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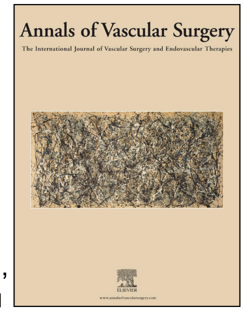


Utilization of Carbon Dioxide Angiography and Percutaneous Balloon Angioplasty for Treatment of Transplant Renal Artery Stenosis

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## ABSTRACT

**Objective**: Transplant renal artery stenosis (TRAS) may lead to graft dysfunction and failure. Progressive deterioration of renal allograft function may be exacerbated by contrast-induced nephrotoxicity during iodine contrast administration for renovascular imaging of allografts. We present our institutional experience of endovascular management for TRAS using $CO_2$ digital subtraction angiography ($CO_2$-DSA) and balloon angioplasty to manage failing renal transplants.

**Methods**: Four patients with renal allografts from March 2017-May 2018 were referred for graft dysfunction and pending renal transplant failure. Indications for referral included refractory hypertension, decreasing renal functioning, and elevated renovascular systolic velocities.

**Results**: Median age of the four patients was 41.5-years-old (22-60-years-old). There were two male and female patients. Chronic hypertension and type 2 diabetes mellitus were the most common comorbidities. An average total of 75 mL of $CO_2$ was used, supplemented with 17.4 mL of iodinated contrast. All patients had improvements in renal function following intervention with a mean decrease in systolic and diastolic blood pressure of 25.8% and 21.4% respectively. We also observed a mean decrease of BUN by 13.6% and creatinine by 37.4%. Additionally, eGFR increased by 37.7%. All allografts survived after surgery and only one patient required repeat angioplasty for recurrence.

**Conclusion**: Use of $CO_2$-DSA with balloon angioplasty can be successfully utilized to salvage deteriorating kidney allograft function in patients with TRAS.

## 1.0 INTRODUCTION

Transplant renal artery stenosis (TRAS) is a common complication of renal transplants and may result in allograft failure. The incidence of TRAS has been reported to be as high as 23% and accounts for 75% of all posttransplant vascular complications.[1] TRAS can occur between 3 months to 2 years after transplantation and commonly presents as refractory systemic hypertension.[2] Symptoms may also manifest as acute renal failure, refractory hypertension, flash pulmonary edema, congestive heart failure, & pedal edema. Risk factors associated with incidence of TRAS include older recipient and donor age, extended criteria donors, cytomegalovirus status, cold ischemia time, immuno-suppression induction, and heart disease.[3–7] In particular, recipients and donors with atherosclerotic risk factors such as diabetes mellitus, hypertension, renal artery calcification, and ischemic heart disease are involved in late re-stensosis.[8,9] It is important for clinicians to identify and manage TRAS quickly as it is associated with nearly a 3-fold risk of graft loss and death.[3]

Percutaneous angioplasty (PTA) is a minimally invasive procedure that has risen to supplant open surgical repair. PTA can restore kidney perfusion in 70-90% of cases and has led to increased kidney functioning.[10–15] Early treatment of TRAS may improve mid- to long-term graft function and overall patient survival – achieving outcomes similar to those of transplant patients unaffected by TRAS. Patel et al. compared the 10-year patient survival rate between patients with endovascularly treated TRAS and patients without TRAS were 89.9% and 84.7% respectively.[16] PTA often requires the use of iodinated contrast to visualize vascular structures and organs intraoperatively. Contrast-induced nephrotoxicity (CIN) is the third-leading cause of hospital-acquired renal failure with hydration as its only proven protective measure.[17] Carbon dioxide ($CO_2$) digital subtraction angiography ($CO_2$-DSA) is a non-nephrotoxic imaging modality currently only indicated in patients with CIN or iodinated contrast allergy. Several studies have paired its use with endovascular procedures.[18–21]

In this report, we aim to describe our experience with $CO_2$-DSA and PTA to treat patients with TRAS.

## 2.0 METHODS

### *2.1 Patient Cohort*

This is a retrospective case series consisting of four patients at a single, academic, tertiary medical center. We reviewed the medical records of patients who were referred for graft dysfunction and underwent renal transplant PTA from March 2017 to May 2018. Demographic information, comorbidities, etiology of end-stage renal disease (ESRD), and indication for intervention were recorded. Pre-operative blood pressure, medications, serum blood urea nitrogen (BUN), creatinine, and glomerular filtration rate (GFR) were collected. Information of the graft used such as type, cold ischemia time, Carrel patch, number of arteries involved, and donor/recipient CMV status were also documented. Indications for intervention included refractory hypertension, decreased kidney functioning, and renal artery stenosis confirmed by duplex ultrasonography. Dialysis vintage years were defined as the total number of years a patient was on dialysis until they received a kidney transplant. Graft age was defined by the time from the allograft transplant procedure until the day of operative intervention for TRAS.

In our institution, we perform arterial duplex ultrasound of the transplanted renal artery immediately in the post-operative period. After this initial imaging, the need for further imaging is reviewed on a case-by-case basis based on symptoms of failing kidney functioning such as low urine output, refractory hypertension, flash pulmonary edema, and rising creatinine. Diagnosis of

TRAS was defined as ≥60% reduction in transplanted renal artery diameter, correlating to a peak systolic velocity of ≥180 cm/s, by duplex ultrasonography.[22] Increasing creatinine, BUN, and declining GFR were used as markers of declining kidney functioning.

Primary outcomes included post-operative changes in blood pressure, serum BUN, creatinine, and GFR. Changes in required hypertensive medications and dialysis were also collected as a secondary outcome. Medical records from outpatient follow-up visits were reviewed until May 2018, the conclusion of the case-series. $CO_2$-DSA was used in all cases to visualize the origin and takeoff of the vasculature flowing towards the transplanted kidneys. Digital subtraction angiography was used to confirm the efficacy of balloon angioplasty. Procedural success was measured by a ≤10% stenosis after angioplasty as measured by angiography and if patient's hypertension has resolved post-operatively. No stents were utilized to maintain patency. If patients were not previously on an antiplatelet regimen pre-operatively, patients were started on clopidogrel 75 mg after angiography. Conversely, patients who were on antiplatelet therapy prior to procedure were kept on their antiplatelet regimen until 2-3 days prior to procedure and were restarted 1 day after procedure (Case #1). Post-operative renal ultrasound was performed 1-2 weeks after the index procedure. Ultrasound Renal Duplex was performed 2, 6, and 12-months after the procedure to monitor for transplant renal artery restenosis. Institutional review board approval was granted for this study.

*2.2 $CO_2$-DSA Technique*

$CO_2$-DSA was used as an imaging modality to visualize renal vascular anatomy in renal transplant patients. After preparing the patient in standard sterile fashion, the right common femoral artery was cannulated with a micropuncture access needle using ultrasound guidance. A

0.018-inch mandril wire was placed through the needle into the right external iliac artery. The needle was replaced with a micropuncture access sheath using the Seldinger technique. A J-wire was then placed into the infrarenal abdominal aorta. After removing the micropuncture access sheath, a 5-french sheath was placed into the right common femoral artery. Then, an Omni Flush catheter is placed over the J-wire into the infrarenal aorta to perform $CO_2$-DSA of the infrarenal aorta and its corresponding branches. Blood is withdrawn and flushed with saline through the infra-renal catheter to confirm access. To prepare for the $CO_2$-DSA, we used a 30mL syringe and tubing directly attached to the $CO_2$ tank (Airgas USA, LLC, Radnor, PA). The tube directly fills the 30mL syringe which is subsequently purged three times to reduce air contamination and vapor lock. A closed $CO_2$ system is created by attaching the syringe to a three-way stopcock at the end of the intra-arterial injection catheter. To obtain angiographic images, hand injection of 30mL of $CO_2$ and DSA was performed with high frame rates of 3-6 frames per second. Frames were combined to produce one image for viewing through stacking technology. $CO_2$-DSA was performed in the anterior-posterior, right anterior oblique, and left anterior oblique positions (*Figure 1*). The position that best demonstrated the origin of the renal artery was used to visualize the TRAS during PTA and multiple images were taken as needed. To confirm the diagnosis, a low volume of iodinated contrast was injected near the origin of the renal transplant artery as needed. Once the diagnosis of TRAS was confirmed, the lesions were treated with balloon angioplasty. The size of balloon used was dependent on the size of the unaffected renal artery adjacent to the stenosis as measured by intraoperative angiography. Repeat angiography was performed again after angioplasty to confirm renal artery patency and technical success.

## 3.0 RESULTS

Six total patients were referred to clinic between March 2017 to May 2018. Two patients were not included in our study because we had deemed that intervention was not indicated at this time. In these two patients, high grade stenosis was appreciated by ultrasound criteria, however, renal function was adequate and patients were asymptomatic. Four patients with TRAS were identified and treated with PTA though 1 patient had their transplant renal artery stenosis recur. All cases were anastomotic stenosis and were diagnosed on average 5 months post-transplant.. The median age of our cohort was 41.5-years-old (22-60-years-old) with two men and two women. Our cohort had varying etiologies of ESRD, and the most common comorbidities were hypertension and type 2 diabetes mellitus (*Table 1*). Among the four patients: three received deceased-donor renal transplants (DDRT) and one received a living-related renal transplant (LRRT). All patients and donors had positive CMV status and an average cold ischemia of 21.67 hours (*Table 2*).

Procedural success was 100%, all allografts demonstrated improved function, and there were no contrast related complications. An average number of five injections per case were used with 15 mL of $CO_2$ per injection. For every case, an average total of 75 mL of $CO_2$ and 17.4 mL of iodinated contrast were used. On average, a 4.1 mm balloon was used. The median follow-up time of patients was six months (range 68-343 days) after surgery. Four of five grafts remained primarily patent with Case #3 having to undergo a second intervention due to recurring TRAS within 71 days.



After each procedure, all patients demonstrated improved kidney functioning. Patients were able to decrease the number of anti-hypertensive medications from three to two. Case #4, who was previously on hemodialysis pre-operatively, did not require any hemodialysis after renal artery angioplasty (*Table 1*). On average, there was a 13.6% decrease in BUN and 37.4%

decrease in serum creatinine levels. An eGFR average increase of 37.7% was observed (*Table 3*). Systolic and diastolic blood pressures decreased by an average of 25.8% and 21.4% respectively (*Table 4*).

**4.0 DISCUSSION**

Deteriorating kidney function after transplantation provides a diagnostic and procedural challenge since iodinated contrast is nephrotoxic. In a select group of patients presenting with pending renal transplant failure due to TRAS, we demonstrate that $CO_2$-DSA with PTA can be utilized to lower blood pressure, creatinine, BUN and increase GFR. $CO_2$-DSA in TRAS can be safely utilized as an intraoperative imaging modality without further exacerbating deteriorating kidney function.

CIN is a common complication of iodinated contrast media exposure and patients with renal transplants are particularly at risk. The incidence of CIN in renal transplant patients is at least 15.3% and may be as high as 42.8% if intravenous hydration prophylaxis is not properly administered.[23] In a multivariate analysis that controlled for risk factors such as total hydration, iodine load, and prior contrast exposure, CIN had more than a 3-fold risk of 30-day mortality.[24] Gadolinium was once considered a viable alternative to iodinated contrast. However, gadolinium may inadvertently cause nephrogenic systemic fibrosis in patients with advanced kidney disease.[25,26] $CO_2$ angiography images were first used in 1956 by Oppenheimer et al. who found its beneficial properties through animal experiments to detect intracardiac structures.[27] In the 1990s, Dr. Irvin Hawkins championed its use because of its nephron-sparing characteristics, relatively low cost, wide availability, use as an intraoperative guide, and rapid clearance from the body.[28–30]

Our case-series shows that $CO_2$-DSA may be a viable imaging modality to preserve kidney functioning that can be applied to patients not just with CIN or contrast allergy. Our results were consistent with the body of literature, supporting $CO_2$ angiography's renal sparing benefits, owing to its solubility and being easily cleared in the lungs.[19,29–32] In addition, compared to previous studies with failing native kidneys, we were able to produce adequate intraoperative images to guide PTA despite using half as much $CO_2$ and iodinated contrast.[19,20] This may prove to be useful as risk for developing CIN is dose dependent.[33] Finally, $CO_2$ angiography is a relatively cost effective study. Intravascular ultrasound (IVUS) has also emerged as an imaging modality to help further minimize contrast administration during the renal transplant artery intervention cases.[34] Although IVUS is a useful modality in diagnosing, locating, and evaluating a lesion, it may not be readily available worldwide because of its' cost and lack of resources for the equipment, personnel, and interpretive skills necessary to maximize its use.[35] Schiele et al. found that procedures involving IVUS were 18% more expensive compared to standard angiography due to the cost of its IVUS catheters and need for more balloons. When taking into account the costs of re-stenosis, the procedural costs of the IVUS were 8.7% higher.[36] Thus, angiography is a viable and cost-effective imaging modality in settings where the resources for IVUS use are not available.

Though $CO_2$ angiography is a relatively safe option, it is important to keep in mind its potential hazards. In a retrospective, single-institutional study of 1,007 $CO_2$ angiography procedures over a 21-year period, Moos et al. found that air trapping, also known as vapor lock, is the most common complication.[32] Because of $CO_2$'s buoyancy, gas can accumulate and become trapped within the vascular space. Although $CO_2$ is highly soluble and is absorbed within 2-5 minutes, vapor lock can occur during large injections or if the interval between $CO_2$

injections is too short.[37,38] Room air contamination may also exacerbate the risk of vapor lock and it is encouraged to minimize the amount of steps required to transfer $CO_2$ from its tank to the patient.[32] Furthermore, nitrous oxide may contribute to the vapor lock phenomena and is relatively contraindicated with $CO_2$ angiography. Nitrous oxide may diffuse into the $CO_2$ bubble, thus increasing its volume and diluting $CO_2$. Finally, it is imperative to use $CO_2$-DSA with caution in patients with severe chronic obstructive pulmonary disease. This is especially true in patients who retain $CO_2$ and cannot expel $CO_2$ with increased ventilation.[29] Given these hazards, meticulous attention to detail when preparing $CO_2$-DSA and reviewing each patient's ability to tolerate the procedure must be considered. Future prospective research is warranted to weight the benefits and hazards of $CO_2$-DSA in renal transplant patients.

**5.0 CONCLUSION**

$CO_2$-DSA and PTA can be used to improve deteriorating kidney function in stenotic kidney transplants. Our case-series demonstrated improved transplant kidney functioning through the utilization of $CO_2$-DSA to minimize iodinated contrast exposure. Kidney allograft function was preserved after PTA, demonstrated by decreased blood pressure, BUN, creatinine and increased eGFR.

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*Table 1. Demographics of patient cohort*

| Case | Age (years), Sex | Comorbidities | ESRD etiology | Pre-operative HTN Medications (#) | Post-operative HTN Medications (#) | Dialysis Vintage Years | Pre-operative Dialysis | Post-operative Dialysis | Balloon Used | Antiplatelet Used |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 60, Male | HTN, T2DM, HBV, HLD | Congenital solitary kidney | Metoprolol 25mg BID, Losartan 50mg, Nifedipine 90mg, Hydrochlorothiazide 25mg (4) | Metoprolol 25mg BID, Losartan 50mg daily, Nifedipine 90mg XL (3) | 4 years | HD | None | 0.5cm balloon | Aspirin 81mg |
| 2 | 22, Female | HTN | Genetic; childhood ATN | Metoprolol 25mg BID, Norvasc 10mg (2) | Metoprolol 25mg BID, Amlodipine 10mg daily (2) | None | None | None | 0.35cm balloon | None |
| 3 | 41, Female | HTN, CAD | Unknown; x2 renal transplant (LRRT 2002) | Clonidine PRN, Hydralazine 50mg BID, Carvedilol 6.25mg (3) | Amlodipine 5mg, Hydralazine 100mg (2) | 5 years | PD | PD | 0.3cm Ultraverse balloon; 0.4cm Lutonix balloon | Clopidogrel 75mg after 2nd TRAS |
| 4 | 52, Male | T2DM, HLD, former smoker | T2DM | Nifedipine 90mg, Hydralazine 100mg TID, Metoprolol 12.5mg BID (3) | Metoprolol 25mg (1) | 6 years | HD | None | 0.5cm Ultraverse balloon | Clopidogrel 75mg started 1 year after |

*HTN = hypertension, T2DM = type 2 diabetes mellitus, HBV = hepatitis B virus, CAD = coronary artery disease, HLD = hyperlipidemia, ATN = acute tubular necrosis, LRRT = living-related renal transplant, HD = hemodialysis, PD = peritoneal dialysis*

*Table 2. Graft characteristics*

| Case | Graft Type | Graft age (months) | Greatest change in peak systolic velocity and location | Cold ischemia time | Carrel patch | Number of arteries | Donor/recipient CMV status |
|---|---|---|---|---|---|---|---|
| 1 | DDRT | 9 | +372 cm/s, proximal portion | 24 hours | Yes | 1 | Positive/Positive |
| 2 | LRRT | 2 | +241 cm/s, anastomosis | N/A | N/A | 1 | Positive/Positive |
| 3 | DDRT | 5 | +219 cm/s, proximal portion | 26 hours | Yes | 2 | Positive/Positive |
| 4 | DDRT | 4 | +285 cm/s, anastomosis | 15 hours | Yes | 1 | Positive/Positive |

*DDRT = deceased-donor renal transplant, LRRT = living-related renal transplant, CMV = cytomegalovirus*

*Table 3. Pre- and post-operative blood urea nitrogen, creatinine, and glomerular filtration rate of patients*

| | **Pre-Op (Average)** | **<5 Days Post-Op (Average)** | **5-15 Days Post-Op** | **16-31 Days Post-Op** | **32-61 Days Post-Op** | **>61 Days Post-Op (Average)** | **% Change from Pre-op to Post-op** |
|---|---|---|---|---|---|---|---|
| **BUN (mg/dL)** | 37.6 | 32.9 | 27.4 | 30.1 | 28.3 | 32.5 | -13.60% |
| **Cr (mg/dL)** | 2.6 | 2.4 | 1.6 | 1.8 | 1.6 | 1.6 | -37.40% |
| **eGFR (ml/min/1.73 m²)** | 34.9 | 39.3 | 41.8 | 39.5 | 42.8 | 48 | 37.70% |

*BUN = blood urea nitrogen, Cr = creatinine, eGFR = estimated glomerular filtration rate*

*Table 4. Pre- and post-operative blood pressure*

| | Pre-Op (Average) | Post-Op (Average) | Change (Average) | % Change |
|---|---|---|---|---|
| **Systolic BP (mmHg)** | 169.4 | 128.3 | 41.1 | -25.80% |
| **Diastolic BP (mmHg)** | 92.6 | 74.3 | 18.3 | -21.40% |

*BP = blood pressure*

*Figure 1. Intraoperative images*


*Intraoperative imaging of A) iodinated contrast pre-PTA, B) $CO_2$-DSA pre-PTA, and C) iodinated contrast post-PTA from Patient 2. The white arrows in each image indicates the area of stenosis. PTA = percutaneous angioplasty.*