

# Kidney Transplantation

## Chapter 6

### Transplant Renal Artery Stenosis - An Update

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#### Abstract

Transplant renal artery stenosis (TRAS) is one of the common and well studied urological complications following renal transplantation. With varied expertise of surgeons performing transplants and with a varied follow-up protocols followed in different centers, the overall incidence of TRAS shows a wide range. With increased usage of advanced imaging modalities, more number of TRAS patients is being diagnosed.

Various factors play a role in the development of TRAS. An immunological causative factor, technical factors related to vascular anastomoses, correlation to cadaveric transplantation, multiple renal arteries, intimal tear and role of Cytomegalovirus and Calcineurin inhibitor toxicity are

all various proposed etiological factors that predispose to TRAS.

TRAS is usually seen within the first 6 months of transplant. The usual manifestations include uncontrolled hypertension, oliguria and elevated serum creatinine levels. As renal allograft recipient with TRAS simulates 1 kidney 1 clip Goldblatt model, treatment should be aimed mainly at control of hypertension, diagnose the exact site of vascular occlusion and appropriate management.

Colour Doppler is widely accepted as the initial investigation of choice to diagnose TRAS. A rise in peak systolic velocity, low resistive index and a prolonged acceleration time are suggestive of TRAS. However, renal arteriography or digital subtraction angiography is diagnostic and needed before angioplasty and stenting or surgical revascularization. CT angiography and MR angiography also add value to the diagnosis.

A high index of clinical suspicion, a pre-planned protocol in the post-transplant period, early diagnosis and appropriate treatment would help prevent allograft dysfunction or renal loss.

**Keywords:** Transplant; Allograft; Stenosis; Artery; Hypertension.

## I. Background

Ever since in 1954, when Joseph Murray performed the first human renal transplantation, the immunological factors were the major causes of renal allograft dysfunction or post-transplant fatalities. With the advent of newer immunosuppressive agents, the overall incidence of graft rejections has come down to 20 to 30% [1].

Before the availability of renal replacement therapies, End-stage Renal Disease (ESRD) was considered one form of a terminal illness. There has been a significant improvement in the quality of life and improvement in survival benefit after renal transplantation [2]. With the advent of hemodialysis and renal allograft transplantation, cardio-vascular causes have been recognized as significant causes of morbidity in patients with ESRD [3,4]. Hypertension after Renal Transplantation is one of the common problems encountered in regular urological practice [5]. It is seen in up to 50-60% of long term functioning allografts [6]. The pathogenesis of post-transplant hypertension is a complex phenomenon, with immunologic and non-immunologic factors playing a significant role in the onset of hypertension in renal allograft recipients. Such hypertension can be classified depending upon the time of onset into immediate, early and delayed hypertension. Such classifications greatly facilitate the nephrologists to identify the etiology of hypertension and also suggest appropriate management for such complexities in the post-transplant period. Transplant Renal Artery Stenosis (TRAS) is one such entity that is

a common cause of resistant hypertension following renal transplantation.

TRAS is a well-recognized and a common vascular complication that commonly results in a more unsatisfactory outcome in renal allograft recipients [7]. The overall incidence of TRAS is reported to vary from 1 to 25% [8]. With the advent of more non-invasive imaging techniques, including colour Doppler ultrasonography, Wong reported an overall increase in the prevalence of TRAS from 2.4% to 12.4% [9]. As Doppler ultrasound is observer-dependent and as renal angiogram is not done routinely in all such patients with hypertension, the true incidence of TRAS may be as high as up to 25% [10].

The complexity of this problem stems from the fact that TRAS can present either as an immediate, early or delayed form of post-transplant hypertension. It may occur anytime after transplant but usually seen between 3 to 24 months following transplant [11]. TRAS is generally seen within the first two years after transplantation. Renal angiography remains the gold standard investigation to confirm the diagnosis and plan appropriate therapy in patients with TRAS [12,13]. However, the ease of performing Doppler ultrasonography, its non-invasiveness, ability to do repetitive imaging as a follow-up tool, its safety in patients with renal compromised status and its high sensitivity and specificity makes it most widely used tool for evaluation and follow up of TRAS [14].

As TRAS is now considered a significant cause of allograft dysfunction, an early diagnosis, prompt treatment and measures taken to prevent TRAS could significantly contribute to the ultimate graft survival. This subchapter illustrates the etiology, pathogenesis, pathophysiology, clinical manifestations, diagnosis and treatment of renal allograft recipients with TRAS.

## **2. Etiopathogenesis**

The aetiology of TRAS is multifactorial. Unlike renal artery Stenosis (RAS) in non-transplant individuals, the aetiology of TRAS is much more diverse and complex to diagnose and understand. Various immunological and non-immunological factors play a role in the development of TRAS [15]. The non-immunological causes include atherosclerosis of the donor renal artery, improper suturing techniques, intimal tear during graft harvesting or perfusion or vascular anastomosis and a kinking of the renal artery due to its redundancy in length.

### **2.1. Immunological**

It has long been debated about the possible role of immunological causes for the occurrence of TRAS. In a Spanish study on pediatric and adult renal transplants, no specific association between cellular rejection and TRAS was identified [16]. However, in his research on 917 renal allograft recipients, Rengel et al. noted a possible immunological cause for the development of TRAS [17]. Of the 77 patients who developed TRAS, they observed a statistically significant

higher incidence of Cellular rejection in the TRAS group than the control group (0.67 vs 0.35 episodes per patient,  $P < 0.01$ ).

Porter et al., postulated an immune causative factor as a significant cause of TRAS. In his study on obliterative vascular changes in renal allograft recipients, he noticed a striking similarity between the histologic changes in the affected vessels and the vascular lesions of graft rejection [18]. Ten years later, O'Connell exposed arterial endothelium to alloantibodies and produced thickening of Tunica intima in experimental rabbits [19]. Documentation of the Complement factor in the affected arterial walls supported a strong immunological correlation [20].

Audard, in his retrospective study to determine the predisposing factors for TRAS, observed that acute cellular rejection occurred in about 48% of patients in TRAS group compared to 27% in the control group [21]. In one of the most extensive series of TRAS patients, Willicombe et al. identified a positive correlation between de novo class II donor-specific antibodies and occurrence of TRAS, concluding that alloimmune factors do play a significant role in the event of TRAS [22].

Macia et al., in their retrospective audit of their 110 allograft recipients observed an 8% incidence of TRAS. A diagnosis of TRAS in patients with absence of intimal injury during harvesting or during anastomosis and correlation of a high degree of immunological intolerance suggested a plausible underlying immunological cause for TRAS [23]. Macia also reported a direct correlation between acute rejection and onset of TRAS. They concluded that TRAS might represent a form of vascular manifestation of immunological damage.

## **2.2. Non-Immunological**

Technical reasons are considered to be common causes for TRAS. A faulty technique, especially in an end-end anastomosis, where arteries of unequal diameters are spatulated and anastomosed could lead to kinking and damage to Tunica intima, resulting in renal artery dissection that might closely resemble TRAS [24]. The severity of TRAS may be proportional to the degree of intimal damage.

## **2.3. Deceased organ donation**

Patel et al. found a higher incidence of TRAS in patients who underwent deceased organ transplantation. A prolonged cold ischemia time further compounded by pulsatile perfusion greatly aided in endothelial damage to renal artery [25]. In one of the most extensive series on 2002 renal allograft recipients, Roberts et al. observed a 1.6% incidence of TRAS of which two-thirds were in cadaveric renal transplants [26]. Sankari et al. observed a prevalence of TRAS to be lower in those with live donors. In their retrospective study on 1,262 renal allograft

recipients, they found that the prevalence of TRAS was 0.3% and 2% in living related and cadaveric transplants respectively [27].

#### **2.4. IVC cuff**

In transplantation cases using a right donor kidney, a disparity between the long renal artery and the short renal vein may cause a torque or twist at the site of arterial anastomosis. This incidence is less common in deceased organ donation. A cuff of Inferior vena cava is taken along with the right renal vein, which would bridge the difference in lengths between the artery and vein. Khan et al., in their observational study on 44 patients with right deceased donor kidney transplantation observed that the right renal artery with the aortic patch is twice the length of the right renal vein [28].

#### **2.5. Kink of artery**

In a study on 119 cadavers, Janschek et al. observed that the median Right renal vein length was only half that of the right renal artery [29]. They proposed that harvesting the renal vein en-bloc with the inferior vena cava facilitated gaining that extra length of the renal vein, that immensely helped the surgeons in transplanting right kidney in obese individuals with deeply located iliac veins. Such disparities in length might cause a kinking of the renal artery after anastomosis [30]. To overcome this problem, if a loss of aortic patch reduces the renal artery length, the lumen also gets narrowed, resulting in a higher chance of TRAS.

#### **2.6. Intimal Tear**

The success of a transplant depends on an adequate arterial flow. Damage to Tunica intima during anastomosis may also lead on to TRAS. A lack of meticulous handling and uneven traction of the artery during anastomosis can cause endothelial damage. Such injuries are more common in live related renal transplantation, where the kidneys' perfusion using plastic cannulas may cause intimal stretch, damage or dissection, resulting in TRAS [31,32].

#### **2.7. CMV Infection**

Cytomegaloviral infection (CMV) is yet another aetiological factor for TRAS. As the intimal damage is followed by a healing process that results in fibrosis, stenosis of the arterial lumen occurs [33]. Ardalan et al., in his report on the role of CMV in TRAS, postulated that CMV initiates vascular damage by direct cellular toxicity or mitogenic potential of viral genes on the endothelial lining cells, smooth muscle cells of the intimal lining of the blood vessels, and fibroblasts. The viral infected endothelial cells initiate inflammation of the arterial intimal layer and release of growth factors, thereby leading to accelerated narrowing of the arterial lumen [34].

## 2.8. Cyclosporine Toxicity

Cyclosporine A was one of the most commonly used and a popular immune suppressant in patients undergoing renal transplantation. The main disadvantage of the drug is its effects on the vasculature [35]. This drug causes a dose-dependent constriction of the renal arterioles, resulting in decreased allograft blood flow. It also results in deposition of proteinaceous material in the tunica intima, resulting in arteriolopathy and increases platelet aggregation leading to arteriolar and capillary microthrombi. Sawaya reports cadaveric renal allograft recipient treated with cyclosporine A who developed angiographic evidence of renal artery stenosis, which resolved after cessation of the drug [36].

## 2.9. Host peripheral vascular disease

Atheroma of the donor renal artery is a well-known cause for TRAS. As most of the allograft recipients are hypertensive and diabetics with pre-existing microangiopathy, such recipients are at a higher risk of developing peripheral vascular diseases. Becker et al., in their retrospective analysis on 819 allograft recipients, concluded that pre-existing peripheral vascular conditions strongly predisposed to the development of TRAS [37]. Such pre-existing lesions might decrease the arterial blood flow to the allograft and present like Pseudo-TRAS. Such cases often present with Late-onset TRAS, where the symptoms develop many years after the transplantation is done.

## 3. Clinical Presentation

TRAS usually occurs between 3 months and two years post-transplant. It usually manifests as uncontrolled hypertension and rising serum creatinine levels. Hypoperfusion of the kidneys secondary to Stenosis may result in a salt-avid state and activate the Renin-Angiotensin-Aldosterone system (RAAS) leading on to fluid retention that can further exacerbate hypertension. Excess fluid accumulation can also lead on to Flash Pulmonary oedema, anasarca and congestive cardiac failure. The authors, in their earlier study on TRAS, had identified uncontrolled hypertension as the most common presentation [38]. Chen et al. reported a case of Flash Pulmonary oedema as the initial presentation of TRAS [39]. Grzelak et al., in their study on 180 renal allograft recipients, observed a higher serum creatinine level in patients with TRAS [40].

In one of the most extensive single-centre study on the vascular complications in renal transplantation spanning over 25 years on 1367 allograft recipients, Dimitroulis et al. observed TRAS as the most common vascular complication [41]. They observed that TRAS might present as sudden or insidious onset of graft dysfunction in the absence of infection, rejection or obstruction.

Patients on diuretic therapy or addition of ACE (Angiotensin Converting Enzyme) inhibitors or Angiotensin II receptor blockers may develop paradoxical hypotension, especially when they are already on anti-hypertensive treatment. Curtis et al., in their study on the influence of ACE inhibitors in post-transplant patients, observed that hypertension in such patients is comparable to the single-kidney Goldblatt model of hypertension [42]. These patients typically have low plasma renin activity with increased extracellular fluid overload and demonstrated a fall in mean arterial pressure in captopril response.

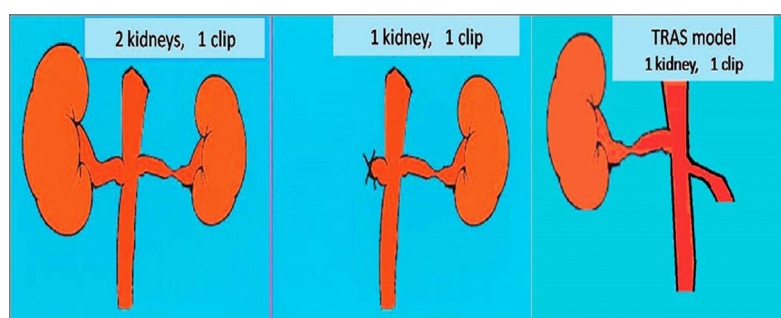
Presence of bruit may raise suspicion of TRAS but need not be pathognomonic and is of little diagnostic value [43,44] Physiological turbulence in the iliac or femoral artery caused by increased perfusion close to anastomosis may also present with bruit. However, Lacombe, in his study on 306 renal transplantations, did not observe bruit in any of the 38 patients who developed TRAS [45].

To sum up, TRAS gains significance when the patient is symptomatically affected or evidence of renal impairment.

#### 4. Anatomical Perspectives

With advancements in imaging technologies and refinements in surgical techniques, the long term allograft survival has increased over the past few decades. On the other hand, surgical complications are still frequently seen. Though we see many nephrological or lymphatic complications after renal transplantation, vascular anastomoses is the one that gets more attention, as vascular complications more often lead to allograft loss [46].

The vascular complications may range from arterial kinks, arterio-venous fistulae, aneurysms, pseudo aneurysms, venous thrombosis, fibro muscular dysplasia and transplant renal artery stenosis [47,48] . Each one of these entities might present in their own way and the symptoms depend on the severity of the complication. A thorough anatomical understanding of the renal vasculature, its variations, anomalies and the autonomic neural control in the denervated allograft is the basic pre-requisite for a successful renal transplantation. A basic knowledge of the autonomic innervations would be helpful to understand the physiological effects of the ultra-microscopic components of the kidney.



**Figure 1:** Illustrates the Goldblatt hypertension model (to be explained under Pathophysiology) in the native kidneys and transplanted kidney.

The afferent and efferent renal sympathetic nerves lie in close proximity to the adventitious layer of renal arteries. These autonomic nerves are essential for production of catecholamines, resulting in hypertension [49]. When efferent sympathetic nerves are stimulated, there is a vasoconstriction, resulting in a decrease in renal blood flow, increased renin secretion, activation of RAAS and renal tubular sodium absorption [50]. On the other hand, the transplanted kidney is stripped off the sympathetic nerves, when TRAS occurs, the decreased renal blood flow does not directly activate the sympathetic nerves, Hypoperfusion of the kidney result in RAAS activation, leading to sodium and water retention, resulting in volume expansion and hypertension. The increasing BP would inhibit the RAAS, resulting in normal to low normal plasma renin activity in patients with TRAS [51].

Coen and Raftery, in their analysis of 513 renal transplants, observed variations in number of renal arteries in up to 31% of cases [52]. Based on their observations, they concluded that the post transplant complications increased proportional to the number of renal arteries anastomosed. It is therefore imperative to understand that it is not just adequate if the recipient team takes enough care, but the donor team should also be equally careful and be meticulous in ensuring that no traumatic clamp is placed directly on the vessels. As the renal segmental arterial branches are end arteries, utmost care should be taken to preserve the smaller aberrant vessels too, in order to avoid untoward nephron loss. Damage to the Tunica intima is considered to be one of the commonest but preventable causes for TRAS.

## **5. Pathophysiology**

The pathophysiology of the development of Reno vascular hypertension (RVHT) in patients with transplanted kidney closely resembles what we see in various experiments conducted by Harry Goldblatt and his associates in the 1930s [53,54]. Goldblatt had described a 1 kidney 1 clip (1K1C) model, where one of the kidneys is removed, and a clip is applied to occlude the renal artery of the contralateral solitary kidney. The physiological events that take place in the Goldblatt model are almost similar to what we see in the transplanted kidney, except that the transplanted kidney is devoid of intrinsic renal autonomic innervation.

Goldblatt applied Silver clips of varying degrees of arterial occlusion and observed that minimal occlusion of the renal artery was adequate to cause hypertension in 1 to 3 days. This feature was peculiar to renal arterial occlusion, as a simultaneous occlusion of the femoral or splenic arteries did not achieve the expected results. He also observed that the release of the vascular clamp led on to the return of normal blood pressure. Blood pressure rose again when the clips were re-applied. Goldblatt also observed that continuous application of clips failed to maintain the rise in blood pressure, as the pressures normalized after 4 to 6 weeks of clip application, partly due to the establishment of sub capsular collateral circulation. Conversely, in a denervated allograft, when the renal artery stenosed, hypertension occurred, but persisted.



Moreover, the ischemia failed to elicit sympathetic stimulation.

An experimental study was conducted to assess the critical degree of renal artery stenosis, causing a rise in blood pressure in dogs. Imanishi et al. observed that irrespective of whether the kidney is innervated or denervated, the blood pressure started to rise when the renal artery's lumen was occluded by 70%. A noticeable reduction in the renal blood flow was observed when the stenosis was 75% [55]. A similar experimental animal study in rats by Liard et al. in 1980 marked a fall in the mean arterial pressure and increased renal plasma flow on the release of renal artery clip [56]. In yet another study in dogs on the baroreceptor reflexes in Goldblatt hypertension, Liard et al. observed an increase in urine output and natriuresis [57]. Bruno et al., in their experimental study using Doppler ultrasonography in humans, observed that TRAS becomes hemodynamically significant when the luminal narrowing is more than 50% [58]. Furthermore, when the renal perfusion pressure decreases by 15 mmHg, TRAS can lead to severe hypertension, renal failure and irreversible renal loss [59].

## 6. Differential Diagnosis

Hypertension is one of the common but very complex vascular comorbidity observed in renal allograft recipients. Renal artery stenosis is one of the potentially treatable conditions that present with high blood pressure. Various metabolic diseases like diabetes mellitus, obesity, hyperlipidemia and atherosclerosis that commonly coexist in allograft recipients also present with post-transplant hypertension. Volume overload due to an excess intravenous fluid administration in the early post-transplant period is one of the common reasons for hypertension. Obstructive sleep apnoea (OSA) is a recognized treatable cause of resistant hypertension post-transplantation. The degree of hypertension in renal allograft recipients varies with the severity of OSA [60].

High dose of corticosteroids that are commonly used in the post-transplant period can also cause hypertension and closely mimic TRAS. Steroid-induced alterations in intrinsic pressor responses leading to increased arterial vascular resistance are considered the causative reason for hypertension in the post-transplant period [61]. A dose of more than 20 mg of corticosteroids per day is likely to cause hypertension that simulates TRAS in renal allograft recipients [62].

Abrupt cessation of the anti-hypertensive drugs in the post-transplant period may cause a rebound rise in blood pressure due to sympathetic over activity. Patients who were on Beta receptor blockers and Clonidine were closely associated with this condition. Rebound hypertension and tachycardia were observed after sudden cessation of the drug post-transplant, in most patients who were on 900 mcg of Clonidine per day for more than a month [63].

Calcineurin inhibitors (CNI) play a significant role in causing hypertension after

renal transplantation [64,65]. Cyclosporine is more dangerous in causing hypertension than Tacrolimus. Hypertension is usually associated with vascular endothelial dysfunction. A reduced glomerulofiltration, vasoconstriction and sodium retention create a clinical picture that closely resembles TRAS. In such instances, it is imperative to weigh the risks of reducing cyclosporine dosage and the risks of uncontrolled hypertension. Diuretics and Calcium channel blockers are found to be beneficial in such instances [66]. Chronic CNI toxicity produces irreversible damage to the vascular endothelium resulting in a permanent allograft dysfunction [67].

Atherosclerotic recipient iliac arterial stenosis is a condition that closely mimics TRAS. Patients on cyclosporine and prednisolone developed hypertriglyceridemia and hypercholesterolemia 90 days after taking these immunosuppressant's [68]. Allograft recipients with pre-existing atherosclerosis develop refractory hypertension which is indistinguishable from that of TRAS.

Chronic allograft nephropathy is associated with a gradual loss of graft function. Worsening hypertension is the hallmark of this condition [69]. Both hypertension and chronic allograft nephropathy are inter-linked and are extremely difficult to differentiate between the cause and effect [70]. Hypertension due to native kidney disease or segmental arterial occlusion should also be considered in the differential diagnosis of TRAS.

## **7. Diagnosis**

The diagnosis of TRAS is never simple or straightforward. A high index of clinical suspicion and a constant vigil is mandatory to make an appropriate and prompt diagnosis. Though renal arteriography is the most accurate investigation to diagnose TRAS, various laboratory tests and non-invasive methods of imaging, including Colour Doppler ultrasonography and isotope renography might be very helpful in making a diagnosis of TRAS.

### **A. Clinical Diagnosis**

High blood pressure after renal transplantation is not an uncommon finding. It is one of the common but severe complications after renal transplantation [71,72]. It is also a significant risk factor that decides the ultimate graft survival [73-75]. The prevalence of hypertension was between 60 and 90% of all patients undergoing renal transplantation [76]. Sudden onset oliguria for which no specific cause could be identified and unexplained fluid retention could point towards early onset TRAS.

Pickering Syndrome is common syndromes associated with bilateral renal artery Stenosis or arterial Stenosis in solitary kidneys. Flash pulmonary oedema is one of the characteristic features of this condition [77,78]. As transplanted kidney simulates solitary kidney status, sudden breathlessness, orthopnea and flash pulmonary oedema can sometimes be indicators/

initial TRAS presentations [79,80].

## **B. Laboratory Diagnosis**

An unexplained rising Serum Creatinine levels may be the initial presentation pointing towards an early onset of TRAS. In their five-year retrospective analysis of 16 patients with TRAS, Qi et al. concluded that those renal allograft recipients suffering from any of the clinical trials of symptoms should be suspected of TRAS [81]. These included

- I. an elevated serum creatinine (Scr) level associated with allograft dysfunction of unknown aetiology,
- II. refractory hypertension and
- III. Oliguria/fluid retention.

A significantly lower Serum creatinine levels and higher glomerular filtration rate were observed in these patients after intervention.

Measurement of plasma renin activity (PRA) may also point towards the diagnosis of TRAS. As various other factors also play a role in regulating the PRA, it is not very specific for the condition. Lower PRA levels may be observed in patients with TRAS due to blood volume expansion due to fluid retention. In such patients, an increase in extra-cellular fluid (ECF) volume may result in hypertension but may not fully activate the rennin-angiotensin system. On the other hand, an elevated PRA may be noted in patients on diuretic therapy (due to a reduction in ECF volume) and in cases of cellular rejection.

Takata et al. describe the clinical utility of Captopril test in hypertensive patients with renal artery Stenosis [82]. In their study on 28 patients with Reno vascular hypertension (RVHT) with renal artery Stenosis, they observed that the Captopril stimulated PRA is a sufficient tool to screen for RVHT in patients with high-renin hypertension. However, measurement of PRA after single-dose Captopril administration in TRAS patients may be fallacious as the pre-existing ECF volume expansion and hypertension might restrict the RAAS activation resulting in a low PRA and a negative Captopril test.

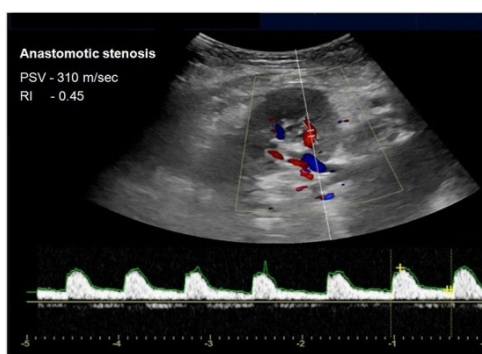
Serum electrolytes are unpredictable in TRAS. Hyperkalemia may occur in such patients but is unreliable in view of high potassium levels seen in patients with allograft dysfunction due to other causes or when on Cyclosporine A or Tacrolimus therapy or too.

## **C. Non-Invasive Diagnosis**

This includes radionuclide scintigraphy, colour Doppler ultrasonography, CT (Computed Tomography) angiography and Magnetic Resonance Angiography.

Colour Doppler Ultrasonography (CDUS) is a well-recognized and a widely used non-invasive screening tool for delineating the vascular flow in the kidneys. Its high reliability, non-invasiveness, ease in handling, inexpensive, a high degree of repeatability makes it a very popular investigation in patients undergoing renal transplantation [83]. Its high sensitivity and specificity make it a very useful study to diagnose TRAS [84]. However, the major limitation of CDUS is its operator dependability and the inherent difficulty in identifying blood flow in situations of multiple renal arterial anastomoses [85,86].

The parameters in CDUS, including Peak systolic velocity, end-diastolic velocity, Resistive Index and Acceleration time are studied with a high degree of accuracy to make a diagnosis of TRAS. An acceleration time of 0.1 seconds or more in the renal arteries, a PSV of more than 200 cm per second within the renal artery and its segmental branches and a ratio of PSV between that in renal and external iliac arteries of more than 1.8 are the most accurate parameters that confirm the presence of TRAS in CDUS [87].



**Figure 2:** Illustrates the Colour Doppler findings of a patient with TRAS. A PSV of 310 cm/sec and a RI of 0.45 is suggestive of TRAS.

Li et al. calculated Pre-PSV ratio (ratio of PSV in renal artery to that in the iliac artery), Post-PSV ratio (ratio of PSV in renal artery to that in interloper arteries) to confirm the diagnosis of severe TRAS. A Post PSV ratio of  $>13$  and Pre-PSV ratio  $>5$  with an acceleration time  $>0.06$  second suggest a severe TRAS [88]. The recent applications of three dimensional (3D) ultrasound that enables direct visualization of the entire arterial anastomosis. A high degree of inter-observer agreement regarding visualization of the vascularity pattern is a hallmark feature of this modality [89].

In cases of clinical suspicion of TRAS, the PSV and EDV are calculated at the interloper arteries of the upper, middle and lower poles of the kidney. A resistive index is calculated using the formula:  $(PSV-EDV)/PSV$ . A low RI of  $<0.6$  is highly suggestive of TRAS [90]. RI is a useful tool for assessing the hemodynamic status of the allograft after angioplasty. An RI of more than 0.9 correlates with allograft rejection or acute tubular necrosis [91].

Contrast-enhanced ultrasound (CEUS) can further complement CDUS in the evaluation of TRAS. It gives a rapid and non-invasive method of assessment of allograft intra-renal perfusion. The time taken by the contrast agent to flow across the intra-renal arteries and

the rate of flow of contrast agent helps make a diagnosis of TRAS [92]. The current contrast agents used include phospholipidic or albumin shell containing microbubbles like Sulphur hexafluoride or perfluorocarbons [93]. The safety profile of contrast agents, rapidity of execution, and accuracy in making a diagnosis are the few advantages of CEUS. CEUS also helps us delineate intra-renal microcirculation, parenchymal abnormalities like acute tubular necrosis, rejection, inadequate perfusion and focal abnormal lesions if any [94]. Given its nil radiation exposure or nephrotoxicity, CEUS may have a wider acceptance amongst the physicians and may be used as a front line investigation tool in future [95].

Radionuclide scintigraphy had been the most popular screening tool for TRAS diagnosis, before the advent of CDUS. Erley et al., in their prospective analysis of 25 patients with clinically suspected TRAS compared Captopril test, renography combined with ACE inhibition and CDUS [96,97]. They observed that the radionuclide scintigraphy showed a specificity of 84% but a low sensitivity of 75%. With the increasing usage of CDUS, isotope renogram is rarely used nowadays.

CT angiography is another non-invasive tool that is freely available and widely used in many centres to diagnose TRAS [98,99]. This test provides a three-dimensional orientation of the renal vasculature. The stenotic areas correlated well with the conventional angiographic images [100]. The lesser usage of contrast media and the absence of a need for arterial access makes this an attractive non-invasive tool in TRAS patients.

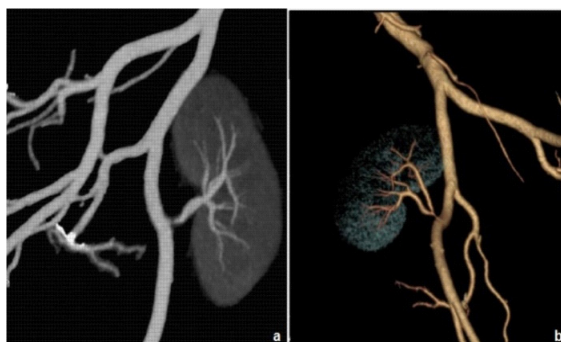
Contrast-enhanced Magnetic resonance angiography can predict accurate arterial anatomy with a high degree of accuracy in patients with TRAS [101-103]. The lack of exposure to ionizing radiation, the relatively less nephrotoxicity of gadolinium when compared to iodinated contrast media and higher sensitivity (67-100%) and specificity (75-100%) makes it superior to CT angiography. [104,105].

#### **D. Invasive Diagnosis**

The arterial anatomy in renal allograft recipients is very complicated, especially with a tortuosity, kinking and overlapping of the vessels that prevent an adequate delineation of the sites of stenosis in patients with TRAS [106]. Digital subtraction angiography (DSA) is considered the Gold standard investigation to diagnose such cases [107].

DSA is a Fluoroscopic technique used these days extensively in interventional radiology to delineate the blood vessels with a high degree of accuracy [108]. This technique helps study the blood vessels located in a dense, soft tissue or bony environment [109,110]. A pre-contrast image is recorded before the contrast agent is administered. The blood vessels opacified after administration of contrast medium are further highlighted by subtracting the pre-contrast images already taken and recorded. This eliminates the artefacts produced by the soft tissue

density or the overlapping bony structures and shows up the arterial architecture with the highest accuracy. As it is done under image intensifier, radiation exposure is minimal compared to the conventional arteriography [111]. The main advantage of this tool is that it provides simultaneous access for other interventional procedures, including balloon angioplasty or vascular stenting.



**Figure 3:** Illustrates the renal DSA of allograft kidney, showing early branching of the renal artery with the stenosis extending on to both the divisions.

Conventional arteriography was considered a gold standard radiological imaging for assessing renal vascular anatomy. This technique more accurately detects the luminal abnormalities in comparison to DSA [112]. However, the ease of technique of DSA, its relatively less exposure to ionizing radiation, the ability to do continuous fluoroscopic screening and also plan simultaneous therapeutic interventions makes conventional arteriography less popular nowadays. An arterial luminal narrowing of more than 50% is considered significant stenosis [113].

Carbon dioxide aided angiography is an emerging technique that has become more popular in selected centres. It decreases contrast volume and preserves renal function in patients with vascular abnormalities of renal allograft [114]. The usage of carbon dioxide as an intravascular agent in patients with TRAS may help perform immediate angioplasty [115,116]. This is especially useful in patients with allergy to iodinated contrast media or who have an allograft dysfunction [117].

Table 1 depicts a summary of the advantages, disadvantages and the current status of the various investigations done for TRAS.

**Table 1:** Comparison of various diagnostic methods for TRAS.

S. No	Test	Merits	Limitations	Current status
1	<b>Clinical diagnosis</b>	Performed by the treating physician	Non-specific, observer-dependent	Aids in the final diagnosis
2	<b>Lab diagnosis</b>	Readily available, Easily done, rapid results	Non-specific, poor sensitivity and specificity	Aids in the final diagnosis
3	<b>CDUS</b>	Rapid test, non-invasive, highly repetitive, no radiation exposure, highly sensitive and specific (upto 100%), confirms the diagnosis, safe in allograft dysfunction	Operator dependent, May have technical difficulty in visualising multiple arteries, more time consuming	Investigation of Choice

4	<b>CEUS</b>	rapid, non-invasive, avoids nephrotoxicity, delineates renal micro-circulation with accuracy, useful to diagnose parenchymal abnormalities.	Operator dependent, Difficulty in visualising multiple arteries	Maybe more widely used as first line tool of investigation in future
5	<b>Radionuclide Scintigraphy</b>	Provides complementary information about the degree of perfusion and function of the allograft. Higher specificity (84%) and moderate sensitivity (75%), non-operator dependent	Not widely used in view of availability of CDUS everywhere.	Though not so popular, still has a significant role to play especially in evaluation of complications following renal transplants.
6	<b>CT Angiography</b>	Freely available, rapid test and widely used, provides 3 dimensional orientation of renal vasculature. Lesser usage of contrast media makes it more attractive.	Contrast allergy, nephrotoxicity and higher cost, radiation exposure.	Attractive non-invasive tool in TRAS patients
7	<b>MR Angiography</b>	No radiation, no contrast injection, nephron-protective, highly sensitive and specific (upto 100%)	High cost, prolonged duration, claustrophobia, gadolinium toxicity, artefacts induced by metal clips	Attractive non-invasive tool in TRAS patients
8	<b>Conventional arteriography</b>	Gold standard test, accurate assessment of renal vasculature,	Need for arterial puncture, need for iodinated contrast agent, radiation exposure, nephrotoxicity, inability to plan simultaneous therapeutic interventions	Most accurate Largely replaced by DSA
9	<b>Digital Subtraction Angiography</b>	Excellent investigation to delineate vascular luminal anatomy, lesser bony artefacts, lesser radiation exposure, lesser need for iodinated contrast media, continuous screening possible, can plan simultaneous angioplasty and stenting.	Limited spatial resolution, artefacts, small visual field.	Most accurate non-invasive tool in TRAS patients

## 8. Treatment

TRAS is a well recognized vascular complication following renal transplantation. The causes are multifactorial, and optimal management is yet to be fully defined. Management of TRAS depends on the patients' symptoms, degree of hypertension, allograft dysfunction, the extent of uremia, sequela of uremia and ultimately, an allograft loss. A prompt, early diagnosis and appropriate treatment would contribute significantly to patient and allograft survival. There are three treatment modalities available for TRAS: optimal medical therapy, percutaneous intervention and surgical revascularization.

### a) Optimal medical therapy

One must understand that not all patients diagnosed to have TRAS need to be intervened. When allograft function is stable, if PSV is less than 180 cm/sec, RI is  $>0.50$ , and

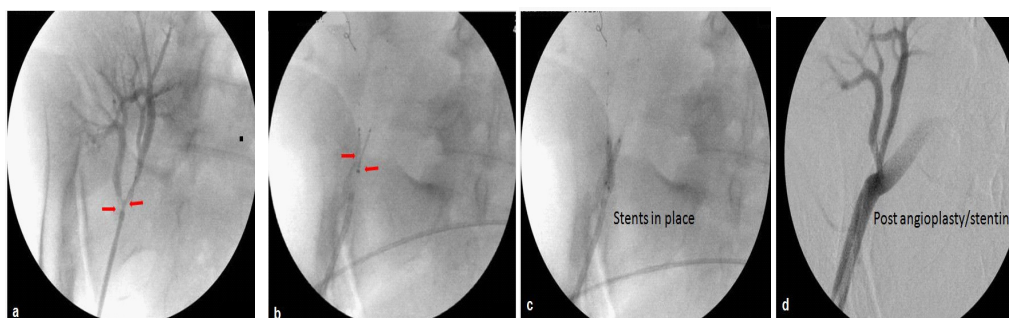
hemodynamically significant stenosis is ruled out, intervention is usually not required [118]. In such instances, when the patient has hypertension alone, and if the graft function is adequate, pharmacological treatment with antihypertensive alone may be sufficient. Angiotensin-converting enzyme (ACE) inhibitors are usually effective and can be safely used in such patients, provided the serum creatinine and serum potassium levels are normal. This drug has not attained widespread acceptance amongst treating physicians for treating hypertension in renal transplant recipients, especially in concomitant cyclosporine use for fear of a possible decreased renal blood flow and a reduction in glomerular filtration rate [119]. Patients on ACE inhibitors need to monitor the serum creatinine levels. On the other hand, conservatively treated patients have to be closely monitored, as they have a higher risk of graft failure [120].

Patients who need long term therapy with ACE inhibitors need to be on constant and regular follow-up, especially after ascertaining the effectiveness and acceptability of the agent. The other advantages of these agents are their Reno protective and cardio protective properties [121]. Patients conservatively managed with pharmacological therapy need to be monitored with CDUS once in 6 months, for fear of worsening of Stenosis [122].

### b) Percutaneous intervention

As long as the hemodynamic stability and renal functions are maintained, one can continue with conservative therapy. When hypertension becomes uncontrolled, or when serum creatinine level increases and CDUS suggests a progression of Stenosis, conventional or digital subtraction angiography is performed before any form of intervention, to ascertain the extent of stenosis. A percutaneous transluminal renal balloon angioplasty (PTRA) with or without stenting can be done simultaneously wherever indicated.

A well-performed angioplasty can restore allograft perfusion in up to 90% of cases [123]. Technical success after PTRA is over 80%, improved BP control in over 75% and a stable graft function in over 80% of patients with TRAS [124]. Angioplasty and stenting are most effective in stenosis that are of short segment and away from the vascular anastomosis [125].



**Figure 4:** illustrates the renal blood flow before and after renal angioplasty and stenting.



Anastomotic stenosis carries more risk of rupture, bleed or recurrences when dilated using balloon angioplasty. Surgical revascularization may be beneficial in such cases, as nodular fibrotic lesions or calcifications at the site of anastomotic strictures might hinder a successful angioplasty [126]. These pathological changes at the site of anastomosis suggest that surgical repair is the treatment of choice. Angioplasty is difficult, technically challenging and carries more morbidity in patients with end to end anastomosis to internal iliac artery [127]. In cases of ostial lesions of TRAS, balloon angioplasty along with stenting could provide an effective revascularization strategy [128].

In patients with end to side anastomosis to the femoral artery, PTRA is best performed through the retrograde ipsilateral femoral approach. On the other hand, in patients who had an end to end anastomosis to internal iliac artery, contralateral femoral artery or brachial artery approach is preferred. In case of compromised graft function, carbon dioxide is administered to monitor the results of balloon angioplasty [129].

Though a safe technique, PTRA may result in complications in up to 10% of cases. Most of them are related to needle prick site injuries, local bleeding, hematoma, ecchymosis and thrombosis, vascular or renal perforation and tearing of the vessel wall. Arterial thrombosis, dissection of the arterial wall, pseudo-aneurysm at the puncture site or rupture of the vessel are seen in less than 4% of cases owing to an improvement in the technical expertise, better tools and gadgets used for monitoring [130].

### **c) Surgical revascularization**

With rapid advancements in imaging technologies, better awareness and knowledge of TRAS amongst the treating nephrologists, with a high index of clinical suspicion and with increasing clinical expertise in performing vascular anastomosis by transplant surgeons or PTRA by interventional radiologists and nephrologists, the overall need for surgical exploration and revascularization has considerably reduced over the years. The surgical approach has been relegated to a mere salvage procedure after all other minimally invasive options are tried out and exhausted.

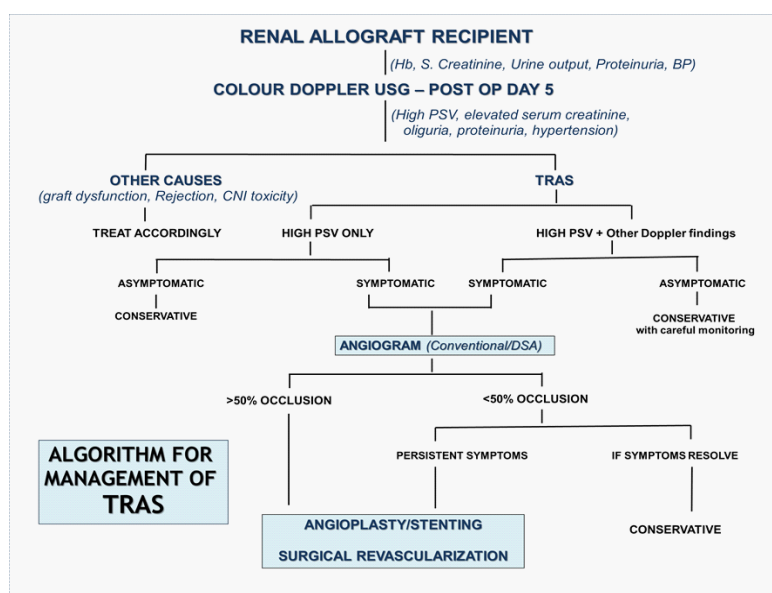
Stenosis at the arterial anastomosis site, vascular kinks, recurrent stenosis, failed PTRA, those vessels inaccessible through percutaneous approach and tight strictures not admitting guidewire to be negotiated across the stenosed site are indications for surgical revascularization.

Multiple reconstructive surgical options are available to repair the stenosis, but no single procedure could claim superiority. The surgical techniques for the repair of TRAS include localized endarterectomy, excision and revision of anastomosis, renal artery patch angioplasty, renal artery bypass using ipsilateral internal iliac artery or saphenous vein graft [131]. The

presence of dense adherent scar tissue around the allograft and adhesions between the artery and the vein or ureter makes surgical repair even more challenging. Various centres have claimed success after surgical repair ranging from 66% to 100% [132,133]. A prompt surgical intervention mostly gives the desired results when stenosis is more than 70%.

Excision of the stenotic segment and preimplantation of the renal artery is not only technically difficult and challenging but also has reported a success rate of 72% and a recurrence rate of 11% [134]. Moreover, an improvement in their blood pressure is appreciable only in those who had physiological evidence of TRAS before surgical repair.

## 9. Algorithm



**Figure 5:** Illustrates a flowchart of management of TRAS. The protocol that is followed from the day of renal transplant to diagnosis and management of TRAS is depicted here.

The main advantages of following such algorithm in TRAS are:

1. It gives a step wise depiction of solutions to any given problem thus enabling a standardized protocol to be followed.
2. It also facilitates an earlier diagnosis of TRAS, as all patients would have undergone a post op day 5 Colour Doppler Ultra sonogram, which would either pick up asymptomatic TRAS (which can be closely monitored) or symptomatic TRAS at much earlier stage.
3. It also facilitates the transplant physician and surgeon to take an earlier decision without any ambiguity and also aids in choosing the appropriate mode of intervention.

## 10. Conclusions

Hypertension, though one of the common sequelae of end-stage renal disease, becomes a complex entity in the post-transplant period. TRAS is one of the most common vascular

complications following renal transplantation. A high index of clinical suspicion is mandatory to pick up this potentially reversible condition at a much earlier stage. A systematic protocol and a liberal usage of CDUS might help the clinicians treat the condition when it is fully reversible. A lack of proper diagnosis or delay in diagnosis might lead to allograft dysfunction and graft loss. More randomized controlled trials and meta-analysis are needed to assess the efficacy and benefits of percutaneous transluminal renal angioplasty and surgical revascularization.

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