CO_2 ANGIOGRAPHY—A TECHNIQUE FOR VASCULAR IMAGING IN RENAL ALLOGRAFT DYSFUNCTION

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Use of iodinated contrast for vascular imaging can be associated with nephrotoxicity and hypersensitivity reactions. Renal injury following conventional angiography is more likely to manifest in the setting of preesisting renal dysfunction. In the setting of suboptimal renal allograft function, these considerations are particularly relevant. Recently, CO_2 has received attention as a nontoxic, injectable, rapidly absorbed gas that is a cost-effective alternative to standard contrast agents in high-risk patients, such as renal transplant recipients. We report the clinical course of a patient with transplant renal artery stenosis and a serum creatinine of 2.8 mg/dl who has successfully undergone angiography and percutaneous transluminal angioplasty using CO_2 as the sole contrast agent. This case illustrates the potential use for CO_2 as a contrast agent for vascular imaging in patients with suboptimal renal function who require definitive vascular imaging or therapy.

Transplant renal artery stenosis is a well-recognized cause of hypertension following renal transplantation (*1*). Characterized by the presence of intractable or new-onset hypertension, graft dysfunction, or bruit over the graft, transplant renal artery stenosis is a potentially reversible cause of hypertension and, ultimately, graft loss (*2*). A variety of noninvasive screening modalities are available and include spiral computed tomography (CT), Doppler ultrasonography, magnetic resonance imaging (MRI), and determination of plasma renin levels following angiotensin-converting enzyme inhibition (*3*). A paucity of data is available regarding the diagnostic accuracy of spiral CT or MRI. Ultrasound is highly sensitive but is associated with a specificity of only 75% (*3*). The captopril test carries a sensitivity of 75% and a specificity of 67% (*4*). As a result, conventional angiography remains the gold standard for diagnosis and, in association with percutaneous transluminal angioplasty (PTA), is the preferred mode of therapy for transplant renal artery stenosis in a number of institutions (*5*). However, in the setting of renal dysfunction, the use of iodinated contrast agents may be associated with a significant risk of renal allograft injury. A number of investigators have documented the relationship between contrast-induced nephrotoxicity and degree of preexisting renal dysfunction (*6*, *7*). In patients with a baseline serum creatinine greater than 2 mg/dl, Hall and coworkers reported a 62% prevalence of acute renal injury following arteriography (*7*). Although these studies were conducted in nontransplant populations, the results warrant consideration when evaluating a renal transplant recipient in potential need of angiography and/or PTA.

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Recently, carbon dioxide (CO_2) has received increased attention as a possible alternative to iodinated contrast agents in those instances where sensitivity to contrast agents or renal insufficiency is a potential contraindication to conventional angiography (*8*). In the renal transplant population with suboptimal graft function, CO_2 may become the preferred contrast agent for angiographic studies. As CO_2 angiography becomes more prevalent, it offers clinicians an effective alternative for diagnosis of transplant renal artery stenosis and other conditions that require angiography-based diagnosis or therapy. In this regard, we present a patient with transplant renal artery stenosis diagnosed and treated using CO_2 as the sole angiographic contrast agent.

The patient was a 44-year-old woman with a 3-year history of end-stage renal disease secondary to systemic lupus erythematosus. She was maintained on peritoneal dialysis until April 1994, when she underwent cadaveric renal transplantation at Stanford University Hospital. Total preservation time was 25.5 hr with a warm ischemia time of 35 min. The arterial anastomosis was performed in an end-to-side fashion to the external iliac artery with a Carrel patch of donor aorta. Her immediate postoperative course was complicated by delayed graft function requiring intermittent hemodialysis. Sequential immunosuppressive therapy was instituted with OKT3, corticosteroids, and azathioprine, followed by substitution for OKT3 of cyclosporine. At the time of hospital discharge on posttransplant day 14, her creatinine was 6.2 mg/dl. Her blood pressure was 138/92, with an antihypertensive regimen of clonidine 0.4 mg b.i.d., metoprolol 50 mg b.i.d., and furosemide 120 mg q.d. The creatinine continued to improve and reached a nadir of 2.0 mg/dl on posttransplant day 22. Her clinical course was then complicated by a bout of corticosteroid-resistant acute rejection necessitating OKT3 therapy. A Doppler ultrasound examination of the graft did not demonstrate vascular abnormalities, extra renal fluid collections, or hydronephrosis. Thereafter, her serum creatinine remained within the range of 1.3 to 1.9 mg/dl until posttransplant month 4. The antihypertensive regimen remained unchanged, with a blood pressure of 150/90. Beginning on posttransplant month 4, the patient's creatinine began to slowly rise and was accompanied by increasingly refractory hypertension. By posttransplant month 6, her creatinine was 2.2 mg/dl, and her blood pressure was 170/110 while on clonidine 0.4 mg b.i.d., furosemide 80 mg q.d., and sustained release nifedipine 30 mg b.i.d. At posttransplant month 9, the patient's creatinine was 2.2 mg/dl, with a blood pressure of 168/110, while on furosemide 40 mg q.d., clonidine 0.2 mg t.i.d., and sustained release nifedipine 30 mg b.i.d.

The patient was otherwise well until she was reviewed at 1 year posttransplant in the transplant clinic with a serum creatinine of 2.8 mg/dl and a blood pressure of 190/100 on clonidine 0.6 mg q. A.M. and 1.0 mg q P.M., furosemide 40 mg q.d., and metoprolol 100 mg q.d. Her physical examination

was notable for the presence of a bruit over her allograft. A color Doppler ultrasound examination of the renal allograft demonstrated the presence of adequate blood flow to the periphery of the kidney. However, a dampened wave form was present within the distal aspect of the main renal artery, and a focal stenosis was present near the transplant renal artery anastomosis. No other abnormalities were present. The patient then underwent selective CO_2 angiography of her left common, external, and internal iliac arteries (Fig. 1). A 95% band-like stenosis was found at the origin of the transplant renal artery. The peak systolic pressure in the distal aorta was 150 mmHg, while that in the transplant renal artery was 100 mmHg corresponding to a gradient of 50 mmHg. Angioplasty of stenotic region was then performed using a 5 mm balloon catheter. Thereafter, there was minimal residual stenosis and no pressure gradient across the anastomosis. The entire procedure was performed without iodinated contrast agent. A repeat Doppler ultrasound exam performed 10 days following PTA demonstrated improved velocities within the transplant renal artery and minimal blunting of the waveform upstroke in the intrarenal arteries. One month following PTA, the patient's creatinine was 2.1 mg/dl; her blood pressure was 160/94 on clonidine and metoprolol alone.

Clinically, Hawkins described the use of CO_2 as an arterial contrast agent in 1982 (*9*). High quality arteriographic images of the abdominal aorta, visceral arteries, renal arteries, and lower extremity vessels became possible only with the advent of digital subtraction technology. Subsequently, CO_2 images have been deemed to be of equal quality when compared with those of iodinated contrast agents. When images were compared between standard techniques and CO_2 angiography for delineation of peripheral vascular disease, 91% of CO_2 studies were deemed to be of excellent or good quality, with agreement between CO_2 and standard studies in 95% of cases (*10*). Furthermore, accurate therapeutic plans based upon results of CO_2 studies were possible in 92% of cases (*10*). However, the principle underlying CO_2 angiographic imaging is quite different. Total displacement of blood volume from the lumen of the vessel is necessary to achieve adequate visualization.

The safety of CO_2 as a contrast agent is well established. A major concern had been that of gas embolization. Studies in animals have demonstrated that 3 ml of CO_2 per pound can be injected into a peripheral vein or pulmonary artery without untoward effects (*11*). As a result of its 20-fold greater solubility in blood in comparison with oxygen and its ability to combine with blood buffers, CO_2 is safely transported to the lungs, where it is eliminated by exhalation (*10*). At the University of Florida, CO_2 angiography has been performed in over 700 patients without an episode of gas embolism (*10*). Additional concern has centered on the potential nephrotoxicity of CO_2. Large volumes of CO_2 have been injected into the renal arteries of dogs without evidence of decreased renal blood flow or function as determined by ^{99m}Tc dimurcaptosuccinic acid and ^{131}iodine sodium iodohippurate scans (*10*, *12*). No histologic changes were noted in the endothelium of major renal arteries or in the glomeruli. Again, in the University of Florida experience, there have been no episodes of renal failure or dysfunction associated with CO_2 angiography (*10*, *12*). In comparison, acute renal dysfunction has been reported in 11.3% of patients undergoing conventional arteriography (*6*). In the setting of preexisting renal insufficiency, 41.7% of patients developed contrast-induced renal dysfunction (*6*). Hall and coworkers also found that preexisting renal dysfunction was associated with an increased incidence of contrast-induced nephrotoxicity. Patients with a serum creatinine greater than 2.0 mg/dl had a 62% prevalence of acute renal dysfunction following angiography with ionic contrast (*7*). Although nonionic contrast agents purportedly are less nephrotoxic, this was not confirmed in a recently published randomized, controlled clinical trial (*13*).

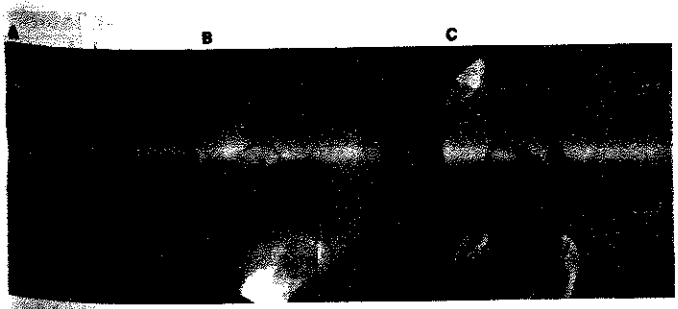

FIGURE 1. CO_2 angiogram of left external iliac artery and transplant renal artery. (A) Initial image demonstrating 95% stenosis at the renal artery–iliac artery anastomosis; (B) 5 mm balloon catheter placed across the stenosis in preparation for angioplasty; (C) post-angioplasty image demonstrating improvement in the stenosis. PTA decreased the transanastomotic pressure gradient from 50 mmHg to 0 mmHg.

While CO_2 has a number of potential advantages over iodinated contrast agents, caveats exist with its use. One is the risk of neurotoxicity. In a study from the University of Florida, neurologic deficits were found in rats after direct injection of CO_2 into the carotid artery (*14*). Histopathologic examination demonstrated multifocal ischemic infarctions with disruption of the blood-brain barrier. The amount of infarcted tissue paralleled the volume of CO_2 injected. Conversely, CO_2 thoracic aortography has been performed in the dog model without detectable alteration in neurologic testing, electroencephalography, or gross pathologic examination (*8*, *11*). In general, CO_2 is not recommended for routine use above the diaphragm. Additional caveats include patients with severe respiratory compromise who may be unable to eliminate the increased CO_2 load, and rapid injection of excessive volumes of CO_2 resulting in "vapor lock" within end organs (*8*). These considerations notwithstanding, CO_2 is considered to be a very safe, nontoxic contrast agent.

In short, CO_2 has a number of properties that make it an attractive alternative to standard iodinated contrast agents. It is nonallergenic and eliminates hypersensitivity reactions that occur in 0.1% of contrast studies (*10*). It is neither nephrotoxic nor hyperosmolar. Preangiographic hydration is no longer a necessity. CO_2 can be used on consecutive days without invoking the additional risk of renal injury. It is cost-effective. A single tank of CO_2, which can be used for 50 studies, costs approximately 225 dollars, while nonionic contrast costs one dollar/ml. Typically, 50–150 ml of nonionic contrast is used per study. The low viscosity of CO_2 allows use of catheters, as small as 3 Fr, with an associated decrease in vascular injury at puncture sites. Therefore, CO_2 is a nontoxic, injectable, rapidly absorbed gas that is a cost-effective alternative to standard contrast agents in high-risk patients such as renal transplant recipients.

In this report, we document the use of CO_2 angiography in the definitive diagnosis and treatment of transplant renal artery stenosis in a patient with a serum creatinine of 2.8 mg/dl. Of note, no iodinated contrast was used for the arteriogram, measurement of the pressure gradients, or the PTA. Although there are limitations to the generalized use of CO_2 as a contrast agent, there are definite advantages in the setting of suboptimal renal allograft function. As experience with this modality increases, transplant surgeons and physicians will have an alternative technique for use in renal transplant recipients who require angiography for diagnosis or therapy of conditions such as transplant renal artery stenosis.

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INCREASED CONTENT OF FIBRONECTIN AND LAMININ IN GLOMERULI ISOLATED FROM CHRONICALLY REJECTED HUMAN RENAL ALLOGRAFTS[1]

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Chronic rejection is frequently associated with the development of glomerular lesions consisting of mesangial cell proliferation, increase in mesangial extracellular matrix (ECM)* along with thickening of glomerular basement membrane (GBM). The GBM and mesangial matrix are composed of a mixture of collagens, glycoproteins, proteoglycans, and glycosaminoglycans that not only create a structural support for glomerular cells but also influence their activity (*1*).

Fibronectin (FN), a 200-kD glycoprotein, is found in plasma as well as in the GBM and mesangial ECM. The FN is a chemotactic factor for monocytes, macrophages, and fibroblasts, and provides a mitogenic signal for fibroblasts and mesangial cells (*2*). The FN seems to play a role in the initiation of in situ immune complexes in some forms of glomerulonephritides (*3*). Laminin (LN) is the major adhesive glycoprotein of GBM and appears as a key molecule in mediating cell interactions with basement membranes (*1*); LN may also possess growth-promoting activity (*4*). Interactions between cells and ECM proteins are mediated through receptors belonging to $\beta 1$ and $\beta 3$ integrin family that are present on glomerular as well as circulating cells (*5*). These cell-matrix interactions may affect migration of lymphocytes as well as provide a costimulatory signal to T cells (*6*).

We measured the content of FN and LN in glomeruli isolated from renal allografts with chronic rejection. Samples of renal tissue were obtained during graftectomy from 13 patients (6 male, 7 female patients) of 33.9±1.6 years (mean ±SEM; range, 36–76 years). All recipients had terminal failure of kidney allograft due to chronic rejection after 32±19 months (mean ±SEM; range, 14–155 months) posttransplant. In all specimens from removed grafts, severe obstructive vascular changes, typical for chronic rejection, were observed as well as mesangial matrix expansion with thickening of basement membrane representing transplant

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* Abbreviations: BCA, bicinochroninic acid; ECM, extracellular matrix; FN, fibronectin; GBM, glomerular basement membrane; LN, laminin.