

## Journal Pre-proof

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

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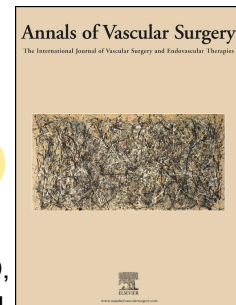
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1       **Utilization of Carbon Dioxide Angiography and Percutaneous Balloon Angioplasty for**  
2       **Treatment of Transplant Renal Artery Stenosis**

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38 **ABSTRACT**

39 **Objective:** Transplant renal artery stenosis (TRAS) may lead to graft dysfunction and failure.  
40 Progressive deterioration of renal allograft function may be exacerbated by contrast-induced  
41 nephrotoxicity during iodine contrast administration for renovascular imaging of allografts. We  
42 present our institutional experience of endovascular management for TRAS using CO<sub>2</sub> digital  
43 subtraction angiography (CO<sub>2</sub>-DSA) and balloon angioplasty to manage failing renal transplants.  
44 **Methods:** Four patients with renal allografts from March 2017-May 2018 were referred for graft  
45 dysfunction and pending renal transplant failure. Indications for referral included refractory  
46 hypertension, decreasing renal functioning, and elevated renovascular systolic velocities.  
47 **Results:** Median age of the four patients was 41.5-years-old (22-60-years-old). There were two  
48 male and female patients. Chronic hypertension and type 2 diabetes mellitus were the most  
49 common comorbidities. An average total of 75 mL of CO<sub>2</sub> was used, supplemented with 17.4 mL  
50 of iodinated contrast. All patients had improvements in renal function following intervention  
51 with a mean decrease in systolic and diastolic blood pressure of 25.8% and 21.4% respectively.  
52 We also observed a mean decrease of BUN by 13.6% and creatinine by 37.4%. Additionally,  
53 eGFR increased by 37.7%. All allografts survived after surgery and only one patient required  
54 repeat angioplasty for recurrence.  
55 **Conclusion:** Use of CO<sub>2</sub>-DSA with balloon angioplasty can be successfully utilized to salvage  
56 deteriorating kidney allograft function in patients with TRAS.

57

## 58 1.0 INTRODUCTION

59 Transplant renal artery stenosis (TRAS) is a common complication of renal transplants  
60 and may result in allograft failure. The incidence of TRAS has been reported to be as high as  
61 23% and accounts for 75% of all posttransplant vascular complications.<sup>1</sup> TRAS can occur  
62 between 3 months to 2 years after transplantation and commonly presents as refractory systemic  
63 hypertension.<sup>2</sup> Symptoms may also manifest as acute renal failure, refractory hypertension, flash  
64 pulmonary edema, congestive heart failure, & pedal edema. Risk factors associated with  
65 incidence of TRAS include older recipient and donor age, extended criteria donors,  
66 cytomegalovirus status, cold ischemia time, immuno-suppression induction, and heart disease.<sup>3-7</sup>  
67 In particular, recipients and donors with atherosclerotic risk factors such as diabetes mellitus,  
68 hypertension, renal artery calcification, and ischemic heart disease are involved in late re-  
69 stenosis.<sup>8,9</sup> It is important for clinicians to identify and manage TRAS quickly as it is associated  
70 with nearly a 3-fold risk of graft loss and death.<sup>3</sup>

71 Percutaneous angioplasty (PTA) is a minimally invasive procedure that has risen to  
72 supplant open surgical repair. PTA can restore kidney perfusion in 70-90% of cases and has led  
73 to increased kidney functioning.<sup>10-15</sup> Early treatment of TRAS may improve mid- to long-term  
74 graft function and overall patient survival – achieving outcomes similar to those of transplant  
75 patients unaffected by TRAS. Patel et al. compared the 10-year patient survival rate between  
76 patients with endovascularly treated TRAS and patients without TRAS were 89.9% and 84.7%  
77 respectively.<sup>16</sup> PTA often requires the use of iodinated contrast to visualize vascular structures  
78 and organs intraoperatively. Contrast-induced nephrotoxicity (CIN) is the third-leading cause of  
79 hospital-acquired renal failure with hydration as its only proven protective measure.<sup>17</sup> Carbon  
80 dioxide (CO<sub>2</sub>) digital subtraction angiography (CO<sub>2</sub>-DSA) is a non-nephrotoxic imaging

81 modality currently only indicated in patients with CIN or iodinated contrast allergy. Several  
82 studies have paired its use with endovascular procedures.<sup>18–21</sup>

83 In this report, we aim to describe our experience with CO<sub>2</sub>-DSA and PTA to treat patients  
84 with TRAS.

85

## 86 **2.0 METHODS**

### 87 *2.1 Patient Cohort*

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

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

104 TRAS was defined as  $\geq 60\%$  reduction in transplanted renal artery diameter, correlating to a peak  
105 systolic velocity of  $\geq 180$  cm/s, by duplex ultrasonography.<sup>22</sup> Increasing creatinine, BUN, and  
106 declining GFR were used as markers of declining kidney functioning.

107 Primary outcomes included post-operative changes in blood pressure, serum BUN,  
108 creatinine, and GFR. Changes in required hypertensive medications and dialysis were also  
109 collected as a secondary outcome. Medical records from outpatient follow-up visits were  
110 reviewed until May 2018, the conclusion of the case-series. CO<sub>2</sub>-DSA was used in all cases to  
111 visualize the origin and takeoff of the vasculature flowing towards the transplanted kidneys.  
112 Digital subtraction angiography was used to confirm the efficacy of balloon angioplasty.  
113 Procedural success was measured by a  $\leq 10\%$  stenosis after angioplasty as measured by  
114 angiography and if patient's hypertension has resolved post-operatively. No stents were utilized  
115 to maintain patency. If patients were not previously on an antiplatelet regimen pre-operatively,  
116 patients were started on clopidogrel 75 mg after angiography. Conversely, patients who were on  
117 antiplatelet therapy prior to procedure were kept on their antiplatelet regimen until 2-3 days prior  
118 to procedure and were restarted 1 day after procedure (Case #1). Post-operative renal ultrasound  
119 was performed 1-2 weeks after the index procedure. Ultrasound Renal Duplex was performed 2,  
120 6, and 12-months after the procedure to monitor for transplant renal artery restenosis.  
121 Institutional review board approval was granted for this study.

122

## 123 *2.2 CO<sub>2</sub>-DSA Technique*

124 CO<sub>2</sub>-DSA was used as an imaging modality to visualize renal vascular anatomy in renal  
125 transplant patients. After preparing the patient in standard sterile fashion, the right common  
126 femoral artery was cannulated with a micropuncture access needle using ultrasound guidance. A

127 0.018-inch mandril wire was placed through the needle into the right external iliac artery. The  
128 needle was replaced with a micropuncture access sheath using the Seldinger technique. A J-wire  
129 was then placed into the infrarenal abdominal aorta. After removing the micropuncture access  
130 sheath, a 5-french sheath was placed into the right common femoral artery. Then, an Omni Flush  
131 catheter is placed over the J-wire into the infrarenal aorta to perform CO<sub>2</sub>-DSA of the infrarenal  
132 aorta and its corresponding branches. Blood is withdrawn and flushed with saline through the  
133 infra-renal catheter to confirm access. To prepare for the CO<sub>2</sub>-DSA, we used a 30mL syringe and  
134 tubing directly attached to the CO<sub>2</sub> tank (Airgas USA, LLC, Radnor, PA). The tube directly fills  
135 the 30mL syringe which is subsequently purged three times to reduce air contamination and  
136 vapor lock. A closed CO<sub>2</sub> system is created by attaching the syringe to a three-way stopcock at  
137 the end of the intra-arterial injection catheter. To obtain angiographic images, hand injection of  
138 30mL of CO<sub>2</sub> and DSA was performed with high frame rates of 3-6 frames per second. Frames  
139 were combined to produce one image for viewing through stacking technology. CO<sub>2</sub>-DSA was  
140 performed in the anterior-posterior, right anterior oblique, and left anterior oblique positions  
141 (*Figure 1*). The position that best demonstrated the origin of the renal artery was used to  
142 visualize the TRAS during PTA and multiple images were taken as needed. To confirm the  
143 diagnosis, a low volume of iodinated contrast was injected near the origin of the renal transplant  
144 artery as needed. Once the diagnosis of TRAS was confirmed, the lesions were treated with  
145 balloon angioplasty. The size of balloon used was dependent on the size of the unaffected renal  
146 artery adjacent to the stenosis as measured by intraoperative angiography. Repeat angiography  
147 was performed again after angioplasty to confirm renal artery patency and technical success.

148

149 **3.0 RESULTS**

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

162 Procedural success was 100%, all allografts demonstrated improved function, and there were  
163 no contrast related complications. An average number of five injections per case were used with  
164 15 mL of CO<sub>2</sub> per injection. For every case, an average total of 75 mL of CO<sub>2</sub> and 17.4 mL of  
165 iodinated contrast were used. On average, a 4.1 mm balloon was used. The median follow-up  
166 time of patients was six months (range 68-343 days) after surgery. Four of five grafts remained  
167 primarily patent with Case #3 having to undergo a second intervention due to recurring TRAS  
168 within 71 days.

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



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

176

#### 177 **4.0 DISCUSSION**

178 Deteriorating kidney function after transplantation provides a diagnostic and procedural  
179 challenge since iodinated contrast is nephrotoxic. In a select group of patients presenting with  
180 pending renal transplant failure due to TRAS, we demonstrate that CO<sub>2</sub>-DSA with PTA can be  
181 utilized to lower blood pressure, creatinine, BUN and increase GFR. CO<sub>2</sub>-DSA in TRAS can be  
182 safely utilized as an intraoperative imaging modality without further exacerbating deteriorating  
183 kidney function.

184 CIN is a common complication of iodinated contrast media exposure and patients with  
185 renal transplants are particularly at risk. The incidence of CIN in renal transplant patients is at  
186 least 15.3% and may be as high as 42.8% if intravenous hydration prophylaxis is not properly  
187 administered.<sup>23</sup> In a multivariate analysis that controlled for risk factors such as total hydration,  
188 iodine load, and prior contrast exposure, CIN had more than a 3-fold risk of 30-day mortality.<sup>24</sup>  
189 Gadolinium was once considered a viable alternative to iodinated contrast. However, gadolinium  
190 may inadvertently cause nephrogenic systemic fibrosis in patients with advanced kidney  
191 disease.<sup>25,26</sup> CO<sub>2</sub> angiography images were first used in 1956 by Oppenheimer et al. who found  
192 its beneficial properties through animal experiments to detect intracardiac structures.<sup>27</sup> In the  
193 1990s, Dr. Irvin Hawkins championed its use because of its nephron-sparing characteristics,  
194 relatively low cost, wide availability, use as an intraoperative guide, and rapid clearance from the  
195 body.<sup>28-30</sup>

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196 Our case-series shows that CO<sub>2</sub>-DSA may be a viable imaging modality to preserve  
197 kidney functioning that can be applied to patients not just with CIN or contrast allergy. Our  
198 results were consistent with the body of literature, supporting CO<sub>2</sub> angiography's renal sparing  
199 benefits, owing to its solubility and being easily cleared in the lungs.<sup>19,29-32</sup> In addition,  
200 compared to previous studies with failing native kidneys, we were able to produce adequate  
201 intraoperative images to guide PTA despite using half as much CO<sub>2</sub> and iodinated contrast.<sup>19,20</sup>  
202 This may prove to be useful as risk for developing CIN is dose dependent.<sup>33</sup> Finally, CO<sub>2</sub>  
203 angiography is a relatively cost effective study. Intravascular ultrasound (IVUS) has also  
204 emerged as an imaging modality to help further minimize contrast administration during the  
205 renal transplant artery intervention cases.<sup>34</sup> Although IVUS is a useful modality in diagnosing,  
206 locating, and evaluating a lesion, it may not be readily available worldwide because of its' cost  
207 and lack of resources for the equipment, personnel, and interpretive skills necessary to maximize  
208 its use.<sup>35</sup> Schiele et al. found that procedures involving IVUS were 18% more expensive  
209 compared to standard angiography due to the cost of its IVUS catheters and need for more  
210 balloons. When taking into account the costs of re-stenosis, the procedural costs of the IVUS  
211 were 8.7% higher.<sup>36</sup> Thus, angiography is a viable and cost-effective imaging modality in  
212 settings where the resources for IVUS use are not available.

213 Though CO<sub>2</sub> angiography is a relatively safe option, it is important to keep in mind its  
214 potential hazards. In a retrospective, single-institutional study of 1,007 CO<sub>2</sub> angiography  
215 procedures over a 21-year period, Moos et al. found that air trapping, also known as vapor lock,  
216 is the most common complication.<sup>32</sup> Because of CO<sub>2</sub>'s buoyancy, gas can accumulate and  
217 become trapped within the vascular space. Although CO<sub>2</sub> is highly soluble and is absorbed within  
218 2-5 minutes, vapor lock can occur during large injections or if the interval between CO<sub>2</sub>

219 injections is too short.<sup>37,38</sup> Room air contamination may also exacerbate the risk of vapor lock  
220 and it is encouraged to minimize the amount of steps required to transfer CO<sub>2</sub> from its tank to the  
221 patient.<sup>32</sup> Furthermore, nitrous oxide may contribute to the vapor lock phenomena and is  
222 relatively contraindicated with CO<sub>2</sub> angiography. Nitrous oxide may diffuse into the CO<sub>2</sub> bubble,  
223 thus increasing its volume and diluting CO<sub>2</sub>. Finally, it is imperative to use CO<sub>2</sub>-DSA with  
224 caution in patients with severe chronic obstructive pulmonary disease. This is especially true in  
225 patients who retain CO<sub>2</sub> and cannot expel CO<sub>2</sub> with increased ventilation.<sup>29</sup> Given these hazards,  
226 meticulous attention to detail when preparing CO<sub>2</sub>-DSA and reviewing each patient's ability to  
227 tolerate the procedure must be considered. Future prospective research is warranted to weight the  
228 benefits and hazards of CO<sub>2</sub>-DSA in renal transplant patients.

## 229 **5.0 CONCLUSION**

230 CO<sub>2</sub>-DSA and PTA can be used to improve deteriorating kidney function in stenotic kidney  
231 transplants. Our case-series demonstrated improved transplant kidney functioning through the  
232 utilization of CO<sub>2</sub>-DSA to minimize iodinated contrast exposure. Kidney allograft function was  
233 preserved after PTA, demonstrated by decreased blood pressure, BUN, creatinine and increased  
234 eGFR.

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389

1 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 2.5mg (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



2 *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

3

4 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
<b>BUN (mg/dL)</b>	37.6	32.9	27.4	30.1	28.3	32.5	-13.60%
<b>Cr (mg/dL)</b>	2.6	2.4	1.6	1.8	1.6	1.6	-37.40%
<b>eGFR (ml/min/1.73 m<sup>2</sup>)</b>	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*

	<b>Pre-Op (Average)</b>	<b>Post-Op (Average)</b>	<b>Change (Average)</b>	<b>% Change</b>
<b>Systolic BP (mmHg)</b>	169.4	128.3	41.1	-25.80%
<b>Diastolic BP (mmHg)</b>	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<sub>2</sub>-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.