Management of Transplant Renal Artery Stenosis

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ABSTRACT

Transplant renal artery stenosis is the most frequent vascular complication of transplantation. Early detection and correction reduce patients' morbidity and allograft dysfunction. Although noninvasive imaging can detect an underlying stenosis, angiography with subsequent angioplasty or stenting, or both, provides definitive diagnosis and treatment. With the introduction of alternative contrast agents and newer catheter and stent technology, these procedures can be performed safely with little risk of contrast-induced nephropathy or allograft loss.

KEYWORDS: Kidney transplantation, balloon angioplasty, stents, renal artery stenosis, hypertension, angiography

Objectives: Upon completion of this article, the reader should be able to (1) outline imaging methods for identifying transplant renal artery stenosis (TRAS), (2) list alternative contrast agents or medications to prevent contrast-induced nephropathy, and (3) list methods for management of TRAS, particularly percutaneous interventions.

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Renal transplantation is the definitive therapy for end-stage renal disease and has especially flourished in the post-cyclosporine-mediated immunosuppression era. Rarely, renal autotransplantation is performed for other reasons, such as for trauma resulting in bilateral renal artery thrombosis.¹ Historically, angiography has been performed for the evaluation for allograft rejection, delineating donor anatomy prior to surgery, and investigating the etiology of declining renal function after transplantation. At present, noninvasive imaging performed with ultrasonography and nuclear medicine in

addition to renal biopsy has supplanted the routine use of potentially nephrotoxic contrast angiography for most renal transplantation evaluations. Newer modalities such as magnetic resonance angiography (MRA) and computed tomographic angiography in addition to carbon dioxide (CO₂) digital subtraction angiography are now used routinely as well. Transplant renal artery stenosis (TRAS) is the most frequent vascular complication in renal transplantation with an incidence varying between 1 and 25%.²⁻⁶ The etiology and management of TRAS vary by location relative to the anastomosis, and it is

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therefore classified relative to this structure. TRAS can occur proximal to the anastomosis (preanastomotic), at the anastomosis, or within the donor artery (postanastomotic). TRAS may be a consequence of faulty surgical techniques, arterial damage during donor nephrectomy or kidney perfusion, kinking and compression of the renal artery, size discrepancy between donor and recipient renal arteries, and chronic rejection.^{5,7,8}

CLINICAL PRESENTATION

Patients can present early or late in the post-transplantation period. They may present with poorly controlled hypertension, compromised function of the allograft, or rejection refractory to immunotherapy. Occasionally, a bruit in the iliac fossa can be heard; this finding is not specific. Although it is the most common long-term complication of renal transplantation, TRAS is the etiology of elevated blood pressure in only 3 to 12% of the hypertensive patients.^{9,10} Hypertension may occur suddenly or may have a more insidious onset. It is typified by refractoriness to multiple drug regimens. Progressive renal insufficiency may manifest itself and be exacerbated by excess diuresis or occur after use of angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors may cause a more rapid decline in renal function that may lead to profound hypertension and acute renal failure.¹¹ A higher incidence of TRAS in transplants from cadavers (13.2–17.7%) compared with live donors (1.3–5.8%) has been reported.^{6,12} The interval between transplantation and diagnosis of TRAS ranges from 2 to 45 months.^{5,13} Acute rejection does not appear to correlate with the development of stenosis.⁵

ETIOLOGY

Mechanical or technical mechanisms of TRAS include atherosclerosis of the donor renal arteries or recipient iliac arteries, or both. In addition, trauma to the vessels during harvesting and transplantation, clamp injury, cannulation for organ perfusion, excess traction on the vessels, and suture techniques are other potential causes. Small subintimal flaps or dissections are thought to occur, leading to intimal scarring and hyperplasia and eventual anastomotic stenosis.¹⁴ Ostial stenosis is less frequent with a Carrel patch, wherein a cuff of donor aorta is harvested along with the renal artery, used frequently in transplants from cadaver donors.

Nontechnical mechanisms or immunologic causes have been suggested to contribute to TRAS. Intimal proliferation was associated with chronic rejection prior to the introduction of cyclosporine, but no consistent correlation has been found between acute rejection and TRAS.^{2,15,16} Cyclosporine has also been suggested as a cause for TRAS by means of inducing endothelial injury

leading to the development of a stenosis.¹⁷ However, no studies have been conclusive.

Early (within a few months of surgery) TRAS is likely to be caused by mechanical or technical trauma, whereas TRAS developing remote (more than 6 months) from the time of transplantation cannot be explained and may be associated with progression of underlying atherosclerotic disease.

RENAL TRANSPLANT SURGICAL TECHNIQUE

Whether the transplant is from a living related or cadaver donor, the renal artery is anastomosed to the internal iliac artery as an end-to-end anastomosis or to the external iliac artery as an end-to-side anastomosis.^{18,19} The kidney is surgically implanted in either iliac fossa from a retroperitoneal approach through an oblique incision extending from the midline 3–4 cm from the inguinal ligament to a point just above the anterior superior iliac spine.²⁰ When there are multiple vessels in a cadaver donor, a Carrel patch of aorta is used.²¹ With living related donors, multiple renal arteries are a surgical challenge because a patch of aorta containing the additional vessels cannot be obtained. If the additional vessel is small and perfuses only a small segment of kidney, it may be ligated. Larger accessory vessels may be anastomosed end to side to the main renal artery, although this may encroach on the main renal artery lumen. Two or more renal arteries can be anastomosed together side to side to create a “double-barrel anastomosis” preserving the lumen of each vessel.²² Other authors have suggested performing separate anastomoses to either the recipient internal or external iliac arteries or one renal branch to each. Another surgical option is to use the recipient's inferior epigastric artery for the accessory vessel.²³ Pediatric cadaveric donors may have both kidneys with a segment of aorta transplanted en bloc through an anastomosis to the recipient iliac artery.²⁴

The renal vein is usually anastomosed to a mobilized recipient iliac vein in an end-to-side fashion.¹⁸ When two or more renal veins are present, the smaller veins are typically ligated, resulting in a single anastomosis of the larger vein with drainage through an intrarenal venous anastomosis.²⁰ When the veins are similar in size, the smaller of the two is first clamped to test for adequate venous collaterals.²¹ When the artery or vein is too short, grafting may be performed, usually with a saphenous vein or occasionally a gonadal vein.²⁵ When significant vascular arterial or venous pathology is present, such as inferior vena cava agenesis, unusual surgical anastomoses may be needed.²⁶ In children, the renal artery and vein may be anastomosed to the lower aorta and inferior vena cava, respectively. Three types of anastomoses are usually performed to create urinary

continuity. The most common is the ureteroneocystostomy, which has the lowest incidence of extravasation. More involved transplant surgeries have now been performed in diabetics utilizing both kidney and pancreatic allografts.^{27,28}

NONINVASIVE IMAGING EVALUATION

Evaluation of TRAS may be performed with both noninvasive and invasive imaging techniques. Color flow duplex ultrasound (CFDU) and MRA have now become the primary noninvasive imaging modalities for diagnosing TRAS. CFDU is highly dependent on visualization of the entire donor renal artery and the surgical anastomosis. This imaging modality is also limited by inability to visualize the iliac vessels completely to exclude inflow stenosis at this level, largely because of the patient's body

habitus and bowel gas. Stenotic segments appear as regions of focal color aliasing, which with duplex Doppler techniques can be characterized and graded.²⁹ Doppler criteria for significant stenosis include (1) peak systolic velocities greater than 2 m/sec (Fig. 1), (2) velocity gradient between stenotic and prestenotic segments of more than 2:1, and (3) marked distal turbulence (spectral broadening).³⁰⁻³²

Although catheter-based angiography has conventionally been held as the "gold standard" in evaluation of arterial stenosis, three-dimensional gadolinium-enhanced MRA has demonstrated 100% sensitivity and 75–98% specificity for greater than 50% stenosis in small studies.³³⁻³⁷ This modality allows evaluation of the iliac arteries, donor artery, arterial anastomosis, and the renal vein (Fig. 2). Both these modalities allow imaging evaluation of the transplant kidney without the use of

Figure 1 (A) Ultrasound Doppler examination of the renal artery anastomosis to the external iliac artery demonstrated velocities exceeding 3 m/sec. (B) Selective right external iliac artery angiogram confirms a focal moderately severe and eccentric stenosis at and just distal to the arterial anastomosis (arrow).

Figure 2 Gadolinium-enhanced three-dimensional MRA reconstructed image demonstrates stenosis of the renal artery distal to the anastomosis. The iliac arteries are completely visualized.

iodinated contrast agents. However, if there is a strong clinical suspicion of TRAS despite negative noninvasive imaging studies, proceeding to angiography should be considered.

RENAL TRANSPLANT ANGIOGRAPHY

Intra-arterial digital subtraction angiography has now replaced film screen ("cut film") imaging for imaging renal transplants. Because of the risk of nephrotoxicity associated with iodinated contrast media, volume should be carefully tailored to the clinical question with careful consideration of the vascular anatomy, clinical scenario, and possible therapeutic intervention.²⁴ Catheter and wire manipulation near the anastomosis or donor transplant renal artery should be kept to a minimum, especially when the transplantation has been recently performed. Consideration should be given to the use of nonionic contrast material because of its possible reduced nephrotoxicity, as its use appears to reduce contrast-induced nephropathy (CIN) by ~50% compared with high-osmolality agents.³⁸ Newer isosmolar contrast media (Visipaque, Amersham Health, Princeton, NJ) are considered to have less nephrotoxic effect than nonionic contrast media.^{39,40}

Ipsilateral or contralateral approaches can be used for donor arteriography when the anastomosis is to the external iliac artery and a contralateral approach when the anastomosis is to the internal iliac artery. A Cobra configuration of catheter works well when performing a contralateral approach. Examination of the distal aorta and common iliac arteries should be performed in hypertensive patients because stenosis related to

atherosclerosis or clamp injuries can cause an impediment to inflow,^{24,41,42} leading to local hypoperfusion.

Contrast injection rates depend on the location of the catheter tip and should be guided by fluoroscopic hand injections. Common iliac artery injections are performed at a rate of 7–15 mL/sec for a total of 12–30 mL and internal iliac artery injections are performed at 5 mL/sec for a total of 10 mL, depending on the type of imaging technique utilized. Selective injection into the renal artery is generally not required⁴³ if image quality is optimal. Initial films can be obtained in the 30-degree left or right posterior oblique projection for the left- or right-sided transplant, respectively, unless a test injection dictates a different view. Multiple projections such as steep obliques or even a lateral projection are generally required to image the course of the arteries adequately and to visualize the in-profile anastomosis, which is typically placed anterior on the vessel. On average, three views are required to image the transplant adequately, although because of overlap of vessels, as many as six images may be required.^{44,45} The introduction of rotational angiography with three-dimensional reconstruction may allow savings in time, radiation, and contrast dose.^{46,47}

The angiographic appearance of a normally functioning transplant is similar to that of a normal native kidney, but its size may vary. A normal transplant may measure up to 16 × 9 cm, and the size increases 10% in the first month and 1% a month for the first year.^{48,49} Complications associated with renal transplant angiography are typical of other similar diagnostic and interventional angiographic procedures. The risk of vascular injury is related to the risk and difficulty of the procedure, and contrast nephrotoxicity is related to underlying impairment of renal function.^{50,51}

If the renal transplant is functioning poorly with an elevated creatinine level and contrast angiography is being considered, CO₂ angiography may be used to confirm or exclude a diagnosis of a vascular abnormality⁵² (Fig. 3). CO₂ acts as a negative contrast agent when combined with intra-arterial digital subtraction angiography and is cleared by the lungs rather than the kidneys.⁵³ Current software allows "stacking" of images, producing image quality similar to that obtained with iodinated contrast agents. Because CO₂ is not nephrotoxic, it can be used in patients with impaired renal function^{53–55} and has not been shown to change renal function significantly with selective injections.⁵⁶ CO₂ works well with renal transplants because the vessels are anteriorly located and the gas rises into the graft, allowing filling of the intraparenchymal arteries.⁵⁶ A sufficient volume of CO₂ has to be injected to avoid underestimating the diameter of vessels and vessel stenosis,⁵⁷ but the amount that can be injected in subdiaphragmatic arterial vessels should be limited to less than 300 cm³.⁵³ The potential for gas trapping or "vapor lock" causing

Figure 3 (A) Carbon dioxide angiogram of the external iliac artery was performed demonstrating focal stenosis (arrow) of the proximal transplant renal artery as demonstrated in Figure 2. (B) Images obtained 0.2 seconds later demonstrate early opacification of the external iliac vein (arrow). (C) Selective injection of a renal segmental arterial branch verifies an arteriovenous fistula (arrow), later corrected with coil embolization.

reduced blood flow in the renal artery is eliminated if the minimal volumes for imaging are injected 1–2 minutes apart.^{52,53} Percutaneous interventions can be performed with CO₂; however, this is more difficult because image quality may be adversely effected by the hardware introduced during the intervention. When CO₂ angiography is inadequate, imaging can be supplemented with gadolinium-based agents.⁵⁴

Gadolinium, a contrast agent primarily administered for contrast-enhanced magnetic resonance imaging, absorbs x-rays similarly to iodinated contrast material. The image quality is inferior to that with iodinated material because of the low concentration of gadolinium (0.5 mmol/mL) (Fig. 4). Image contrast with gadolinium is typically 25–50% that of images obtained with traditional full-strength contrast agents. In doses injected for magnetic resonance examinations

(0.1 to 0.4 mmol/kg body weight) there has been no associated nephrotoxicity in patients with renal insufficiency.^{58–60} However, there has been a report of worsening renal function following a lower extremity angiogram using gadolinium when a dose of 0.44 mmol/kg was used.⁶¹ For this reason, we do not exceed a dose of 0.4 mmol/kg or, as a basic rule, we do not use more than 30 mL of gadolinium. Gadolinium can be hand or pump injected in a manner similar to injection of iodinated contrast material. It is advantageous to combine gadolinium imaging with CO₂ to reduce the amount of gadolinium required for diagnostic images and therapeutic interventions.

Two supplemental medications can be administered to reduce the risk of CIN. Fenoldopam is similar to dopamine, acting on the DA-1 receptor. This medication is a potent renal vasodilator resulting in increased

Figure 4 (A) Angiogram performed with gadolinium prior to intervention. (B) Following intervention, an angiogram was performed with a hand injection of iodinated contrast material demonstrating improved contrast resolution compared with gadolinium. The tip of a guiding sheath is visualized in the proximal renal artery.

renal blood flow.⁶² Acetylcysteine, a thiol-containing antioxidant, has been shown to reduce CIN in high-risk patients.^{63,64} Dosing is 600 mg orally twice a day the day before and the day of contrast administration. Although these agents show promise, few studies validating their effectiveness have been published.

MANAGEMENT OF TRANSPLANT RENAL ARTERY STENOSIS

Three different treatment methods are available:

1. Medical management may be used to control hypertension with unknown effect on kidney function. This approach is indicated if the degree of stenosis is not considered hemodynamically significant or the risk of percutaneous intervention is considered high for graft loss, or both. Intervention is justified if there is a reasonable expectation of success in improving hypertension and renal function or stopping progressive renal deterioration.^{8,16,65}
2. Surgical intervention with revascularization. This is considered a major operation with graft loss following vascular reconstruction approaching 30% with a recurrence rate of ~12%.⁶⁵⁻⁶⁷ There is also an increased risk of ureteral injury with surgery. Surgical correction is the preferred method for treatment of kinking of the proximal transplant renal artery.⁶⁸
3. Percutaneous endovascular management using transluminal angioplasty (PTA) or metallic stent placement, or both.

There are several locations that can develop stenoses. An arterial stenosis may be¹ preanastomotic, which is usually due to atherosclerosis or a clamp injury¹⁸; at the anastomosis, which is usually due to a technical problem related to surgery¹⁹; just distal to the

anastomosis, which is usually due to immune reactions or hemodynamic turbulence from the anastomosis causing an intimal hyperplasia²⁰; or intrarenal due to chronic rejection.^{21,24,69} Postanastomotic strictures tend to be more severe and associated with end-to-side anastomoses as compared with end-to-end anastomoses, which tend to be at the anastomosis.^{69,70} Iliac artery stenosis ipsilateral and proximal to the renal artery anastomosis can also lead to allograft dysfunction, particularly in the elderly population.^{12,71-74}

PTA is recognized as the initial treatment of choice for TRAS and does not preclude subsequent surgical correction.^{15,69,75-78} However, prior to the introduction of current catheter and wire technology, some investigators had high complication rates up to 20% with low clinical responses.^{65,79,80} Initial technical success of PTA has been reported to be over 80% and clinical success is ~74 to 87%.^{2,70,75,77,78,81} Long-term clinical success, defined as either improvement in blood pressure control or stabilization or improvement in renal function, is between 53 and 70% at 1 year^{67,75,77} with the restenosis rate of PTA of TRAS to be in the range of 10 to 33%.^{15,67,75,76,78,79} Complication rates are generally low with the rate of graft loss lower for PTA than for surgery; however, Roberts et al reported their loss after PTA to be as high as 13%, higher than their surgical, which may have resulted from dated (1989) angioplasty catheters and wires compared with devices that are available today.^{16,65,69,70,75,81}

PTA/stenting of an end-to-side anastomosis can be performed from the contralateral or ipsilateral side, depending on the angle of the anastomosis (Fig. 5). An end-to-end anastomosis, which is generally to the hypogastric artery, is performed from the contralateral side or by a left brachial artery approach. Serious complications, which may lead to graft loss, include acute thrombosis, arterial dissection, renal artery rupture, branch occlusion,

Figure 5 (A) Prior to angiography, ultrasonography demonstrated a velocity of 6 m/sec at the external iliac artery–renal artery anastomosis. Gadolinium angiogram confirms stenosis (arrow) in this location. (B) Following angioplasty with an 8-mm balloon catheter, the pressure gradient dropped from 54 mm Hg to less than 10 mm Hg.

distal embolization, and contrast-induced renal failure. As with any renal artery angioplasty, complications are reduced by utilizing adequate heparinization, vasodilators, minimal wire manipulations, proper balloon sizing, and inflation pressures. Because of the potential for a false-positive angiogram, Roberts et al suggested that an angiographic stenosis should demonstrate some physiological significance prior to performing an intervention such as a captopril-associated rise in creatinine or large pressure gradient.⁶⁵

Metallic stents have been inserted for treatment of recurrent or ostial stenosis, although limited studies have been performed to date. Insertion is associated with high initial technical success and a good patency rate with minimal complications.^{82–84} Serious complications of PTA can be salvaged with stents. In addition, elastic recoil can lead to restenosis. Metallic stents are

commonly used, primarily to treat ostial stenosis in native renal arteries and now in transplanted kidneys^{13,82,83} (Fig. 6). Complications related to stent insertion include thrombosis, peripheral embolization, transient renal failure, subintimal dissection, stent misplacement or migration, and restenosis related to myointimal hyperplasia from the normal healing process. Newman-Sanders et al reported stable allograft function in four patients with follow-up of 4 to 24 months,⁸³ and Nicita et al reported a positive outcome using Palmaz[®] stents in five of seven patients at a median follow-up of 14.8 months.¹³ Bertoni et al implanted nine Palmaz[®] stents for TRAS with no complications with a significant decrease in peak blood flow velocity.⁸²

When performing PTA/stenting, we attempt to place the vascular access sheath tip adjacent to the arterial anastomosis (Fig. 4). This allows monitoring

Figure 6 (A) Injection of gadolinium in the external iliac artery demonstrates a focal eccentric stenosis at the anastomosis (arrow) extending into the renal artery. (B) A balloon-expandable stent (4.5 mm × 12 mm length) was primarily deployed and expanded to 4.5 mm. Prior to stenting, the pressure gradient was 77 mm Hg. Following deployment, the gradient normalized.

Figure 7 (A) Iliac angiogram demonstrates a focal osteal or anastomotic stenosis (arrow) of the transplant renal artery. (B) The lesion was primarily stented with a Palmaz 154 stent dilated to 6 mm. Use of a balloon-expandable stent allowed accurate placement.

the progress of the intervention by angiograms performed with wire access, either a 0.035 or 0.018 access, maintained across the lesion. The vascular sheath can also act as a buttress against a deployed stent to prevent stent migration when removing the deployment balloon. Our indications for PTA include greater than 50% luminal narrowing with angiography or a systolic pressure gradient of 10 mm Hg across the stenotic segment, or both.⁸⁵ Angioplasty balloon and stent sizing may be obtained with the aid of software found on most modern digital subtraction angiography units. Indications for stent use at our institutions include greater than 30% residual stenosis following PTA, persistent systolic pressure gradient greater than 10 mm Hg following angioplasty, flow limiting dissection, and early recurrent clinically significant stenosis within 3 months of angioplasty. We prefer to use balloon-expandable stents for higher radial strength and accurate placement compared with self-expanding stents (Fig. 7). Previous limitations of balloon-expandable stents have now been resolved with the introduction of multiple new stent platforms by a variety of medical device companies; these have a reduced profile and good trackability over the aortic bifurcation and are premounted, preventing migration of the stent off the deployment balloon.

CONCLUSION

Advances in diagnostic and device technology have allowed improved diagnosis and percutaneous management of TRAS. The use of alternative contrast agents and supplemental medications reduces the likelihood of CIN. Percutaneous transluminal angioplasty with

or without intravascular stenting has high technical success with an acceptable complication rate and is the preferred initial therapy in these patients. The introduction of newer technology such as lower profile balloon catheters, premounted balloon-expandable stents, and cutting angioplasty balloon catheters is likely to improve the outcome of percutaneous interventions for TRAS. The success of these interventions requires appropriate selection of patients and attention to meticulous technique.

ABBREVIATIONS

TRAS	transplant renal artery stenosis
PTA	percutaneous transluminal angioplasty
CFDU	color flow duplex ultrasound
MRA	magnetic resonance angiography
CO ₂	carbon dioxide
CIN	contrast-induced nephropathy

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