Gadolinium-based Contrast and Carbon Dioxide Angiography to Evaluate Renal Transplants for Vascular Causes of Renal Insufficiency and Accelerated Hypertension[1]

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Abbreviations: DSA = digital subtraction angiography, PTA = percutaneous transluminal angioplasty, RAS = renal artery stenosis

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PURPOSE: To evaluate the utility and potential nephrotoxicity of gadolinium-based contrast angiography when used with carbon dioxide angiography in renal transplant patients with suspected vascular causes of renal insufficiency and/or accelerated hypertension.

MATERIALS AND METHODS: Thirteen consecutive renal transplant patients with suspected vascular causes of renal insufficiency and/or accelerated hypertension were evaluated with gadolinium-based contrast and CO_2 angiography with use of digital subtraction techniques. Stenotic lesions were treated with angioplasty with/or without stent placement. No iodinated contrast agents were used. Serum creatinine levels were obtained before and at 24 and 48 hours after the procedure. An increase in creatinine levels greater than 0.5 mg/dL (44 μmol/L) was considered significant.

RESULTS: Nine patients were studied for renal insufficiency, two for accelerated hypertension, and two for both. All 13 studies were considered diagnostic. Significant stenoses were treated in four patients with angioplasty with or without stent placement. Two patients had progression of their renal insufficiency. One of these patients underwent biopsy and was found to have both acute and chronic rejection. The other patient underwent cardiac catheterization 2 days after a transplant renal artery angioplasty. In the remaining nine patients with renal insufficiency (creatinine range, 1.8–3.9 mg/dL [159–345 μmol/L]; mean, 2.7 mg/dL [239 μmol/L]), renal function improved or did not worsen.

CONCLUSION: Based on this limited study, gadolinium-based contrast angiography appears to be a promising supplement to CO_2 angiography for the diagnosis and treatment of vascular lesions in patients with renal transplant insufficiency and/or accelerated hypertension. Further study is necessary to determine safety, optimal gadolinium dosage, and imaging parameters.

TRANSPLANT renal artery stenosis (RAS) is an infrequent yet important cause of hypertension after renal transplantation. Patients present with either progressively severe hypertension, fluid retention, or renal insufficiency, especially in the setting of concurrent angiotensin converting enzyme (ACE) inhibitor use (1–3). Iliac artery stenosis

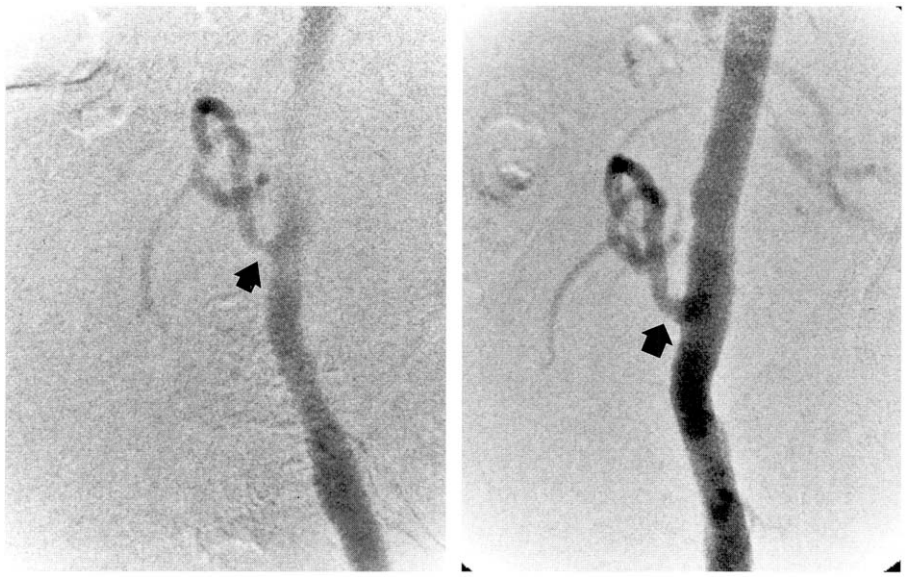
Renal Transplant Patients Evaluated with Gadolinium/CO_2 Angiography as Part of Work-up for Increase in Serum Creatinine and/or Hypertension

Pt No./ Sex/Age (y)	Indication	Procedure	Creat Levels (mg/dL)			Total Gd Dose (mL)	Miscellaneous
			Day of Procedure	PPD1	PPD2		
1/M/38	↑ creat	Diagnostic arteriogram	2.3	2.4	2.5	16	US negative
2/F/49	↑ HTN	Diagnostic arteriogram	1.1	0.9	N/O	18	US negative
3/M/41	↑ creat	Diagnostic arteriogram	2.7	2.4	N/O	20	US N/O
4/M/49	↑ HTN	Diagnostic arteriogram	1.3	1.5	N/O	20	US suggestive of Tx RAS f/u creat 5 days after procedure = 1.6 mg/dL
5/M/47	↑ creat	Iliac PTA ipsilateral/ proximal to Tx	3.9	3.7	N/O	40	US N/O f/u creat 10 days after procedure = 3.3 mg/dL
6/M/65	↑ creat	Diagnostic arteriogram	3.0	2.9	3.3	20	US N/O
7/M/53	↑ creat	Iliac PTA/stent, ipsilateral/proximal to Tx	2.5	2.1	N/O	40	US negative; f/u creat 5 days after procedure = 1.7 mg/dL
8/M/64	↑ creat	PTA, Tx renal artery	3.1	3.5	3.6	60	US N/O; Pt underwent cardiac cath with iodinated contrast on PPD2. Started on dialysis 3 days after cath with creat = 6.6 mg/dL and symptoms of acute renal failure
9/M/47	↑ creat/ ↑ HTN	Diagnostic arteriogram	1.8	N/O	1.8	20	US negative
10/F/53	↑ creat ↑ HTN	Diagnostic arteriogram	2.8	1.4	1.2	20	US N/O; improvement in creat secondary to hydration
11/M/48	↑ creat	Diagnostic arteriogram	2.8	1.9	N/O	20	US N/O
12/F44	↑ creat	Diagnostic arteriogram	5.1	5.4	6.1	20	US negative; Serum creat 2 days before procedure = 4.1 mg/dL; Tx renal bx on PPD1 showed acute and chronic rejection
13/M/36	↑ creat	PTA/stent Tx, renal artery	2.2	2.6	2.4	36	US N/O f/u creat PPD 4 = 2.2 mg/dL

Note.—Pt = patient; f/u = follow-up; PPD = postprocedure day; Gd = gadolinium-based contrast; ↑ = increase in; creat = creatinine; HTN = hypertension; N/O = not obtained (decision by transplant team); Tx = renal transplant; RAS = renal artery stenosis, bx = biopsy.

ipsilateral and proximal to the renal transplant is a less recognized but important cause of hypertension and claudication in renal transplant recipients. This is especially true in the older patient population receiving a renal transplant (4–7). Arterial stenosis of transplant renal artery has been reported to occur in between 5% and 25% of patients who have a renal transplant (3). If renal angiography is performed routinely in renal transplant patients with hypertension and/or increase in serum creatinine, approximately 5% will have a significant stenosis of the transplant renal artery. However, in patients without evidence of rejection and with acute onset of hypertension and/or sudden rise in creatinine, RAS can occur in as many as 25% of patients (8). Therefore, early, accurate and safe identification of RAS and/or iliac artery inflow disease is important to minimize ischemic injury to the allograft. Once diagnosed, renal percutaneous transluminal angioplasty (PTA) has been shown to be a useful therapeutic modality in this setting (9,10).

Noninvasive testing with ultrasound (US), magnetic resonance (MR) angiography, and radionuclide imaging have been advocated as screening modalities to detect RAS or iliac artery stenoses in this patient population. However, limitations with each of these techniques have been described (11–13). Therefore, contrast angiography remains the "gold standard" for the diagnosis of transplant renal artery stenosis and vascular inflow disease but is limited by concerns with contrast-induced nephropathy. Recently, carbon dioxide angiography has been described in patients with renal insufficiency and/or a history of a severe reaction to iodinated contrast material. However, these images obtained with CO_2 angiography are not always satisfactory. Bowel gas artifacts or difficulty with opacifying the transplant renal artery or the main segmental branches can result in poor vascular definition and/or overestimation of the degree of stenosis. In addition, CO_2 trapped within mesenteric arterial branches can lead to abdominal pain and the need to terminate the study prior to its completion. In these patients, a non-nephrotoxic angiographic contrast agent may be helpful in detecting a vascular cause for renal insufficiency and/or accelerated hypertension. Intraarterial gadolinium-based contrast agents have been used safely in patients with



a. b.

Figure 1. **(a)** Transplant renal arteriogram obtained with CO_2 suggests a moderate stenosis in the proximal transplant renal artery (arrow). **(b)** Gadolinium-based contrast angiogram in the same patient reveals a widely patent transplant renal artery (arrow). In this patient, the CO_2 angiogram overestimated the degree of stenosis.

renal insufficiency for angiographic diagnostic and interventional studies in selected patients (14–16).

We describe our preliminary experience in 13 consecutive renal transplant patients with accelerated hypertension and/or worsening renal insufficiency using CO_2 and gadolinium-based contrast angiography.

MATERIALS AND METHODS

We prospectively studied 13 consecutive renal transplant patients with either a cadaveric or living-related renal transplant and history of accelerated hypertension and/or worsening renal function between February 1997 and November 1997. No renal transplant recipients presenting for angiographic evaluation were excluded during this time period. Renal transplant patients were referred for angiography following evaluation by the renal transplant team, which included a nephrologist and transplant surgeon. Eight patients were evaluated with duplex sonography prior to undergoing angiography. For all renal transplants studied, the arterial anastomosis was constructed with use of an end-to-side technique (donor renal artery to the side of the recipient iliac artery). In all 13 patients, only a single donor renal artery was present. Hydration protocols before and after angiography were not standardized and varied from patient to patient. The number and type of medications the patients were taking were variable and adjusted by the transplant nephrologist.

Arterial access was obtained by using the common femoral artery in all patients. The initial angiogram was obtained with use of CO_2 gas delivered via a 4-F straight flush catheter (Angiodynamics, Glenfalls, NY) in patients with ipsilateral access and via a 5-F Sos Omni catheter with extra side holes (Angiodynamics) in patients with contralateral access. The single patient who had bilateral femoral artery punctures underwent diagnostic angiography by means of a contralateral approach with use of the Sos Omni catheter and balloon angioplasty from an ipsilateral approach.

The CO_2 gas (30–50 cm^3) was delivered using a plastic bag system and manual injections as previously described by Hawkins et al (17). Radiographic images were obtained with use of angiography units (Siemens Medical Systems, Iselin, NJ) with a 40-cm image intensifier and a high-resolution digital imaging system. Anteroposterior CO_2 angiograms were obtained to evaluate the lower abdominal aorta and aortoiliac bifurcation. Additional CO_2 angiograms were obtained with the side of the pelvis ipsilateral to the renal transplant elevated on a 45° wedge cushion. The image intensifier was also angled in multiple obliquities to optimize the profile of the ipsilateral iliac artery, renal transplant artery, and the arterial anastomosis. CO_2 images were obtained with digital subtraction angiography (DSA) at 85 kV with a frame rate of 4 frames per second for 3 seconds followed by 2 frames per second.

Once the optimal obliquity to evaluate the ipsilateral iliac artery and renal transplant artery was identified, a gadolinium-based contrast arteriogram was obtained with delivery of 8–10 mL/sec of gadopentetate dimeglumine (0.5 mmol/mL) (Magnavist, Berlex Laboratories, Wayne, NJ) or gadodiamide (0.5 mmol/mL) (Omniscan; Nycomed, Princeton, NJ) power injected intraarterially for 2 seconds (total dose, 16–20 mL). Radiographic images were obtained with use of high-resolution DSA. Gadolinium-based contrast angiograms were obtained at 96 kV at a film rate of 3 frames per second for 3 seconds followed by 2 frames per second. Images were interpreted by one of four interventional radiologists (D.J.S., A.H.M., J.F.A., K.D.H.). Images were evaluated subjectively during the procedure to determine the extent of RAS and adequacy of treatment when intervention was performed.

Iliac and renal artery angioplasty and stent placement were performed as previously described (10,18). Selective angiography of the

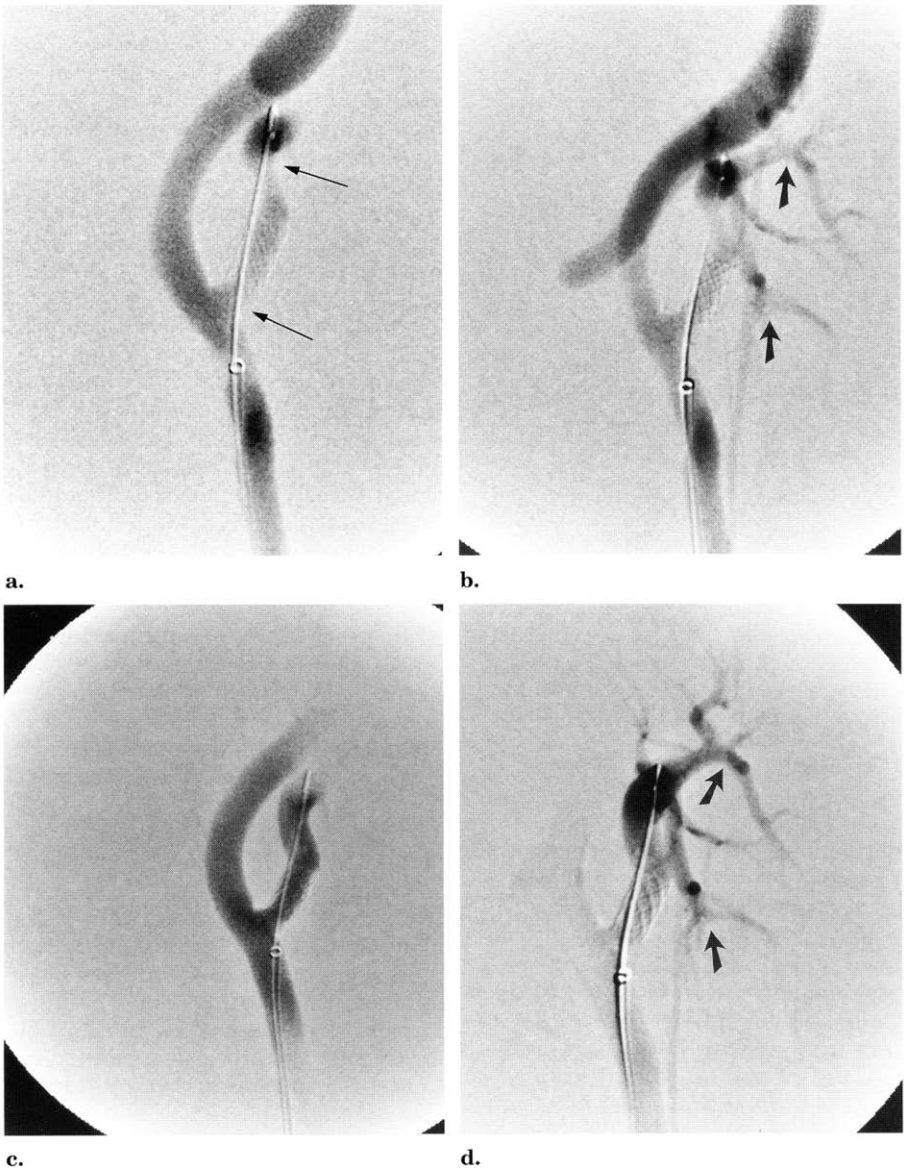


Figure 2. **(a)** CO_2 angiogram after angioplasty and stent placement across a stenosis in the main transplant renal artery demonstrates a patent renal stent and transplant renal artery. However, it is difficult to determine on this study if residual narrowing is present (arrows). **(b)** Intrarenal branches are also difficult to evaluate with CO_2 angiography (arrows). **(c)** A gadolinium-based contrast angiogram demonstrates a widely patent main transplant renal artery and stent. **(d)** The intrarenal branches are also more clearly identified with the gadolinium-based contrast angiogram (arrows).

transplant artery before and after the intervention were performed with 10–20 cm^3 of CO_2 and 4–6 mL of gadolinium-based contrast agent delivered via manual injection.

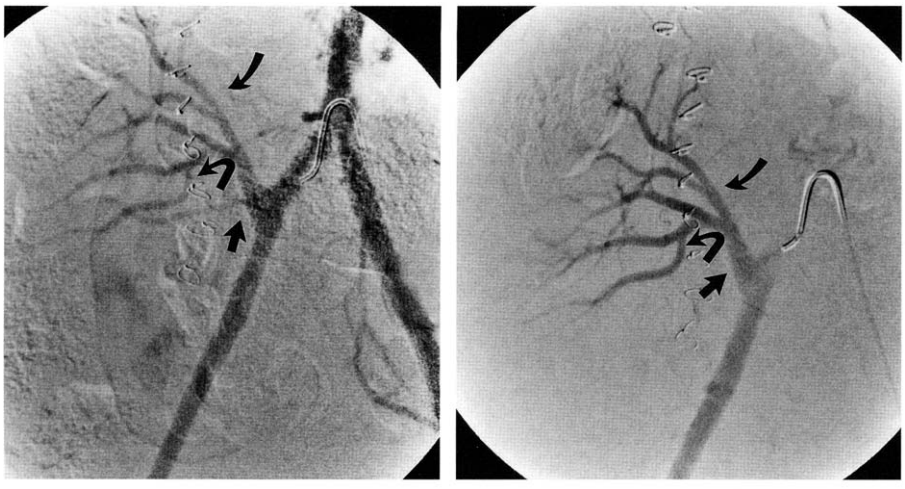
Serum creatinine levels were obtained on the day of the procedure, approximately 24 hours after the procedure, and approximately 48 hours after the procedure, unless the transplant team decided that acquisition of a serum creatinine level at either of these follow-up times was not indicated. Additional follow-up serum creatinine levels were obtained at the discretion of the transplant team. A change in the serum creatinine level of greater than 0.5 mg/dL (44 μmol/L) was considered clinically significant (19).

RESULTS

The **Table** summarizes the results in the 13 patients studied. Ten men and three women, with a mean age in both groups of 49 years, were included in the study. Nine patients were studied because of renal insufficiency, two for accelerated hypertension, and two for both accelerated hypertension and renal insufficiency. Nine patients underwent diagnostic angiography without percutaneous intervention. Four patients underwent percutaneous intervention. Two patients were treated with PTA of the transplant renal artery and one of these patients received a stent in the transplant renal artery. The other two patients were treated for iliac inflow disease ipsilateral and proximal to the renal transplant. One of these patients was treated with PTA alone, and the other patient underwent PTA and stent placement.

In the four patients treated with PTA with or without stent placement, renal function improved in two patients, was unchanged in one patient, and worsened in one patient. The patient with worsening renal function (patient 8, **Table**) had a mild increase in serum creatinine level 48 hours after transplant renal artery PTA. However, because of a 2-week history of congestive heart failure and angina, the patient underwent cardiac catheterization with iodinated contrast material 2 days after PTA. Three days after cardiac catheterization, the patient's serum creatinine increased to 6.6 mg/dL (583 μmol/L). The patient started dialysis for symptoms of acute renal failure.

In the nine patients undergoing diagnostic angiography, the serum creatinine level remained stable or improved in eight patients. In one



a. b.

Figure 3. **(a)** CO_2 angiogram demonstrates a widely patent transplant renal artery (straight arrow). The intrarenal branches appear patent (curved arrows). **(b)** A gadolinium-based angiogram demonstrates the main renal artery to be widely patent (straight arrow) and there is better definition of the intrarenal branches (curved arrows).

patient, the serum creatinine level increased from 4.1 to 5.1 mg/dL (362–451 μmol/L) in the 48 hours prior to the procedure and subsequently increased from 5.1 to 6.1 mg/dL (451–539 μmol/L) 48 hours after the angiogram. A percutaneous renal biopsy demonstrated acute and chronic rejection.

In all patients, the angiographic images were of sufficient diagnostic quality (**Fig 1**). Subsequent intervention with PTA with or without stent placement was successfully performed in the four patients in whom the intervention was undertaken (**Fig 2**). No iodinated contrast material was used in any of the 13 patients in this study.

The gadolinium-based angiographic images appeared superior to the CO_2 angiograms in evaluating the intrarenal branches of the transplant kidney and ipsilateral iliac arteries, particularly when overlying bowel gas was present (**Figs 2b, 2d, 3**). The gadolinium-based angiograms appeared comparable to or superior to the CO_2 angiograms in the evaluation of the transplant renal artery anastomosis, the main transplant renal artery segment, and the ipsilateral iliac artery (**Fig 4**).

DISCUSSION

The etiologies for renal transplant dysfunction can be divided into two broad categories based on the therapeutic intervention: medical and surgical. Medical causes include rejection, infection, and drug toxicity. Surgical etiologies include vascular abnormalities such as arterial inflow problems, venous outflow disease, or arteriovenous fistulas, urinary tract outflow obstruction, urine leaks, and peritransplant fluid collections. Transplant RAS or proximal artery iliac disease is an important cause of renal dysfunction as it can cause hypoperfusion of the transplant kidney, and lead to accelerated hypertension and/or renal insufficiency.

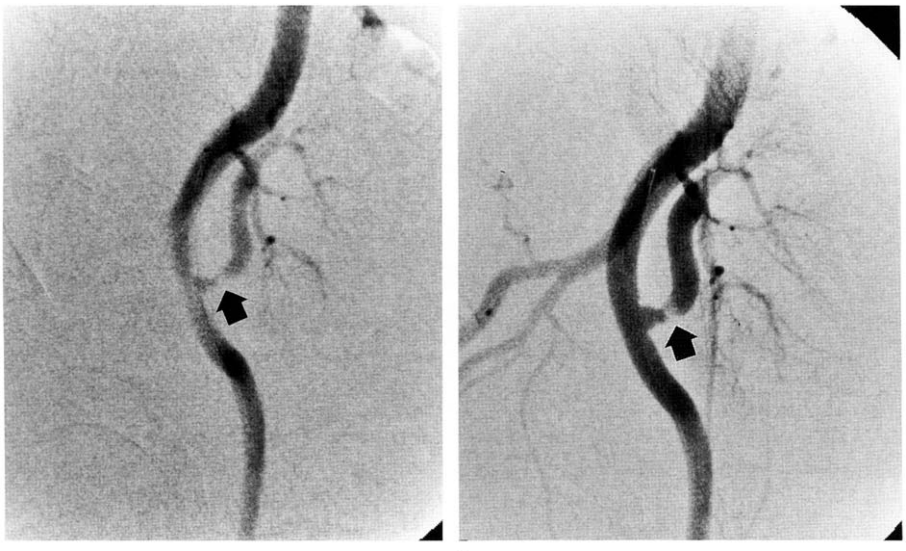
Several noninvasive methods such as noninvasive vascular laboratory testing, duplex US, radionuclide imaging, and MR imaging have been utilized to screen for the presence of transplant RAS or iliac inflow disease ipsilateral to the transplant kidney, but each has its shortcomings.

Angiography remains the "gold standard" for the diagnosis of transplant RAS and aortoiliac arterial disease. To limit the amount of iodinated contrast material administered to the renal transplant patient, intraarterial DSA techniques have been advocated (20). Nevertheless, particularly in the setting of renal insufficiency, there remains concern that iodinated contrast agents are potentially nephrotoxic. Although we are aware of no specific study that evaluates the risk of contrast-induced nephropathy in renal transplant patients with renal insufficiency, a number of investigators have demonstrated a relationship between contrast-induced nephropathy and pre-existing renal insufficiency in native kidneys (21,22).

Identification of transplant RAS and/or aortoiliac disease is important because percutaneous treatment of these lesions with balloon angioplasty with or without stent placement may potentially result in better control of hypertension, improvement in renal function, and preservation of renal function (1,2,9,10).

CO_2 angiography has become an appealing alternative to iodinated contrast angiography due to recent improvements in CO_2 imaging and delivery (23,24). CO_2 produces negative contrast in relation to the surrounding tissues due to its low atomic number. DSA and computer software that allows "stacking" of optimal CO_2 images produces a contrast "column" similar to that of iodinated contrast material.

However, there are some drawbacks to CO_2 angiography. Because CO_2 is a gas, it does not mix with blood but floats above it. Enough CO_2 must be administered to fill the entire vessel to avoid underestimating the diameter of the vessel and completely delineate the posterior wall of the vessel. Incomplete filling of vessels with CO_2 probably accounts for several investigators reporting on the overestimation of the degree of stenosis with use of CO_2 angiography (25,26). CO_2 images can also be degraded by patient motion as well as superimposed bowel gas. The anterior position of the transplant renal artery and kidney could potentially result



a. b.

Figure 4. **(a)** Transplant renal arteriogram obtained with CO_2 suggests a high-grade stenosis in the proximal segment of the transplant renal artery (arrow). **(b)** A gadolinium-based contrast angiogram confirms the presence of a high-grade stenosis in the proximal transplant renal artery (arrow).

in excess accumulation of CO_2 gas causing a vaporlock in the arteries of the transplant kidney. Although this is a theoretical concern, it is uncertain how much CO_2 can safely be accumulated within a renal transplant without compromising renal function.

Gadolinium has an atomic number of 64 and a K edge of 50. Although gadolinium has been shown to absorb sufficient energy to be visualized with DSA, the image quality with gadolinium is consistently inferior when compared to iodinated contrast agents. Yet, images of diagnostic quality can be obtained (27,28). In the 13 patients in this series, the total dose of gadolinium was limited to less than or equal to 0.3 mmol/kg body weight. Gadolinium doses at this amount have not been associated with nephrotoxicity in patients with renal insufficiency (29–32).

However, this dosage is based on intravenous studies in small groups of patients with renal insufficiency (glomerular filtration rate between 20 and 60 mL/min) or renal failure (29,33,34). In one study, 11 patients with varying degrees of renal insufficiency received a 0.1 mmol/kg dose of gadolinium-based contrast agent intravenously and showed no significant increase in serum creatinine level up to 5 days following gadolinium administration (34). In another study, 31 patients with a serum creatinine level greater than 1.5 mg/dL (133 μmol/L) showed no significant rise in serum creatinine (an increase of greater than 0.5 mg/dL [44 μmol/L]) following the administration of a dose of gadolinium-based contrast agent in the range of 0.2–0.4 mmol/kg (29).

Reports describing intraarterial use of gadolinium-based contrast agents are limited. Fobbe et al describes the use of a fixed dosage (40 mL) of gadolinium-based contrast agent administered intraarterially and imaged with DSA in 15 patients (none with renal insufficiency) (27). Schild et al described the use of up to 40 mL of gadolinium-based contrast agent injected intraarterially and imaged with DSA without complications; however, no patients with renal insufficiency were included (35). Several individual reports have been published describing patients with renal insufficiency who were treated safely with use of intraarterial gadolinium-based contrast agents as the angiographic contrast agent for diagnosis with or without interventional treatment (14–16,28).

During this preliminary experience with gadolinium-based contrast DSA imaging, these images appeared helpful in confirming the focal areas of stenosis in the ipsilateral iliac artery and transplant renal artery that were either identified or suggested with CO_2 angiography. In addition, gadolinium-based angiography appeared to provide better visualization of the intrarenal branches compared to CO_2 angiography. Gadolinium-based angiography also appeared helpful in more accurately defining the result of the percutaneous intervention when compared to CO_2 angiography. However, CO_2 angiography was helpful in identifying the transplant renal artery and determining the optimum position in which to image its origin. This allowed us to minimize the amount of the gadolinium necessary to define the anatomy and perform the intervention.

In our study, two of the 13 patients developed worsening renal function following CO_2 and gadolinium-based angiography. In one patient, results of a transplant renal biopsy 1 day after the procedure demonstrated acute and chronic rejection. In the second patient, iodinated contrast material administered for a cardiac catheterization on postprocedure day 2 most likely contributed to subsequent acute renal failure requiring dialysis.

In the remaining 11 patients, nine of which had serum creatinine levels between 1.8 and 3.9 mg/dL (159–345 μmol/L) (mean, 2.7 mg/dL [239 μmol/L]), no significant deterioration in renal function occurred.

Despite the high cost of gadolinium (approximately $3–$5 per milliliter compared with nonionic iodinated contrast material, $1 per milliliter), gadolinium-based contrast agents appear to be helpful in better defining and confirming the presence of stenoses seen with CO_2 angiography, while allowing for excellent delineation of the results of

interventional procedures. These agents also provide diagnostic images of the arterial inflow, transplant renal artery, and intrarenal branches, even in the presence of overlying bowel gas. Gadolinium-based contrast in conjunction with CO_2 angiography were helpful in accurately diagnosing and guiding treatment of transplant RAS without the use of iodinated contrast material. Further studies are needed to determine if this combination of potentially less nephrotoxic contrast agents may lead to reducing the risk of contrast nephropathy associated with iodinated contrast angiography, thereby allowing a more aggressive approach utilizing diagnostic angiography and endovascular techniques to detect and treat underlying vascular lesions in patients with renal artery allografts.

In conclusion, gadolinium-based angiography supplemented with CO_2 angiography may be a useful alternative to traditional iodinated contrast angiography in the diagnosis and treatment of vascular causes of renal transplant insufficiency and accelerated hypertension. Further evaluation is necessary to determine if gadolinium-based angiography, in conjunction with CO_2 angiography, provides a safe and cost-effective alternative to iodinated contrast angiography in renal transplant patients.

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