

GENITO-URINARY

Carbon dioxide guided endovascular renal artery intervention: initial results

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SUMMARY. We evaluated the technical and clinical efficacy of carbon dioxide (CO₂) as a contrast media for endovascular intervention in patients with symptomatic renal artery stenosis.

Data analysis for the treatment of 11 main renal artery stenosis in 10 patients utilizing 18 CO₂ guided interventions (11 percutaneous transluminal angioplasties [PTA] and seven endovascular stent placements) were performed comparing clinical indications, previous surgical or endovascular treatment, comorbidity, complications, creatinine level, mean arterial pressure (MAP), and number of antihypertensive medications for the period of February 1996 to May 1997 at a tertiary care institution. One to four month postintervention follow-up was performed.

The mean preprocedure creatinine level, MAP, and number of antihypertensive medications were 3.47 mg/dL +/- 1.27, 113 mmHg +/- 20 and 2.82 +/- 1.32, respectively. Seven (64%) of 11 percutaneous transluminal renal angioplasties (PTRA) required adjuvant endovascular stenting. Nine (82%) of 11 procedures required iodinated contrast supplementation with a mean of 36 cc +/- 32 cc per exam. Postprocedure (24-72 h) creatinine level, MAP and number of antihypertensive medications were 3.50 mg/dl +/- 1.64 ($P < 0.10$), 99 mmHg +/- 14 ($P = 0.004$), and 2.45 +/- 0.82 ($P = 0.045$), respectively. At 1-4 months follow-up (mean 1.6 months) the creatinine level, MAP and number of antihypertensive medications were 3.27 mg/dL +/- 2.11 ($P < 0.10$), 100 mmHg +/- 12 ($P = 0.01$) and 2.36 +/- 1.03 ($P = 0.045$), respectively. Two procedural complications occurred without long-term sequela.

CO₂ guided endovascular renal artery intervention is a technically feasible alternative for treating patients with symptomatic renal artery stenosis in whom iodinated contrast must be minimized.

INTRODUCTION

Potential limitations in angiographic evaluation and endovascular treatment of symptomatic renal

artery stenosis in patients with azotemia can arise secondary to the use of iodinated contrast. These agents are known to be nephrotoxic in patient with pre-existing renal insufficiency and potentially fatal in individuals with a known history of contrast-induced anaphylaxis.¹ Lautin shows that the incidence of contrast-induced nephropathy in azotemic patients (creatinine > 1.5 mg/dl) receiving a mean of 77.9 cc of low osmolar contrast was 10%.¹ Typically, diagnostic renal angiography requires 50-120 cc of iodinated contrast.²

Endovascular intervention with percutaneous transluminal angioplasty (PTA) and stenting of

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the main renal artery is known to be a safe surgical alternative for the treatment of symptomatic renal artery stenosis.⁵ However, these procedures generally require the use of iodinated contrast which can potentially impair renal function. Carbon dioxide (CO₂) has been shown to be an effective alternative to iodinated contrast for imaging of the renal arteries.^{6,7} The purpose of this retrospective study was to evaluate the technical and clinical efficacy of CO₂ guided endovascular renal artery intervention in azotemic patients with symptomatic renal artery stenosis.

MATERIALS AND METHODS

Eleven procedures performed on 10 patients for treatment of symptomatic renal artery stenosis utilizing 18 CO₂ guided interventions at the Johns Hopkins Hospital were evaluated for the time period between February 1996 to May 1997. Hospital, referring physician and outpatient records and radiology reports were utilized. This patient group consisted of three men with a mean age of 70 years (range, 61–81 years) and seven women with a mean age of 69 years (range, 28–86 years). CO₂ guided intervention was indicated for all cases due to azotemia and the presence of significant renal artery stenosis. Of these 10 patients, one patient had a known contrast allergy.

Baseline patient characteristic noted included presentation, previous intervention, pertinent past medical history, creatinine level, mean arterial pressure (MAP) as calculated by blood pressure cuff measurements, and number of antihypertensive medications. Angiographic intraprocedural characteristics noted included the use of supplemental iodinated contrast, type and quantity of iodinated contrast, type of intervention and complications. Follow-up data analysis was performed 24–72 h and 1–4 months after intervention and compared with preprocedural data.

After informed consent was obtained, aortic catheterization was performed in all patients from a right common femoral artery approach using standard techniques. A 5 French pigtail catheter (Tennis Racket, Medi-Tech, Watertown, MA USA) was placed at the level of the renal arteries. Using a 60 cc syringe and a 3 way stopcock, 50 cc of medical grade CO₂ was drawn

from a tank. The CO₂ filled syringe and stopcock were connected to the catheter and 5 cc of CO₂ were used to clear the catheter of blood and/or saline. A digital subtraction (DSA) technique was utilized with rapid injection of the 45 cc CO₂ bolus after the mask image was obtained. The patient was obliqued using a wedge with the side of interest up if additional images of one or the other renal artery was required. Three to five minutes was allowed in between injections to allow for CO₂ resorption and prevention of a vapor lock in visceral, renal or lower extremity vessels. If the renal vasculature was still not adequately visualized, a small amount of nonionic low osmolar iodinated contrast (Omnipaque 350, Winthrop Pharmaceuticals, NY, NY, USA; Optiray 350, Mallinckrodt Medical, St Paul, MN, USA) was hand injected. Significant renal artery stenosis (<65% diameter reduction) were initially treated with percutaneous transluminal renal angioplasties (PTRAs) using standard techniques previously described.^{8,9} Renal arteries with unsatisfactory post-PTRA results (>30% residual stenosis) were adjuvantly treated with stent placement (type used at operator's discretion) as previously described.^{10,11} Following intervention, results were documented with a follow-up CO₂ injection with DSA imaging. All patients were admitted for overnight observation and discharged the following morning. Clinical follow-up was scheduled with the referring physician for adjustments in antihypertensive medications.

The paired Student *t*-test was used to compare pre-, postprocedure and follow-up creatinine levels, MAP and number of antihypertensive medications. A *P* value of less than 0.05 was determined to be significant.

RESULTS

Eleven procedures performed on 10 patients for treatment of symptomatic renal artery stenosis utilizing 18 CO₂ guided interventions were evaluated. PTRA was initially utilized in all 11 procedures. Seven procedures required post-PTRA stent placement (Wallstent, Schneider, Minneapolis, MN, USA *n*=5; Palmaz Stent, J & J Warren, NJ, USA *n*=2). A mean of 7 cc/kg of CO₂ (490 cc for 70 kg patient) was utilized per procedure. Of the 11 procedures, nine (82%)

required supplemental iodinated contrast with an average of 36 cc \pm 32 (Omnipaque 350 was utilized in eight procedures at a mean dose of 47 cc [range, 10–110 cc] and Optiray 350 was utilized in one procedure at 20 cc).

The mean preprocedural creatinine level was 3.47 mg/dL \pm 1.27, MAP was 113 mm Hg \pm 20 and number of antihypertensive medications was 2.82 \pm 1.32. One patient was dialysis dependent. Comorbidity most commonly included coronary artery disease (CAD), tobacco abuse, previous endovascular renal artery intervention and peripheral vascular disease (Table 1). Post-procedure creatinine, MAP and number of antihypertensive medications were 3.50 mg/dL \pm 1.64 ($P < 0.10$), 99 mm Hg \pm 14 ($P = 0.004$) and 2.45 \pm 0.82 ($P = 0.085$), respectively.

Clinical follow-up was obtained at a mean of 1.6 months (range, 1–4 months). Creatinine level, MAP and number of antihypertensive medications were 3.27 mg/dL \pm 2.11 ($P < 0.10$), 100 mm Hg \pm ($P = 0.01$) and 2.36 \pm 1.03 ($P = 0.045$), respectively. Three patients at the time of follow-up were on dialysis, inclusive of one patient who was dialysis dependent prior to intervention (Table 2). Upon chart review, dialysis dependency was not secondary to complications of the renal artery intervention or iodinated contrast-induced nephropathy.

There were two procedural complications. One patient developed acute thrombosis in the distal main renal artery during intervention which was successfully lysed utilizing a direct intrarenal urokinase (Abokinas, Abbott Laboratories,

Chicago, IL, USA) infusion at 2000 IU/min for 15.5 h. A second patient's initial Wallstent migrated distally into the renal vasculature. This was resolved by placement of a second Wallstent. There were no long-term direct sequelae from either of these procedural complications.

DISCUSSION

Contrast-induced renal failure and anaphylaxis in patients with azotemia or contrast allergy, respectively, is a well-described phenomenon with both ionic high osmolar and nonionic low osmolar iodinated contrast agents. Moore shows that in patients with a known azotemia (creatinine > 1.5 mg/dL), the incidence of nephrotoxicity has been stated to occur in 10.9% of patients receiving high osmolar and 4.2% of patients receiving low osmolar iodinated contrast.¹² Lautin, who utilized different parameters for evaluating nephrotoxicity, showed that azotemic patients (creatinine > 1.5 mg/dL) receiving low osmolar and high osmolar iodinated contrast agents experienced contrast nephropathy of 10% and 41%, respectively.¹ CO₂, on the other hand, has been shown to be a safe, efficacious alternative for iodinated contrast in those patients with known azotemia.⁶ Concerns arise because CO₂ use can lead potentially to embolization to both nontarget and target vessels with resultant vessel occlusion from a 'vapor lock'. Vapor lock can potentially occur when there is inadequate blood flow to absorb the injected carbon dioxide. This

Table 1 Patient comorbidity for CO₂ guided renal artery intervention

Comorbidity	No. (percentage)
Coronary artery disease	6(60)
Tobacco abuse	5(50)
Previous renal stent/intervention* on affected side	3(30)
Peripheral vascular disease	3(30)
Diabetes mellitus	2(20)
Abdominal aortic aneurysm history	2(20)
Cerebral vascular accident	1(10)
Connective tissue disease	1(10)
Dialysis dependent	1(10)
Transplant kidney	1(10)
Contrast allergy	1(10)
Fibromuscular dysplasia	1(10)
Thrombocytosis	1(10)

* One patient had a history of both a renal artery thrombectomy and previous stent placement.

Table 2 Creatinine level, MAP and number of antihypertensive medications change pre-, post- and at follow-up for CO₂ guided intervention

	Creatinine (mg/dL) ¹	SD	MAP (mmHg) ²	SD	MEDS ³	SD
Preprocedure	3.47	1.27	113	20	2.82	1.32
Postprocedure	3.50	1.64	99	14	2.45	0.82
Follow-up (1-4 months)	3.27	2.11	100	12	2.36	1.03

¹ $P > 0.10$ at follow-up (paired Student *t*-test); ² $P = 0.01$ at follow-up (paired Student *t*-test); ³ $P = 0.045$ at follow-up (paired Student *t*-test).

can be prevented by allowing adequate resorption time between injections and being particularly careful in patients with abdominal aneurysms because blood flow in the aneurysm is turbulent and CO₂ washout is impaired. However, clinically significant gas embolization events are extremely uncommon.¹³ Hawkins et al. have shown that 11-13 cc/kg of medical grade CO₂ injected directly into the canine kidney does not cause changes in renal function or histology. This is secondary to CO₂'s known high plasma solubility and low toxicity.^{13,14} In general, 7 cc/kg (490 cc for 70 kg patient) of CO₂ is utilized at our institution during CO₂ guided intervention.

Renal CO₂ angiography is an evolving imaging modality. With proper software, fluoroscopy settings and a safe gas delivery system, CO₂ can be useful when there are iodinated contrast contraindications. In a double-blind prospective study, Shreier demonstrated that for evaluating renal artery anatomy, CO₂ angiography has a sensitivity and specificity of 83% and 99%, respectively, when compared with iodinated contrast.

Surgical revascularization and endovascular renal artery intervention have both been shown to correct renovascular hypertension.^{4,5,15,17} Correction of azotemia has been less defined for PTRAs. Hallet has shown that surgical renal artery bypass has been able to stabilize or improve renal function in 72.7% of 304 patients as measured by serum creatinine.¹⁵ Pattynama has shown in his PTRAs series that there was a mean creatinine rise of 0.5 mg/dL after intervention.⁵ Bonelli's PTRAs series noted that there was no change in serum creatinine after intervention.⁷ Taylor reports stabilization or improvement in renal function in 62% of patients who underwent PTRAs and stent placement.¹⁷

Reported complications associated with renal artery bypass vs endovascular renal artery intervention vary. Hallet's surgical renal artery bypass

series had a 30 day mortality rate of 5.6% to 15.5% depending on comorbidity including heart disease, creatinine ≥ 3 mg/dL and age > 70 years.¹⁵

Morbidity associated with endovascular renal artery intervention has ranged from 2.2% to 17% and includes subintimal dissection, acute tubular necrosis, hemorrhage, cerebral vascular accident, myocardial infarction and thrombosis.^{3,5,17,18} Of the 389 aggregate patients cited in the three aforementioned PTRAs articles,^{4,5,17} there were eight deaths (2%) within 30 days of intervention. Pattynama notes that the PTRAs complication rate was 15% for azotemic (creatinine > 1.5 mg/dL) patients vs 6% for nonazotemic patients with symptomatic renal artery stenosis. The mean preprocedure creatinine for our group was 3.47 mg/dL with no significant improvement or demise noted postprocedure or at the time of follow-up. We had two complications (18%), neither of which resulted in long-term sequelae.

Careful review of the sequence of radiographs from this study indicate that although the gross architecture of the aorta and proximal main renal artery was adequately delineated with CO₂ in most cases, a low volume iodinated contrast injection was required in 82% (9/11) of cases to allow for the detailed evaluation necessary to properly size the angioplasty balloon or endovascular stent. In addition, the secondary and tertiary divisions of the renal artery were often difficult to fully evaluate. Schreier notes similar findings in his renal CO₂ vs iodinated contrast study.⁷ For this reason, CO₂ may not provide for adequate evaluation of patients with renal artery disease not involving the main vessel, such as that which can occur with fibromuscular dysplasia. Supplemental hand injections of iodinated contrast can further delineate vasculature when CO₂ is inadequate.

A CO₂ flush aortogram can provide for identification and evaluation of visceral vessels, as well



Fig. 1 (A) CO₂ abdominal aortogram in a 61-year-old Caucasian man with unilateral left kidney 7 months after Palmaz stent placement for left renal artery stenosis. Patient presented with rising creatinine. CO₂ arteriogram confirms significant intrastent intimal hyperplasia with near total occlusion of the renal artery. (B) A P154 Palmaz stent was telescoped within the existing stent and (C) dilated with a 5 mm balloon. (D) The follow-up CO₂ arteriogram demonstrates that the main renal artery is now clearly patent.

as proximal characterization of the main renal arteries. This strategy can minimize the amount of supplemental iodinated contrast required thereby limiting potential nephrotoxicity. Alternatively, patients often arrive for their scheduled intervention with prior angiographic films or other radiologic imaging. Based on previous studies, selective CO₂ angiography can be used for confirming and further delineating known renovascular lesions. This algorithm can

further limit or obviate the need for supplemental iodinated contrast. In general, it is accepted that there is a positive correlation between iodinated contrast volume administered and iodinated contrast induced-nephropathy, particularly in those patients with pre-existing azotemia and diabetes.

When supplemental iodinated contrast was required in our study, the mean volume infused was 36 cc (range 10–110 cc). Beregi notes that

50–120 cc of iodinated contrast is required for diagnostic renal angiography.² Routinely, additional iodinated contrast injections may be necessary, beyond the typical 50–120 cc required for diagnostic studies, for a successful renal artery intervention. Our results are encouraging since iodinated contrast was not required in two cases and reduced in nine. However, these results also show the potential limitation of carbon dioxide guided endovascular intervention; in most cases, supplemental iodinated contrast is required for adequate imaging. Nevertheless, CO₂ as the initial imaging modality holds promise for minimizing the administration of iodinated contrast during endovascular renal artery procedures as DSA equipment and software continue to improve.

Potential improvements in imaging during an intervention include limiting gas fragmentation and adeptly handling the inherent buoyancy of CO₂. Gas fragmentation is thought to occur when manual injection rates are too slow to replace the blood volume into which the CO₂ was injected and/or a nonuniform injection rate secondary to operator error. Buoyancy of CO₂ can actually be used to the operator's advantage. For instance, a wedge placed under the patient's right side during CO₂ injection can better visualize the right renal artery.

Study improvements include quantifying the amount of CO₂ administered and incorporating paired-controls to examine clinical outcome and iodinated contrast volume reduction for CO₂ dioxide vs iodinated contrast assisted endovascular renal artery intervention. Fortunately, there are adequate studies delineating complications and associated risk factors with the use of iodinated contrast.^{11,12,19} Our small study population would probably have not shown a statistically significant difference in clinical outcome between CO₂ and iodinated contrast assisted procedures if a paired-control study were utilized. Our purpose was to show the feasibility of CO₂ guided endovascular renal artery intervention in minimizing iodinated contrast and showing that clinical outcomes were similar to previously published reports on iodinated contrast assisted procedures.^{15,17,18} This study achieved its stated objectives.

In summary, CO₂ guided endovascular renal artery intervention with PTRAs and stenting will

allow for a larger population of patients with multidrug resistant hypertension and known azotemia to be more aggressively evaluated and treated for renovascular hypertension. The statistically significant decline in MAP and number of blood pressure medications we documented at follow-up are encouraging, as it indicates that CO₂ is an effective alternative for iodinated contrast in guiding complex endovascular procedures. Because CO₂ is not nephrotoxic, comparison of creatinine levels pre- and postangiography and intervention should be less confounding compared to current data based on iodinated contrast procedures. This data suggests that the role of CO₂ guided endovascular renal artery intervention in azotemic patients should be more fully explored.

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