**0.004**	0.05
Medullary D ($\times 10^{-3}$ mm^2/s)	1.53 ± 0.10	1.57 ± 0.12	1.44 ± 0.12	1.39 ± 0.14	**0.002**	0.88	0.34	**0.006**	0.21	**0.01**	0.79
Cortical Fp	0.382 ± 0.041	0.382 ± 0.054	0.337 ± 0.058	0.263 ± 0.064	< **0.001**	0.99	0.23	< **0.001**	0.40	< **0.001**	**0.02**
Medullary Fp	0.387 ± 0.064	0.390 ± 0.102	0.354 ± 0.076	0.286 ± 0.111	**0.007**	0.99	0.83	**0.007**	0.87	0.06	0.33

Abbreviation: ANOVA = one-way analysis of variance. P_{12}, P_{13} and P_{14} denoted comparisons of Normal with Mild TRAS, Moderate TRAS and Severe TRAS respectively. P_{23} and P_{24} denoted comparisons of Mild TRAS with Moderate TRAS and Severe TRAS respectively. P_{34} denoted comparison between Moderate TRAS and Severe TRAS.

Table 3
Receiver-operating characteristic curve analysis of IVIM-DWI parameters for differentiating moderate and/or severe TRAS from normal and mild TRAS.

	Differentiating no less than moderate TRAS from no more than mild TRAS				Differentiating severe TRAS from normal, mild and moderate TRAS			
	Cut-off	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Cut-off	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cortical ADC_T	2.09×10^{-3} mm^2/s	0.953 (0.853, 0.993)	0.870 (0.664, 0.972)	0.926 (0.757, 0.991)	2.07×10^{-3} mm^2/s	0.930 (0.821, 0.983)	0.938 (0.698, 0.998)	0.824 (0.655, 0.932)
Medullary ADC_T	1.92×10^{-3} mm^2/s	0.899 (0.780, 0.966)	0.783 (0.563, 0.925)	0.889 (0.708, 0.976)	1.97×10^{-3} mm^2/s	0.883 (0.761, 0.957)	0.938 (0.698, 0.998)	0.735 (0.556, 0.871)
Cortical D	1.51×10^{-3} mm^2/s	0.750 (0.608, 0.862)	0.565 (0.345, 0.768)	1.000 (0.872, 1.000)	1.51×10^{-3} mm^2/s	0.806 (0.670, 0.904)	0.750 (0.476, 0.927)	0.971 (0.847, 0.999)
Medullary D	1.43×10^{-3} mm^2/s	0.798 (0.660, 0.898)	0.652 (0.427, 0.836)	0.926 (0.757, 0.991)	1.43×10^{-3} mm^2/s	0.788 (0.649, 0.891)	0.750 (0.476, 0.927)	0.853 (0.689, 0.950)
Cortical Fp	0.335	0.879 (0.75, 0.954)	0.826 (0.612, 0.950)	0.852 (0.663, 0.958)	0.315	0.921 (0.809, 0.978)	0.875 (0.617, 0.984)	0.912 (0.763, 0.981)
Medullary Fp	0.271	0.742 (0.599, 0.856)	0.522 (0.306, 0.732)	1.000 (0.872, 1.000)	0.265	0.787 (0.648, 0.890)	0.625 (0.354, 0.848)	0.971 (0.847, 0.999)

Abbreviations: AUC = area under the curve; CI = confidence interval.

Table 4
Comparison of clinical and IVIM-DWI parameters for the 8 patients before and after balloon angioplasty.

		Clinical parameters			IVIM-DWI parameters					
		eGFR (ml/min/1.73m^2)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Cortical ADC_T ($\times 10^{-3}$ mm^2/s)	Medullary ADC_T ($\times 10^{-3}$ mm^2/s)	Cortical D ($\times 10^{-3}$ mm^2/s)	Medullary D ($\times 10^{3}$mm^2/s)	Cortical Fp	Medullary Fp
Successful angioplasty (N = 7)	Pre-angioplasty	46.3 ± 19.8	142 ± 9	82 ± 12	1.91 ± 0.20	1.83 ± 0.17	1.48 ± 0.16	1.47 ± 0.11	0.294 ± 0.065	0.355 ± 0.123
	Post-angioplasty	55.4 ± 20.5	129 ± 8	75 ± 12	2.07 ± 0.20	1.98 ± 0.19	1.57 ± 0.18	1.52 ± 0.12	0.355 ± 0.055	0.386 ± 0.084
	P value	**0.016**	**0.009**	**0.026**	**0.001**	**0.010**	0.084	0.065	**0.048**	0.101
Unsuccessful angioplasty (N = 1)	Pre-angioplasty	82	160	95	1.64	1.52	1.34	1.11	0.147	0.129
	Post-angioplasty	71	152	101	1.61	1.48	1.24	1.14	0.180	0.303

will experience improved renal functions after interventions [15]. In contrast, initial experiences in TRAS suggested that the majority of TRAS patients responded favorably to angioplasty. Although the exact reasons for this disparity remain elusive, it is postulated that differences in etiologies may be partially responsible. Renal artery stenosis of the native kidneys is mainly caused by renal artery atherosclerosis, which is generally insidious with a long medical history. On the other hand, TRAS is predominantly caused by mechanical narrowing of the transplant renal artery with a much shorter disease history. Moreover, it has been recently noticed that renal artery stenosis of the native kidneys induces kidney peritubular capillary dropout and interstitial fibrosis, perpetuating intrinsic kidney injury that is unresponsive to angioplasty [16].

This study showed that IVIM-based analysis of DWI signals is a powerful technique that could afford noninvasively important quantitative information in kidney transplant patients with TRAS. Moreover, our study indicated that no tissue diffusion and perfusion impairment was induced by mild TRAS, which is consistent with clinical approach of conservative management in this subpopulation. Nevertheless, severe TRAS caused significant reductions of tissue diffusion and capillary perfusion properties. Additionally, given that allograft dysfunction and hypertension were often present in this patient group, clinically they are frequently managed with balloon angioplasty or stenting. Furthermore, several DWI-yielded quantitative parameters ameliorated in keeping with increased eGFR and decreased blood pressure after successful angioplasty, suggesting DWI is a feasible imaging tool for evaluating severe TRAS.

NC-MRA was used in this study as the reference standard to diagnose TRAS due to its reported high accuracy compared with ultrasonography [17] and non-ionizing characteristic in contrast with CTA. In an earlier study, Tang and associates [18] successfully employed another unenhanced MRA technique to depict transplant renal artery anatomy and post-surgical vascular complications. However, no interrogation of functional alterations in TRAS was carried out in that study. In this small patient population, we noticed that NC-MRA slightly overestimated stenotic degree compared with DSA, which was in line with previous findings [19,20]. Signal intensity-dropout along the margin of the stenotic lumen and the section thickness causing partial volume averaging effect may account for this overestimation [21]. Therefore, the criterion we arbitrarily set to define mild stenosis was stenosis > 10%.

In addition to morphologic evaluation of TRAS by NC-MRA, we employed IVIM-DWI that is capable of unraveling perfusion and diffusion alterations in various degrees of TRAS. IVIM-DWI is a robust and reproducible technique that has been employed in the investigation of a variety of kidney diseases, such as kidney fibrosis in the native kidneys [22] and functional evaluation in delayed graft function [23]. In a previous study, Thoeny et al. [24] demonstrated that DWI was feasible and reproducible in healthy volunteers and patients with kidney parenchymal diseases. In a later report, Steiger et al. [25] found that IVIM-DWI could predict histopathologic severity of kidney allografts. In another study [19] that evaluates renal artery stenosis in the native kidneys with DWI, the authors noticed significantly reduced ADC in patients with renal artery stenosis than in healthy controls, which was compatible with our findings.

A frequently encountered clinical conundrum for physicians caring for kidney transplant patients with TRAS is to which degree TRAS should be intervened [1,26]. Frequently employed clinical markers by clinicians to help assess the impact of TRAS on allograft included eGFR and blood pressure. We observed no changes of ADC_T, D and Fp in mild TRAS, supporting the notion that mild TRAS had minimal impact on renal allograft function and thus may be managed without angioplasty. DWI interrogation of moderate TRAS suggested that cortical ADC_T, which is sensitive to tissue vascular perfusion and tubular flow, decreased significantly as compared with that of normal control. Subsequent IVIM analysis indicated tissue diffusion and perfusion did not

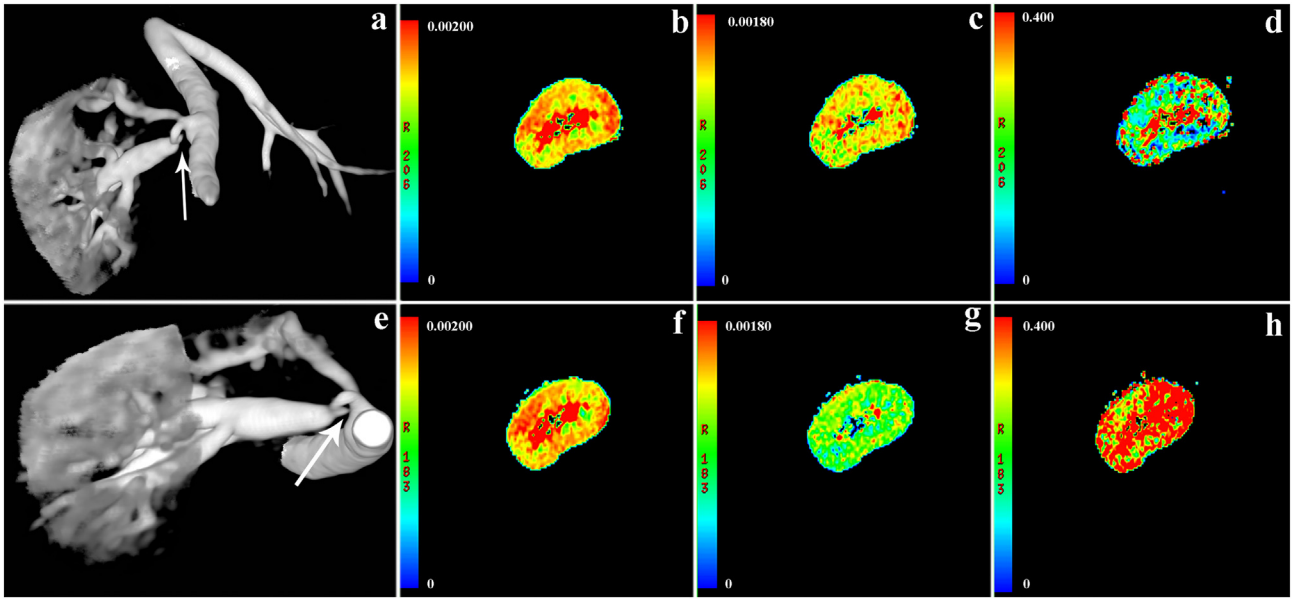

Fig. 1. Non-contrast enhanced magnetic resonance angiography and DWI images of the patient before and after unsuccessful angioplasty. a: Maximal intensity projection before angioplasty showed severe TRAS (arrow). b–d: ADC_T, D and Fp of this patient before angioplasty. e: After angioplasty, maximal intensity projection of non-contrast magnetic resonance angiography revealed still severe TRAS (arrow). f–h: ADC_T, D and Fp of this patient after angioplasty.

differ significantly between these 2 groups. Therefore, cortical ADC_T is probably the most sensitive DWI parameters to reflect impaired allograft function in moderate TRAS. The changes of DWI parameters were compatible with clinical indicator of decreased eGFR in severe TRAS in which angioplasty is often necessary. We also demonstrated that several DWI parameters increased significantly following successful angioplasty, indicating that DWI is potentially an alternative radiologic biomarker for assessing microstructural and hemodynamic alterations in severe TRAS. Furthermore, DWI parameters performed well in differentiating severe TRAS who needs treatment from patients with no more than moderate TRAS. Therefore IVIM-DWI could reflect TRAS-induced tissue diffusion and perfusion characteristics that can thus potentially contribute to multilateral assessment of kidney function for optimal decision-making.

To our knowledge, this is the first clinical study investigating the potential applicability of DWI in assessing tissue diffusion and perfusion characteristics in TRAS patients. A previously published study [9] reported that both D and Fp values were impaired in experimentally induced renal artery stenosis of pigs due to ischemia-induced cortical and medullary fibrosis. In another case report [27], Herrmann et al. found significantly reduced ADC_T, Fp and slightly reduced D value in a 10 month-old child with renal artery stenosis. Compared with traditional DWI that only affords overall ADC, IVIM-DWI is capable of separating true diffusion from pseudo-diffusion linked with blood perfusion.

Our study is subject to limitations that are inherent in clinical studies involving human subjects. TRAS patients were identified retrospectively while the normal controls were recruited prospectively, thus probably introducing selection bias. Additionally, it is ideal to design a prospective study to repeat NC-MRA and DWI in all patients to elucidate morphologic and hemodynamic changes after angioplasty. Another limitation is that ROIs were manually drawn, which might have introduced some biases to our analyses. Additionally, we did not analyze changes of pseudo-diffusion coefficient in TRAS. Nevertheless, it has been shown that pseudo-diffusion coefficient suffers from notoriously poor reproducibility, limiting its clinical significance [28]. Finally, our study is also limited by its small sample size in various TRAS groups, particularly mild and moderate TRAS groups. The number of patients who underwent repeated IVIM-DWI after angioplasty is also small; however, the result of our preliminary study would encourage larger-scale prospective studies addressing this issue in the future.

In conclusion, we demonstrate that IVIM-DWI is a robust technique that revealed no tissue diffusion and perfusion impairment in mild TRAS. ADC_T has good sensitivity and specificity for identifying patients with severe TRAS which significantly impairs tissue diffusion and perfusion properties. DWI is potentially an alternative radiologic biomarker for assessing microstructural and perfusion alterations in TRAS. DWI is useful in detecting renal functional recovery following successful angioplasty.

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