ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2020; 25: e918076
DOI: 10.12659/AOT.918076

Received: 2019.06.13
Accepted: 2019.10.10
Published: 2020.02.04

Diagnosis and Treatment of Renal Artery Stenosis in China in the Era of Donation After Cardiac Death

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Source of support: This study was supported by the National Natural Science Foundation of China (81800660)

Background: The aim of this study was to investigate the clinical features and treatment strategies of transplant renal artery stenosis (TRAS) with kidneys from donation after cardiac death (DCD).

Material/Methods: We collected the clinical data of donors and recipients of single-center DCD-induced TRAS from January 2015 to June 2017.

Results: All the 8 cases of TRAS were from hypertensive cerebrovascular accident DCD-originated kidneys. The mean donor age was 53.5 (45~57) years, with mean BMI 27.8 (26.4~32.3) kg/m^2, atherosclerosis index 5.8 (4.9~7.0), and renal atherosclerotic plaque. Clinical features of TRAS were: refractory hypertension with elevated serum creatinine >50%, and negative urine protein and occult blood. Ultrasound of transplanted kidneys showed renal blood flow index 0.49 (0.43~0.55). Angiography confirmed the diagnosis of renal artery trunk or secondary branch stenosis. There were 2 cases of moderate stenosis and 6 cases of severe stenosis. Six patients underwent stent implantation and 2 patients underwent balloon dilatation. Seven patients had serum creatinine recovery after interventional therapy during follow-up. The transplanted kidney of 1 patient ruptured 6 h after interventional therapy and was then resected.

Conclusions: The incidence of TRAS with hypertensive cerebrovascular accident DCD-originated kidneys is relatively high, which is a warning to kidney transplant physicians. Digital subtraction angiography (DSA) is the most reliable diagnostic means of TRAS and can be performed concurrently with intervention therapy. If the donor has severe atherosclerosis, plaques that are visible to the unaided eye in the renal artery trunk should be removed as completely as possible.

MeSH Keywords: **Atherosclerosis • Hypertension • Kidney Transplantation • Renal Artery Obstruction**

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/918076

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Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

Transplant renal artery stenosis (TRAS) severely affects hemodynamics of the grafted kidney. It can cause refractory hypertension and renal dysfunction, and can even progress to graft failure, which ultimately may reduce the survival rate of grafted kidneys [1–3]. The incidence of TRAS varies greatly depending on the diagnostic method used, ranging from 1% to 23% [4–6]. At present, the main source of organ donation in China has been completely transformed from traditional judicial channels to DCD, which is different from traditional judicial channels for kidney supply in terms of donor risk, donation procedure, organ function quality assessment, organ harvesting and preservation, and perioperative management of recipients [7–11]. With the new characteristics of kidney donation in the DCD era, donor-derived transplant renal artery stenosis (TRAS) has become a complication of DCD-originated kidneys that requires more attention. With the changes in the source of donor kidneys in the DCD era, patients who died of cerebrovascular accidents such as cerebral hemorrhage or cerebral infarction have become the main group of organ donors, and they often are accompanied by long-term hypertension or diabetes history, as well having atherosclerotic plaques of large arteries, which can lead to the formation of branching atherosclerotic plaques of the renal artery trunk and even to the renal artery, resulting in stenosis of the renal artery. Therefore, donor-derived transplant renal artery stenosis (TRAS) has become a complication of concern that needing for more attention to protect the DCD renal supply. In this paper, we retrospectively analyzed the clinical data of donors and recipients of TRAS in the 8th Medical Center of the Chinese PLA General Hospital (former 309 Hospital), explored the causes of TRAS in the DCD era, summarized the typical clinical manifestations of TRAS, improved the understanding and diagnosis of this complication, summarized the treatment methods and effects of TRAS, and proposed treatment strategies for renal artery stenosis.

Material and Methods

General information

A total of 453 patients with DCD donor kidney transplant at the Organ Transplantation Center, the 8th Medical Center of the PLA (formerly 309 Hospital), from January 2015 to June 2017 were selected, and 8 patients confirmed as renal artery stenosis were screened for clinical observation study. This study was approved by the Ethics Committee of the 8th Medical Center of the PLA (formerly 309 Hospital) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Diagnostic methods

TRAS should be suspected when the recipients of renal transplantation show the following symptoms: (1) the increase amplitude of serum creatinine is similar to AR, which is more than 50% that of basal creatinine; (2) blood pressure elevation with unknown origin and/or refractory malignant hypertension, which is often accompanied by history of oral ACEI/ARB-aggravated disease conditions; (3) normal or decreased urine output, routine urine protein, negative occult blood; and (4) no abnormal feeling in the transplanted kidney. Color Doppler flow imaging (CDFI) examination was performed in the suspected TRAS recipients, and the diagnostic criteria were [12,13]: peak systolic velocity at stenosis >180 cm/s, ratio of the peak velocity of renal artery to the abdominal aorta at the renal artery level during systole ≥3.5; the acceleration time after stenosis >0.07 s (formation of small slow wave) and the acceleration at early systole <300 cm/s; and the difference between renal artery trunk and segmental arterial resistance index >0.15. The initial diagnosis of TRAS was confirmed by DSA of the transplanted kidney. According to the diameter of the stenotic vessel, the degree of stenosis was divided into [14]: mild (25%≤ stenosis ≤50%), moderate (50%< stenosis <75%), and severe (stenosis ≥75%). The donors underwent routine BMI, cervical vascular ultrasound, and donor arterial stiffness index (AI) (calculation method:

AI=[blood total cholesterol–high-density lipoprotein]÷high-density lipoprotein).

Treatment

TRAS was mainly treated by interventional therapy, which was immediately performed after DSA confirmation. Patients with mild stenosis underwent balloon dilatation, and those with moderate or severe stenosis underwent insertion of an appropriate arterial stent according to the vessel diameter and length of stenosis, and the cases without ideal results of stent expansion then underwent balloon re-expansion.

Perioperative management and postoperative follow-up

Blood pressure, serum Cr, and transplanted kidney CDFI were monitored regularly during the perioperative period. Surgery-related complications, such as hemorrhage, pseudoaneurysm, and infection were recorded. For patients with suspected renal artery stenosis, oral clopidogrel (75 mg/d, Sanofi (Hangzhou) Pharmaceutical Co., Hangzhou, China) and aspirin enteric-coated tablets (100 mg/d, Bayer Medicine Health Care, Italy) were routinely given 3 days before surgery for antiplatelet therapy and maintained for 3 months after surgery, followed by 1-year administration of daily oral aspirin enteric-coated tablets (100 mg/d). The patients were postoperatively followed

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up by clinic service or telephone, as well as routine laboratory tests, anti-rejection drugs, or ultrasound examinations.

Statistical analysis

This was a clinical observational study. The data were processed using SPSS 19.0 statistical software. The measurement data and count data were analyzed by the *t* test and corrected chi-square test, respectively, and are expressed as median or mean±standard deviation ($\bar{\chi}\pm s$), with $P<0.05$ being considered as statistical significance.

Results

General information

The 8th Medical Center of the Chinese PLA General Hospital (former 309 Hospital) managed 453 cases of DCD-originated kidney transplantation from January 2015 to June 2017, including 108 cases of hypertension-induced cerebrovascular accident (23.8%), 285 cases of brain injury (62.9%), and 60 other cases (13.3%). There were 335 males and 118 females, with an average age of 43 (24~63)) years old. Among these, there were 8 patients with confirmed TRAS, accounting for 1.77% of all kidney transplantations and 7.40% of hypertensive cerebrovascular accident DCD-originated kidneys. Their median onset time was 4 (1–6) months after kidney transplantation. These 8 TRAS patients were 2 females and 6 males, with an average age of 45 (35~56) years old; 2 cases were from the same kidney donor, and 6 cases were from different donors. All 8 patients with TRAS were transplanted with hypertensive cerebrovascular accident DCD-originated kidneys. The mean age of donors was 53.5 (45~57) years, and an average cold ischemia time of 2.0 (0.5~3.5) h. The anastomosis method combined the abdominal aorta valve of the donor kidney with the recipient's external iliac artery. All 8 patients with TRAS were treated with antithymocyte globulin (ATG, Isetix-SangstatTra) for immunotherapy. For postoperative immunosuppressive regimen, 4 patients received prednisone (Tianjin Jinyao Group Co.)+Mycophenolate (Shanghai Roche Pharmaceutical Co.)+tacrolimus (Astellas Pharma, Inc., Japan), and 4 received prednisone+Mycophenolate+cyclosporine soft capsule (Novartis Pharma, Switzerland).

Clinical characteristics of donors

There were 7 hypertension cerebrovascular accident DCD donors. Their history of hypertension was 9.5 (7~14) years. Five of these donors (71.4%) also had diabetes. The average BMI of donors was 27.8 (26.4~32.3) Kg/m^2, with an average AI of 5.8 (4.9~7.0) and 100% carotid atherosclerotic plaque formation rate. Observation during renal trimming revealed that the abdominal aortic sclerosis rate was 100% and the positive rate of atherosclerotic plaque of renal artery trunk was 85.7% (6/7). In the renal trimming surgery, the main renal artery can pass the 8F red single-lumen catheter, and the lumen was unobstructed (Table 1).

Table 1. General information of DCD donors.

Indexes	Results	
DCD donors (n)	7.0	
Age (years)	53.5	(45~57)
Sex (Male) (n, %)	6.0	(85.7%)
BMI	27.8	(26.4~32.3)
History of hypertension (years)	9.5	(7~14)
DM (n, %)	5.0	(71.4%)
AI	5.8	(4.9~7.0)
Carotid artery plague (n, %)	7.0	(100%)
Abdominal aorta plague during renal trimming (n, %)	7.0	(100%)
Renal aorta plague during renal trimming (n, %)	6.0	(85.7%)
Cold ischemia time (h)	2.0	(0.5~3.5)

DCD – donation after cardiac death; BMI – body mass index; AI – atherogenic index.

Clinical characteristics of TRAS

The median onset time of the 8 cases of TRAS was 4 (1-6) months after renal transplantation. Clinical manifestations were: renal vascular hypertension and ischemic nephropathy of grafted kidney, increased Cr >50% of basal Cr (Table 2), pre-TRAS serum Cr 125.6±37.8 μmol/L, and serum Cr of TRAS-induced ischemic nephropathy 224.5±59.4 μmol/L, $P=0.00<0.05$. Two patients also had previously been treated with oral valsartan (Changzhou Si Yao Pharmaceutical Co., Changzhou City, Jiangsu Province) and losartan potassium tablets (Hangzhou Merck East Pharmaceutical Co.) for ARB antihypertensive drugs-aggravated disease conditions of negative urine protein and occult blood. Auxiliary examination: CDFI examination: 6 cases (75%) exhibited increased renal aortic blood flow velocity PSV >180 cm/s, 2 cases (25%) exhibited increased renal aortic blood flow velocity while PSV <180 cm/s; the acceleration time of the 8 cases after stenosis was >0.07 s, indicating small slow wave formation. The blood flow index was 0.49 (0.43~0.55). Digital subtraction angiography (DSA) and interventional therapy (Table 3) showed that all the 8 patients had clear diagnosis of TRAS, 6 of whom were from different donors while 2 were from the same donor (Figure 1A, 1B). The transplanted renal artery of 7 cases showed predominant stenosis (Figure 1C),

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Table 2. Changes of serum Cr of 8 cases of TRAS before and after treatment.

	Before TRAS (μmol/L)	During TRAS (μmol/L)	After TRAS treatment (μmol/L)
1	175.0	269.2	170.0
2	101.0	202.0	*
3	85.0	163.5	90.0
4	90.0	176.5	87.0
5	105.0	145.3	112.0
6	185.0	293.7	170.0
7	134.0	257.7	154.0
8	130.0	288.0	135.0

* The transplanted kidney raptured 6 hr after DSA treatment, so it was resected. TRAS – transplant renal artery stenosis.

Table 3. Clinical features of 8 cases of TRAS.

Indexes	Characteristic	Results	Characteristic	Results
Features of onset	Unilateral kidney	6 (75%)	From the same donor	2 (25%)
Renal artery stenotic site	Renal artery trunk (non-vessel anastomotic opening)	7 (87.5%)	Secondary branch of renal artery	1 (12.5%)
Transplanted renal artery anastomotic site	End-to-side anastomosis with abdominal aorta	8	End-to-end anastomosis of renal artery and endoscopic artery	0 (0%)
Treatment	Stenting	6 (75.0%)	Balloon expansion	2 (25.0%)
Outcome	Cr returns to the level before DSA	7 (87.5%)	Resection due to renal rupture Transplanted 6 hr after DSA	1 (12.5%)

TRAS – transplant renal artery stenosis.

and 1 case showed secondary stenosis (Figure 1D), eccentric stenosis, constricted stenosis, or occlusion. No anastomotic stenosis of the grafted renal artery was observed. TRAS were moderate in 2 patients and severe in 6 patients. All the patients underwent interventional therapy immediately after DSA diagnosis. Six patients underwent intraoperative arterial stenting together with balloon dilatation, and 1 patient only underwent balloon expansion because the secondary renal artery was stenotic for stenting. There were 2 balloon dilatations, and the interval was 3 months); 1 case was ineffective due to severe renal artery stenosis, and the stent could not be implanted, which ruptured and was removed 6 after the operation, while the other patient had the transplanted kidney resected due to transplanted kidney rupture.

Treatment outcomes

As of December 2018, the follow-up period ranged from 18 to 48 months. There were no complications, such as arterial thrombosis, restenosis, or pseudoaneurysm formation, after interventional therapy in 6 patients with TRAS. The blood pressure was easily controlled in the normal range. In the patient who underwent only balloon expansion due to secondary renal artery stenosis, balloon expansion was re-performed 3 months after interventional therapy due to re-stenosis. The patient with transplanted kidney rupture successfully underwent a second kidney transplant. Seven patients with TRAS treated with DSA re-gained their preoperative Cr level (131.1±35.5 μmol/L).

Discussion

TRAS is a common vascular complication after renal transplantation and is an important factor leading to renal failure and postoperative hypertension [1–3]. According to reports, the incidence of TRAS varies greatly depending on the diagnostic method, ranging from 1% to 23% [4–6]. Most studies on TRAS are single-center retrospective studies. For example, Rengel et al. [15] reported the incidence of TRAS as 4.5% in 286 kidney transplant recipients between 1990 and 1997. The cumulative incidence of TRAS

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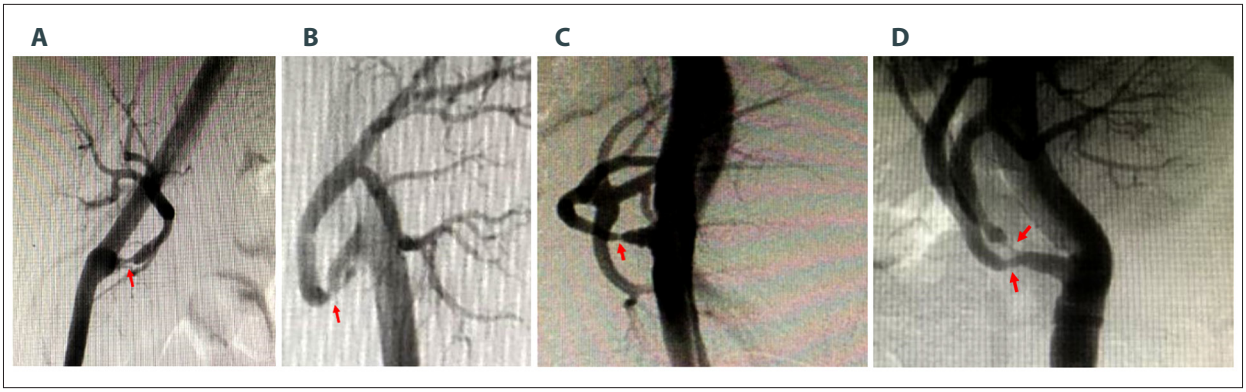

Figure 1. Stenosis of grafted renal artery trunk under DSA guidance. (**A, B**) Stenosis of grafted renal artery trunk of right and left kidneys from the same donor source (H02034200, H02019166). (**C**) Stenosis of grafted renal artery trunk (H01742917). (**D**) Stenosis of initial part of secondary branch of grafted renal artery trunk (H0152592).

in a 3-year clinical observation by Hurst et al. [16], which analyzed a total of 42 403 kidney transplant recipients registered in the United States kidney data system from 2002 to 2005, was 2%, and the total incidence was 8.3 cases/1000 patients/year (95% CI 7.8–8.9). The prevalence of TRAS in pediatric renal transplantation seems to be lower than in adult renal transplantation. A single-center study [17] showed that the prevalence of TRAS in a retrospective study targeting 216 pediatric patients from 2001 to 2011 was 4.6%. TRAS is the main cause of graft loss and premature death in transplant recipients, accounting for 1–5% of post-transplant hypertension cases and 75% of post-transplant vascular complications [18,19]. According to the USRDS registry, the adjusted risk ratio of death and graft loss in TRAS transplant recipients was 2.84 (95% CI 1.70–4.72) compared with transplant recipients without TRAS [15]. Among the 453 cases in our center, 8 were diagnosed with TRAS, accounting for 1.77% of all kidney transplants. We also found that TRAS mainly occurred in hypertensive cerebrovascular accident DCD-originated kidneys. TRAS accounted for 7.40% of hypertensive cerebral hemorrhage DCD-originated kidneys. Therefore, the incidence of TRAS in kidney transplant recipients from the donors with such diseases will increase significantly.

Studies have shown that the occurrence of TRAS is related to the following factors: surgical operation, cold ischemia time, delayed recovery of transplanted kidney function, rejection, CMV infection, atherosclerosis, CNI application, expanded standard donor kidney, mechanical compression, and donor kidney accessory artery, which is often characterized by stenosis at the anastomotic site of blood vessel [19–23]. The incidence of TRAS will be significantly reduced by improving the follow-up by kidney transplant specialists to monitor for these problems and to improve technologies. With the full conversion of major organ sources into DCD transplantation in China, hypertensive cerebrovascular accident has become one of the main sources of DCD donor kidneys. The hypertensive cerebrovascular accident DCD-originated kidneys accounted for 23.8% of the total transplants in our center (108/453 cases). It was also observed that TRAS occurred in the patients with hypertensive cerebrovascular accident DCD-originated kidneys. The DSA-defined stenosis was located in the trunk or secondary branch of the transplanted renal artery, which was eccentric, constricted, or occluded. No anastomotic stenosis was observed at the transplanted renal anastomotic site, which is in contrast to previous clinical evidence for TRAS. Renal artery stenosis (RAS) is one of the important causes of hypertension and/or renal dysfunction. It is generally divided into 2 categories: atherosclerosis and non-atherosclerosis. Most RAS is caused by atherosclerosis [24, 25]. Fuwai Hospital summarized the etiology of RAS in 2047 hospitalized patients consecutively from 1999 to 2014 [26]: 1668 (81.5%) cases of atherosclerosis, 259 (12.7%) cases of arteritis, 86 (4.2%) cases of fibromuscular dysplasia (FMD), and 34 cases (1.6%) of other. Among the 1728 patients >40 years of age, the leading cause was atherosclerosis (94.7%), followed by arteritis (3.8%). Based on Chinese and international research on the etiology and clinical practice of RAS, the China Healthcare International Association for Promotion of Vascular Diseases and Hypertension has come to a consensus on the 3 main criteria for the diagnosis of RAS; namely, the diagnostic criteria for atherosclerotic RAS [27,28], which consist of the following: (1) with at least 1 risk factor for atherosclerosis (obesity, diabetes, hyperlipidemia, age >40 years old, or long-term smoking); and (2) with at least 2 atherosclerotic imaging findings (stenosis or occlusion of the renal artery, eccentric stenosis, irregular plaque, calcification, mainly involving the proximal segment of the renal artery and opening, and atherosclerotic findings in other abdominal vessels. There were 7 DCD donors with hypertensive cerebrovascular accident in our center, with a history of hypertension as (9.5 (7~14)) years, and 5 cases were combined with diabetes (71.4%); the donor's average BMI was 27.8 (26.~32.3) kg/m^2, with the average AI as 5.8 (4.9~7.0) and carotid atheroma plaque formation rate as 100%. Clinical observation during renal trimming showed that the abdominal aortic sclerosis rate was 100% and positive rate of atherosclerotic plaque in the renal artery was 85.7% (6/7).

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Stenosis was confirmed by DSA to be located in the trunk or secondary branch of the transplanted renal artery. The stenosis was eccentric stenosis, constricted stenosis, or occlusion. Renal atherosclerotic RAS was confirmed as the underlying cause of TRAS. In this study, the site with renal atherosclerotic plaque at the renal artery can pass the 8F red single-lumen catheter, and the renal artery was unobstructed according to clinical experience, with stenosis less than 50%. The plaques were not removed during surgery because we thought that the trunk residue would be relatively short, thus affecting the vascular anastomosis. Postoperative factors, such as surgical procedures, vasospasm, infection, or other factors, re-aggravated stenosis on the pathological basis of atherosclerosis-caused RASD, which led to ischemic nephropathy.

Conclusions

In the era of DCD-originated kidney transplantation, DCD donors with hypertensive cerebrovascular accidents have a high incidence of donor-derived TRAS, which should cause concern among kidney transplant physicians. Typical manifestations are: elevated serum Cr (similar to rejection), but urine protein is always negative, Doppler ultrasound renal blood flow index is at the lowest limit or lower than normal index, and renal artery blood flow velocity is increased >180 cm/s, and formation of small slow waves (representative ultrasound feature of TRAS). DSA is the most reliable way to diagnose TRAS and can be performed concurrently. In patients with severe atherosclerosis, naked eye-visible plaques should be removed as much as possible to avoid end-to-side anastomosis of the abdominal aortic valve and the external iliac artery, and the end-to-end anastomosis with the internal iliac artery should be preferred.

Limitations of this study

The limitations of this study are that it was a retrospective study with limited clinical observation and short follow-up period. Prospective, longer-term clinical observations are needed to improve diagnosis and treatment in kidney transplantation.

Conflicts of interest

None.

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