CO_2 Digital Subtraction Angiography for Renal Artery Angioplasty in High-Risk Patients

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OBJECTIVE. The efficacy of CO_2 digital subtraction angiography for performing renal artery angioplasty in high-risk patients was evaluated.

SUBJECTS AND METHODS. From January 1997 to July 1998, 21 high-risk patients underwent 29 renal artery angioplasties using carbon dioxide as the principal contrast agent. Six patients had a known allergy to iodinated contrast material and 15 had elevated levels of creatinine. Iodinated contrast material was used only if necessary. All periprocedural allergic reactions were recorded. Before and 24 hr after the procedure, serum creatinine levels were obtained. If the creatinine level had become significantly elevated (>0.5 mg/dl), the creatinine level was acquired a second time.

RESULTS. Twenty-one patients (13 men and eight women) underwent 29 angioplasties (two were bilateral and six were repeated). Four kidney transplantation patients had ostial stenosis and the remaining 17 patients had nonostial stenosis. For all patients except one angioplasty initially was a technical success, as defined by a residual stenosis of less than 30%. Supplemental iodinated contrast material was used in only six patients (average dose, 8.5 ml). A range of 80–200 ml of carbon dioxide per procedure was used (average dose, 114.6 ml). One renal artery dissection occurred, which was unrelated to the carbon dioxide. There were no allergic reactions. The level of serum creatinine remained the same after 11 procedures, decreased after 12 procedures, and increased minimally after four procedures (<0.5 mg/dl).

CONCLUSION. On the basis of our preliminary findings in a small group of patients, using carbon dioxide as an intravascular contrast agent to perform renal artery angioplasty in patients who have an allergy to iodinated contrast material or who suffer from renal insufficiency is safe and efficacious.

Since the first description of renal artery angioplasty by Gruntzig et al. [1] in 1978, this procedure has been used successfully in the treatment of both renal failure and renovascular hypertension [1–5]. Although various advancements have been made in the arsenal of interventional devices, the basic procedure has changed very little. Depending on the operator's preference for arterial access, any number of different wires, catheters, and balloons can be advanced into the renal artery to achieve successful angioplasty. Experience has shown that despite these diverse approaches, using renal artery angioplasty to treat nonostial lesions or those caused by fibromuscular dysplasia is more likely to yield a favorable result [2, 3]. For other stenoses, especially ostial, simple angioplasty may not be adequate and stenting might be required to achieve the desired effect [6, 7].

Irrespective of the slight differences in renal angioplasty methods, each approach requires administration of some form of intraarterial contrast material to perform the procedure. Traditionally, this has been the role of iodinated contrast material. Unfortunately, the indiscriminate use of this agent is contraindicated in patients at high risk for contrast-associated nephropathy. Considering the substantial cost and debilitation that result from this complication, it would be ideal to use an imaging agent that is not nephrotoxic [8]. On the basis of our previous experience with CO_2 digital subtraction angiography, we thought this agent might be more suitable in patients at risk for renal compromise [9–13]. Moreover, carbon dioxide has the advantage of not being associated with allergic complications. To measure the safety of using carbon dioxide as an intraar-

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terial contrast agent in a group of patients at high risk for developing contrast-associated nephropathy or allergy, we performed 29 renal artery angioplasties using carbon dioxide as the principal or exclusive contrast agent.

Subjects and Methods

During an 18-month period beginning in January 1997, 21 consecutive high-risk patients (13 men and eight women; age range, 22–81 years) requiring 29 renal artery angioplasties (27 procedures: two were bilateral and six were repeated) were examined prospectively to determine the effect of CO_2 angiography on renal function and allergy. Patients were considered high-risk because of either an elevated baseline level of creatinine (1.2 mg/dl is considered to be the upper limit of normal in our laboratory) or a history of urticaria or more severe reaction to iodinated contrast material. Six patients had a known allergy to IV ionic contrast material and, by our laboratory standards, 15 had elevated creatinine levels (1.3–5 mg/dl). The mean serum creatinine value for our patients was 2.3 mg/dl, whereas the median value was 2.2 mg/dl. Additionally, three patients had a serum creatinine level of greater than 4 mg/dl. Five patients with an increased creatinine level also had insulin-dependent diabetes. Four of the patients had ostial renal artery transplant stenosis, whereas the other 17 patients had nonostial stenosis. Our institutional review board approved the use of intravascular carbon dioxide and consent was obtained from all patients. Every individual in the current study was examined and subsequently treated because of volatile hypertension and a high clinical suspicion for renal artery stenosis. All patients underwent diagnostic angiography using either an Angioflex DFE-60A (Toshiba America Medical System, Tustin, CA) or model LU (Philips Medical System, Shelton, CT) followed by renal artery angioplasty using carbon dioxide as the predominant or exclusive contrast agent. Patients who required stenting after angioplasty were excluded from this study for incorporation into another subset of patients for a study evaluating carbon dioxide and renal artery stent placement.

Carbon dioxide was obtained from a disposable medical-grade cylinder (Custom Medical Devices, Gainesville, FL). A previously described [14] modified fluid management system (Angioflush; AngioDynamics, Glens Falls, NY) was used for delivery of uncontaminated nonexplosive carbon dioxide with a 25- or 50-ml syringe. All arteriograms were obtained from the common femoral artery approach. Using carbon dioxide, a preliminary aortogram with anteroposterior and bilateral oblique projections was obtained with a 4-French flush catheter (Omni Flush; AngioDynamics). In kidney transplantation patients, similar views were obtained with the inclusion of a steep oblique or lateral projection. If the renal arteries were not well visualized on the initial images, the patient was placed in the semi- or complete decubitus position to capitalize on the buoyancy of carbon dioxide and improve visualization of the nondependent vessel. Subsequently, if a renal artery was not easily discerned or if it appeared abnormal, a selective injection was performed with a 4-French hook catheter (Shephard Hook; AngioDynamics).

A stenosis was considered significant if it exceeded 50% or showed a gradient of greater than 20 mm Hg compared with the aorta. Stenoses were crossed with a 0.035-inch guidewire (Glidewire; Boston Scientific Vascular, Watertown, MA) and hook catheter. The guidewire was then exchanged for a 0.035-inch curved J wire (Rosen wire; Cook, Bloomington, IN). Because the stiffness of the curved J wire often distorted the anatomy of the renal artery, carbon dioxide was introduced between the guidewire and catheter using a Y adaptor (Schneider/NAMIC, Glens Falls, NY) to confirm the position of the stenosis.

The hook catheter was subsequently exchanged for an appropriately sized diamond balloon catheter (Boston Scientific Vascular, Watertown, MA). Using the method discussed previously, we injected carbon dioxide between the balloon catheter and the guidewire to once again confirm the position of the stenosis. After balloon dilatation, the balloon was withdrawn, leaving the wire across the lesion, and a second injection was performed in the same manner to evaluate the result. When necessary, dilatation was repeated. Angioplasty was considered successful if residual stenosis was less than 30%. After the procedure, a CO_2 aortogram was also obtained for added confirmation. Furthermore, if at any time during the procedure the CO_2 images appeared questionable, a small volume of dilute iodixanol (Visapaque; Nycomed, Princeton, NJ) was used for assessment.

All periprocedural allergic symptoms were recorded. Renal function was evaluated by comparing the creatinine level before the procedure with that 24 hr after the procedure. If the follow-up level had increased to greater than the 10% variation acceptable in our laboratory, additional creatinine levels were obtained at 48 and 72 hr. In all patients, irrespective of the initial serum creatinine level after the procedure, the creatinine level was determined at approximately 1 week after the procedure.

Results

Twenty-seven separate procedures were performed in which 21 patients had 29 angioplasties for renal artery stenosis in the presence of labile hypertension. All stenoses had features typical of atherosclerosis or intimal hyperplasia (renal transplants). Six patients required a second procedure for repeated dilatation and two patients were treated bilaterally at the initial setting. Each procedure except one was initially a technical success, which was defined as a residual stenosis of 30% or less. Carbon dioxide was the exclusive intraarterial contrast material in 15 patients (21 procedures) including the six patients with an allergy to iodinated contrast material. The volume of carbon dioxide delivered ranged from 80–200 ml, with an average of 114.6 ml per procedure. No difference in volume was noted for renal transplantation patients. Supplemental nonionic contrast material was used in six patients, ranging from 2–10 ml with an average of 8.5 ml per procedure. Nonionic contrast material was diluted in a 1:1 mixture with normal saline to provide more volume; it was used for selective injections when the significance of the pre- or postangioplasty stenosis (or both) was questionable with carbon dioxide. Nonionic contrast material was not necessary to visualize the renal ostia because they were readily visualized with carbon dioxide using either positional maneuvers (described in Subjects and Methods section) or selective injections.

There were no periprocedural allergic complications. Twenty-four hours after the procedure, the creatinine level had remained the same (11 procedures) and had decreased (12 procedures). In the remaining four patients (four procedures) the creatinine level became slightly elevated with an average rise of 0.22 mg/dl. Only one of the four patients had a rise in creatinine level that exceeded 10%, but creatinine level was less than 0.5 mg/dl at 24 hr. At 1 week follow-up, none of the patients had a serum creatinine level that exceeded a 0.5-mg/dl rise from baseline. The most significant rise in creatinine was 0.4 mg/dl. This rise occurred in a patient with insulin-dependent diabetes who received 10 ml of nonionic contrast material as a supplement to carbon dioxide. Additionally, in this patient insertion of the balloon, wire, or both resulted in unresolved spasm. The curved J wire was inadvertently withdrawn and when subsequently replaced, it irreparably dissected the renal artery, which eventually resulted in the loss of the patient's kidney.

Discussion

In the United States approximately 1 million adults suffer from hypertension caused by correctable renovascular disease [15, 16]. Likewise, the same etiology is responsible for another 10–15% of individuals with renal insufficiency [17]. For years, medical management and surgical reconstruction were the only modes of therapy available. Regrettably, as efficient as current antihypertensive therapies are, they may be counterproductive in the presence of renovascular disease by denying blood flow to an already deprived kidney. Although medical therapy may mask renovascular hypertension, Hunt and Strong [18] reported surgical reconstruction to be more efficacious. These researchers found the death rate after 7–14 years follow-up to be 16% for patients treated surgically and 40% for those treated medically. The surgical alternative, however, has significant morbidity and mortality, especially for patients with an underlying renal insufficiency [19]. Patients who require renal artery revascularization with a creatinine level of greater than 2 mg/dl reportedly have an increase in operative mortality from 3.5% to 7.1% [20]. Inherently, a substantial number of patients with renovascular disease also have an elevated creatinine level.

In 1978, Gruntzig et al. [1] introduced renal artery angioplasty as a less invasive means of treating renal artery stenosis. Since its inception, this procedure has been refined commensurate with the development of improved imaging, less invasive catheters, balloons, and wires. The basic pretext, however, remains the same. If clinically indicated, diagnosis of renal artery stenosis is made by any number of imaging techniques. Access to the affected renal artery is achieved, and a balloon is positioned and inflated within the stenosis. Finally, the patient undergoes imaging again to judge the success of the procedure.

Currently, there are a multitude of noninvasive imaging techniques by which to diagnose renal artery stenosis other than angiography, including helical CT, Doppler sonography, and MR angiography [21–23]. Regardless of the diagnostic method of choice, some form of intraarterial contrast material is necessary to guide and achieve successful angioplasty. This has been the conventional role of iodinated contrast material. Unfortunately, both ionic and nonionic contrast material can exacerbate renal failure in this group of individuals who have a propensity for renal insufficiency [24, 25]. It has been estimated that ionic contrast material has a 62% likelihood of inducing some degree of acute renal dysfunction in individuals who have a baseline creatinine level of 2 mg/dl or higher [25]. In three previously published articles the incidence of contrast-associated nephropathy after renal artery angioplasty was 5.5–8% [2–4].

It would appear intuitive that a nonnephrotoxic intraarterial contrast material would be more appropriate for individuals at risk for the development of contrast-associated nephropathy. Carbon dioxide and, more recently, gadolinium have been used for this purpose [9, 26, 27]. Although there have been recent reports extolling intraarterial gadolinium, we have used it sparingly. The belief that intraarterial gadolinium is not nephrotoxic has been, in part, extrapolated from the IV experience [28]. Because gadolinium is excreted by the kidney similarly to iodinated contrast material, it is possible that gadolinium may also be more nephrotoxic if it is more concentrated and injected closer to or more directly into the renal artery [29, 30]. In addition, there has been at least one reported case of renal failure in which intraarterial gadolinium was used [31]; its usefulness is also diminished by poor visualization, limited maximum dose, high viscosity, and high cost. Although we believe there may indeed be a role for intraarterial gadolinium, we think additional investigation is warranted before its indiscriminate use.

Carbon dioxide has been used successfully as an intraarterial contrast material since the 1970s [9]. When used appropriately, carbon dioxide is both safe and efficacious [10]. Although carbon dioxide has been touted as a nonnephrotoxic contrast agent, we wanted to see if it could be used with impunity in high-risk patients requiring intervention for renal artery angioplasty. As previously stated, we performed 29 renal artery angioplasties in 21 patients, of whom six had an allergy to iodinated contrast material and the remaining 15 had varying degrees of renal failure. Carbon dioxide was the exclusive intraarterial contrast agent in all patients except six. Occasionally, motion or bowel gas limited the diagnostic capability of carbon dioxide and in these patients a small amount (average, 8.5 ml) of nonionic contrast material was administered. Our rate of repeating angioplasty is acceptable when compared with the response obtained by other authors using iodinated contrast material and similar parameters.

The purported attributes of carbon dioxide, including the fact that it is not associated with nephrotoxicity or allergy as well as its low viscosity and cost, make it an ideal intravascular contrast agent for intervention [9, 10, 12, 13]. With the appropriate dose, carbon dioxide does not significantly occlude blood vessels because it rapidly dissolves in blood (20 times faster than oxygen), undergoes degradation in the intra- and extracellular fluid, and is eliminated by the lungs. Therefore, if carbon dioxide lacks nephrotoxicity, there should be no limit to either the total volume used or the number of direct renal artery injections, even in patients with renal insufficiency. The major drawback of carbon dioxide is its inability to allow easy visualization of the peripheral renal artery branches. This is related to the posterior orientation of the renal arteries. Using positional techniques and selective injections, we achieved either good or excellent visualization of the main renal arteries. However, unless the patient is placed almost entirely in the decubitus position, peripheral visualization may be suboptimal. Fortunately, if carbon dioxide is indeed nonnephrotoxic, selective injections with different positions can be repeated until visualization is optimal.

To ensure safety, strict adherence to the principles of intravascular carbon dioxide delivery and its precautions must be maintained [10]. Contamination can be avoided by obtaining medical-grade carbon dioxide from a disposable cylinder and delivering carbon dioxide through a closed system with limited stopcocks. Stopcocks are a weak link for contamination. The system should not be connected directly to the cylinder but instead should have a nondistended reservoir containing a limited amount of carbon dioxide. This arrangement will eliminate the accidental infusion of massive volumes of pressurized carbon dioxide and permit controlled nonexplosive delivery. A pause of 1–2 min between injections is advisable to allow carbon dioxide to be absorbed. This pause helps prevent trapping (vapor lock) in nondependent structures. Because of the shape and location, an aortic aneurysm is particularly vulnerable to this phenomenon. If the aneurysm is associated with a patent inferior mesenteric artery, trapping and bowel ischemia is a possibility. Renal transplants may also be in potential jeopardy because of their nondependent position. Therefore, in these vulnerable patients, it is prudent to wait longer than the standard 1–2 min between injections. Regardless, if trapping occurs, it can be readily relieved by repositioning the nondependent structure to the dependent location. This maneuver can be repeated as necessary.

In all our patients, confirmatory evidence of renal artery stenosis was obtained with CO_2 digital subtraction angiography as described in the Subjects and Methods section. Usually a controlled nonexplosive injection of 25–50 ml of carbon dioxide in 1–2 sec was sufficient to visualize the renal arteries (Fig. 1). If not sufficient, the same dose was administered with the patient in the semi- or complete decubitus position. This technique uses the buoyancy of carbon dioxide and accentuates the nondependent vessel (Fig. 2). Multiple injections were performed with the assumption that the total carbon dioxide dose

Fig. 1.—57-year-old man with volatile hypertension. CO_2 digital subtraction aortic angiogram that was obtained using 35 ml of carbon dioxide in 1–2 sec shows left renal artery stenosis.

was unlimited. After these preliminary diagnostic runs, we performed multiple carbon dioxide selective injections into the involved renal arteries (Figs. 3 and 4). No limitation was placed on the number of injections. Adequate visualization most commonly was achieved with carbon dioxide (5–10 ml in 1 sec). Once the stenotic lesion was identified and characterized, carbon dioxide was used to direct precise placement of the balloon catheter to prevent unnecessary dilatation and potential dissection of a normal artery.

Using a Y adaptor, the low viscosity of carbon dioxide (400 times < the viscosity of ionic contrast material) permitted its delivery between either the diagnostic or balloon catheter, while the guidewire remained in place. To be effective, either catheter must be purged before the definitive injection. Because of the lack of space between the catheter and wire, the first purge (approximately 10 ml) usually requires a forceful, prolonged injection using a large (20-ml) syringe. During the initial purge, delivery of carbon dioxide is delayed and does not provide a diagnostic injection. Subsequent injections still require a fair amount of forceful compression with less delay but will now yield a diagnostic digital subtraction image. The buoyancy and low viscosity of carbon dioxide and the more anterior position of the proximal renal arteries cause the carbon dioxide to reflux into the aorta. Therefore, the position of the stenosis and its relationship to the aorta are usually well delineated. The same technique can be used to check the result of the angioplasty once the balloon is deflated and retracted proximally. The wire never has to be removed from its secure position in the event that dilatation must be repeated. Using carbon dioxide is an improvement over using liquid contrast material, which is more viscous and therefore requires the placement of a guide catheter or sheath at the level of the renal artery. Because we were trying to optimize safety for these patients, we preferred the lower profile system. To avoid upsizing, Tegtmeyer et al. [32] advocated placing a 0.018-inch wire through the 0.035-inch endhole selective renal artery catheter to achieve the same purpose with iodinated

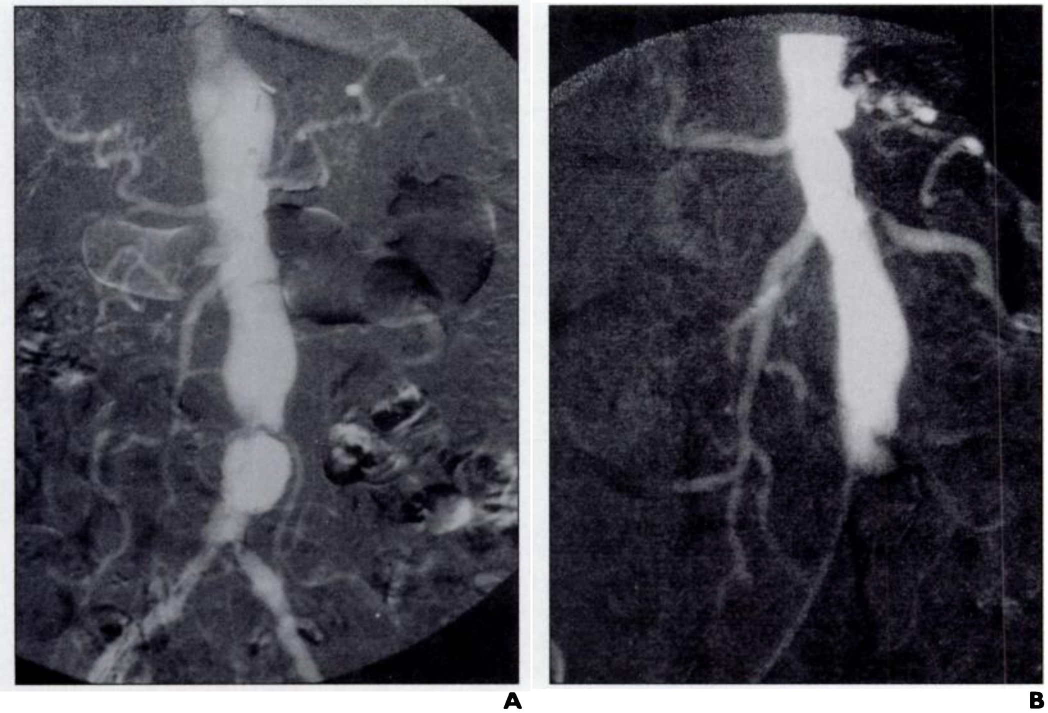

Fig. 2.—72-year-old man with labile hypertension.

A, CO_2 digital subtraction aortic angiogram with patient in supine position does not allow visualization of left renal artery.

B, CO_2 digital subtraction aortic angiogram with patient in right lateral decubitus position causes carbon dioxide to rise and opacify left renal artery, revealing underlying stenosis.

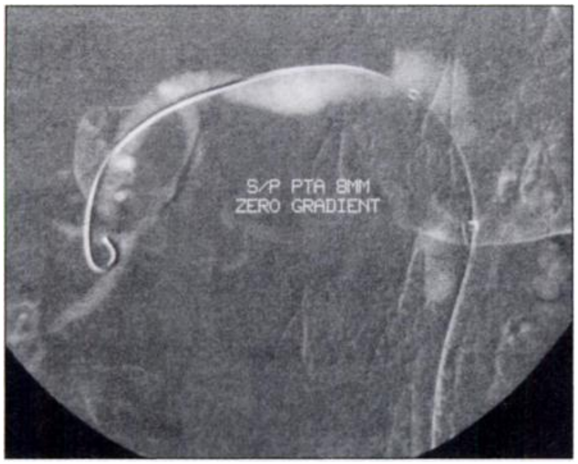

Fig. 3.—67-year-old man with hypertension. CO_2 digital subtraction angiogram of right renal artery in low viscosity of CO_2 permits delivery of carbon dioxide through balloon catheter with 0.035-inch wire in place.

Fig. 4.—53-year-old woman with hypertension. CO_2 digital subtraction angiogram of left renal artery for which carbon dioxide was injected through selective diagnostic catheter placed distally in renal artery but refluxed proximally into aorta to show ostium.

contrast material. We believe this technique adds an additional step and jeopardizes renal artery access with a less substantial wire. Furthermore, using carbon dioxide obviates multiple injections of iodinated contrast material directly into the renal artery.

We judged the potential nephrotoxicity of our methods by evaluating the level of creatinine before and 24 hr after the procedure as suggested by Lautin et al. [33]. Using the commonly accepted criteria put forth by Solomon et al. [34], we considered a rise of 0.5 mg/dl in creatinine level significant. Using an average of 114.6 ml of carbon dioxide per procedure, we found that none of our patients had a significantly elevated serum creatinine level. Our study population included the five insulin-dependent diabetics who statistically were at even greater risk for contrast-associated nephropathy. The greatest elevation of serum creatinine (0.4 mg/dl) was in a patient who experienced loss of the involved kidney due to dissection and thrombosis that was unrelated to carbon dioxide. In fact, in the process of attempted treatment of the dissection, the patient received 10 ml of iodinated contrast material. In addition to the lack of nephrotoxicity, none of the six patients with an allergy showed any periprocedural allergic symptoms.

The attributes of carbon dioxide as an intraarterial imaging contrast agent have been shown to be effective in diagnostic and, less frequently, interventional procedures [9, 12, 13]. Regarding angioplasty, the low viscosity of carbon dioxide assists in accurate repetitive visualization of the stenosis for precise balloon dilatation without loss of access. This property, in addition to the purported lack of nephrotoxicity by us and other authors [9–13], make carbon dioxide a beneficial imaging agent for performing renal artery angioplasty in patients with renal insufficiency.

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