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Safety of Carbon Dioxide Digital Subtraction Angiography

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Objective: Reports of fatality following carbon dioxide digital subtraction angiography (CO_2-DSA) have raised concerns regarding its safety. This study reviews the safety of CO_2-DSA.

Design: Single-institution retrospective review.

Setting: Tertiary care teaching hospital in Los Angeles, California.

Patients: A total of 951 patients who underwent 1007 CO_2-DSA procedures during a 21-year period.

Main Outcome Measures: Preprocedure and postprocedure creatinine values and periprocedural morbidity and mortality.

Results: A total of 632 arterial CO_2-DSA were performed; 527 were aortograms with or without extremity runoff; 100, extremity alone; and 5, pulmonary. Venous CO_2-DSA included 187 inferior vena cavagrams, 182 hepatic or visceral, 5 extremity venograms, and 1 superior vena cavagram. Associated endovascular procedures were performed in 499 cases; 162 were arterial interventions including 62 endovascular aneurysm repairs, 53 visceral or renal percutaneous angioplasty with/without stent, 41 extremity percutaneous angioplasty with or without a stent, and 4 cases of thrombolysis or embolization; 176 caval filters, 98 transjugular intrahepatic portosystemic shunts, 54 transjugular liver biopsies, and 9 other venous interventions. The mean preprocedure creatinine level was 2.1 mg/dL; postprocedure, 2.1 mg/dL ($P=.56$). There were a total of 61 (6.1%) procedural complications including 4 (0.4%) mortalities. Two were procedure-related complications: 1, suppurative pancreatitis following aortogram; and 2, hepatic bleed following failed transjugular intrahepatic portosystemic shunts. Two were attributable to patient disease; 1, metastatic adenocarcinoma; and 2, refractory, end-stage cardiomyopathy.

Conclusion: Carbon dioxide digital subtraction angiography is a versatile technique that can be safely used for diagnostic and therapeutic endovascular procedures. Morbidity and mortality are acceptable with preservation of renal function. Thus, CO_2-DSA is a safe alternative to iodinated contrast.

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SEVERAL INSTITUTIONS HAVE DEscribed their experience with catheter-based angiography using carbon dioxide (CO_2) as the radiographic contrast agent for the evaluation of arterial and venous diseases. Reported uses have included diagnostic evaluations of the abdominal and extremity vessels, renal transplants, tumors, and hemodialysis access sites. Therapeutic interventions such as balloon angioplasty, stent placement, caval interruption procedures, thrombolysis, and transjugular intrahepatic portosystemic shunts (TIPS) have also been reported.

There are several potential benefits of CO_2 over iodinated contrast media for vascular imaging. Carbon dioxide is an inexpensive gas that is widely available, providing cost savings compared with traditional iodinated contrast agents. It is highly soluble in blood and is rapidly eliminated via the lungs, allowing the injection of almost unlimited quantities of gas as long as adequate time for elimination is allowed between injections. CO_2 has no known inherent nephrotoxicity, making it desirable for evaluating patients with evidence of renal dysfunction. Also, there is no potential for allergic contrast reactions. Because of the low viscosity of CO_2, smaller angiographic catheters may be used and filling of severely diseased stenotic vessels may be enhanced.

Previous articles from our institution have focused on the utility of CO_2 digital subtraction angiography (CO_2-DSA) for the evaluation and treatment of patients with lower extremity and renal artery occlusive disease.[1-4] However, case reports of severe morbidity and mortality associated with this imaging technique have

Table 1. Procedural Indications

Procedural Indication	No. (%) (n=1007)
Limb ischemia	347 (34)
Aortic aneurysm	84 (8)
Renal or visceral occlusive disease	164 (16)
Pulmonary embolism	188 (19)
Portal hypertension	116 (12)
Hepatic dysfunction	54 (5)
Other (miscellaneous)	54 (5)

questioned its safety.[5,6] This review was undertaken to analyze a large, single-institution experience with CO_2-DSA, specifically regarding CO_2-DSA–dependent procedural complication rates.

METHODS

Over a 21-year period (1988-2009), 951 patients underwent CO_2-DSA at University of Southern California hospitals. Patient medical records were reviewed for demographic data, procedure type, concomitant use of iodinated contrast, and creatinine levels before and after CO_2-DSA. In the hospital, 30-day procedural complications and mortality rates were tabulated. The research protocol was reviewed and approved by the institutional review board. Indications for CO_2-DSA included renal dysfunction (serum creatinine level >1.5 mg/dL), institutional review board approval of protocol, or iodine contrast allergy.

Our current technique of CO_2-DSA has been previously described and used since 2005.[7] In brief, a sterile bag (Angioflush 3 fluid collection bag; Angiodynamics, Queensbury, New York) with attached tubing (Connecting tube; Boston Scientific, Natick, Massachusetts) with a stopcock is inflated with CO_2. The bag is purged and inflated with CO_2 3 times to eliminate room air contamination. The attached stopcock is closed, and the inflated bag disconnected and then connected to tubing with 1-way valves and a sidearm (Angiodynamics, Queensbury, New York). The sidearm of the tubing is connected to a 60-mL Luer lock syringe. The syringe is filled and purged at least 3 times. These steps create a closed CO_2 system.

Hand injection of no more than 50 mL using digital subtraction imaging is used. High frame rates of 3 to 6 frames per second and stacking technology is required to produce adequate images. Multiple injections in various imaging planes, rotation of the patient, or both may be required to demonstrate the anatomy of interest. Concomitant use of iodinated contrast was used to improve visualization of vascular anatomy when required. We have previously described the limitations and specific procedural techniques to optimize CO_2-DSA imaging of the aortic, renal, and lower-extremity vascular beds.[1-4,7]

Statistical comparison of preoperative and postoperative creatinine level for all individuals was performed using the 2-tailed *t* test. $P<.05$ was considered significant.

RESULTS

Nine hundred ninety-one patients underwent a total of 1007 CO_2-DSA procedures. The distribution of procedural indications is shown on **Table 1**. The patient population was predominantly male (60.4%), with an average age of 64 years. Procedural indications included limb ischemia, aortic aneurysm, renal or visceral occlusive disease, prophylaxis or treatment of pulmonary embolism, portal hypertension, and hepatic dysfunction. Owing to concerns of air embolus, CO_2-DSA was specifically not used to image the cerebral or brachiocephalic vascular beds.

Three hundred twenty studies were performed with CO_2 using a mean of 186 mL of gas CO_2 (range, 10-1080 mL) or with the addition of iodinated contrast in 502 (median, 8.5 mL; range, 2-550 mL) (**Table 2**). For 185, whether additional iodinated contrast was injected was not recorded.

Six hundred thirty-two arterial (63%) studies were performed. Aortograms were performed in 527, many in conjunction with imaging of 1 or both lower extremities or selective renal and/or visceral arteries. Imaging of the lower extremities only, without aortography, was performed in 100. Five patients underwent pulmonary arteriograms.

A total of 375 venous studies were performed, including 187 inferior vena cavagrams, 182 hepatic or visceral and 5 extremity venograms, and 1 superior vena cavagram.

Concomitant endovascular procedures were performed in 499 studies. A total of 162 arterial interventions were performed: 62 endovascular aneurysm repairs (**Figure**), 53 visceral percutaneous angioplasty with or without a stent, 41 extremity percutaneous angioplasty with or without a stent, and 6 catheter-directed embolizations. The CO_2-DSA was used to guide inferior vena cava filter placement in 176 studies, TIPS procedures in 98, transjugular liver biopsies in 54, and miscellaneous venous interventions in 9.

Sixty-one (6%) complications were documented in 951 patients. The most common included puncture-site hematoma (16 patients; 25%) and abdominal pain (10 patients; 16%). A complete listing of complications by procedure is found in **Table 3**.

Of the 10 patients who experienced abdominal pain, all followed aortography and occurred prior to conversion in 2005 to our current CO_2 delivery technique. In 6, the pain was transient and the CO_2-DSA procedure was completed uneventfully. In 4 patients, the pain persisted and biochemical evidence of pancreatitis (amylase level of 318-9000 U/L; to convert to microkatal per liter multiply by 0.01667) developed. Pancreatitis resolved with supportive care in 3 patients, and 1 patient went on to develop suppurative pancreatitis.

Preprocedure and postprocedure serum creatinine data were available for 700 (74%) patients. The mean preprocedure value was 2.1 mg/dL (to convert to micromoles per liter, multiply by 88.4). After the procedure, this value was unchanged (2.1 mg/dL). Of the 504 patients with a preprocedure creatinine level greater than 1.3 mg/dL, 39, or 8%, had an increase in serum creatinine level of more than 0.5 mg/dL after the procedure (**Table 4**). For 245 patients with a preprocedure serum creatinine level greater than 2 mg/dL, there was, as a group, no change in the postprocedure serum creatinine level, with 27 (11%) experiencing an increase of more than 0.5 mg/dL. Additional data concerning the risk of renal dysfunction stratified by preprocedure renal function (serum creatinine) can be found in Table 4.

Four patients died. Two died of unrelated disease—metastatic lung cancer and refractory congestive heart failure. Two deaths were related to the angiographic procedure. The first was a 66-year-old cirrhotic patient who had a TIPS procedure for deteriorating liver function. During the pro-

Table 2. Contrast Used, by Procedure

Procedure	CO_2 Only, No. (%)	Median Amount, mL	CO_2 + Iodine, No. (%)	Median Amount, mL
Aortography (n=527)	246 (46.7)	240	281 (53.3)	15
Renal/visceral PTA/stent (n=53)	12 (22.6)	225	41 (77.4)	10
Extremity PTA/stent (n=41)	31 (75.6)	180	10 (24.4)	4
EVAR (n=62)	21 (33.9)	180	41 (66.1)	30
TIPS (n=98)	27 (27.6)	100	71 (72.4)	125
TJLB (n=54)	48 (88.9)	60	6 (11.1)	10
IVC (n=176)	170 (96.6)	60	6 (3.4)	3
Hepatic venography (n=30)	25 (83.3)	60	5 (16.7)	30

Abbreviations: EVAR, endovascular aneurysm repair; IVC, inferior vena cava; PTA, percutaneous transluminal angioplasty; TIPS, transjugular intrahepatic portosystemic shunt; TJLB, transjugular liver biopsy.

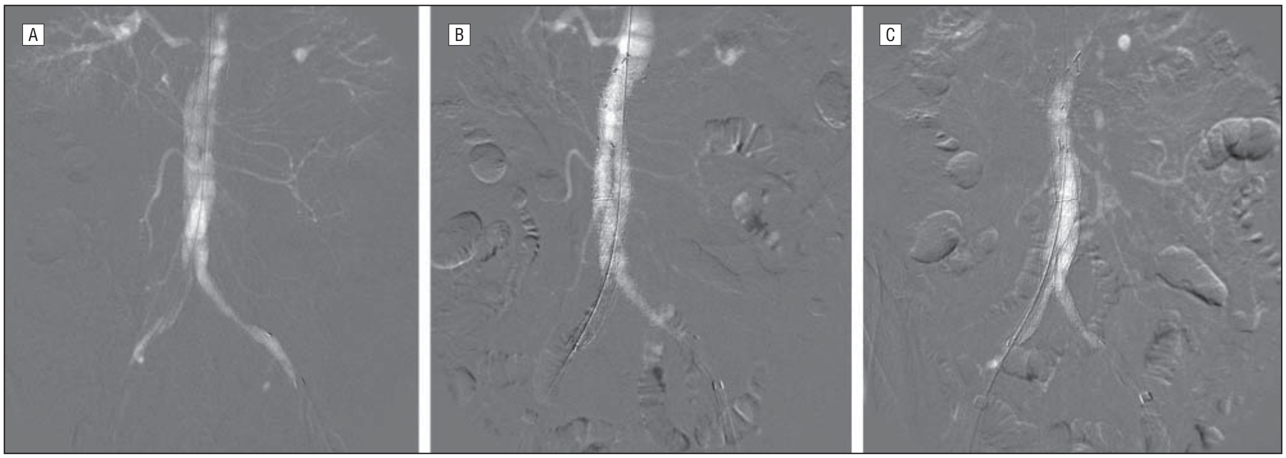

Figure. Carbon dioxide digital subtraction angiography on completion in the anterior-posterior (A), left lateral oblique (B), and right lateral oblique (C) planes after successful endovascular aneurysm repair.

cedure, cannulation of the portal vein was unsuccessful. After the procedure, the patient developed hypotension requiring repeated venography. This revealed a perforated left hepatic vein. The bleeding was controlled by embolization, but the patient died of multisystem organ failure.

The second patient, previously mentioned above, underwent evaluation for hypertension and ischemic nephropathy. Angiographic findings included severe atherosclerotic pararenal aortic disease, near occlusion of the infrarenal aorta, occlusion of the left renal artery, severe stenosis of the right renal artery, and occlusion of the superior mesenteric artery. Following diagnostic angiography, the patient developed suppurative pancreatitis complicated by pancreatic abscess formation and died. Pancreatic and visceral atheroemboli were documented at autopsy.

COMMENT

A recent contemporary review of all diagnostic procedures (angiography, computed tomographic scans, etc) that use iodinated contrast reported a respective complication and mortality rate of 25% and 7.8% in patients who develop contrast-induced nephropathy.[8] Iodine contrast nephrotoxicity occurred in 1% to 2% of patients with normal renal function, 10% in patients with creatinine levels of 1.3 to 1.9 mg/dL, and up to 62% in those with levels greater than 2 mg/dL.[9] Intravenous administration of iodinated contrast has a significantly greater effect on mortality than intra-arterial administration. This review of a large, single-institution experience with the alternative intravascular contrast agent, CO_2, provides comparative information for safety, particularly in the patient with renal dysfunction.

The initial use of intravascular injection of CO_2 for diagnostic purposes was in the 1950s. Intravascular CO_2 was used to diagnose pericardial effusions by injection of a large bolus (100-200 mL) of gas into an antecubital vein.[10-13] Effusions could be visualized between the gas-filled right atrium and the adjacent lung. The atrial gas bubble was short-lived, as the CO_2 was rapidly absorbed by the blood and eliminated via the lungs.

Intra-arterial use of CO_2 was first described by Hawkins[14] and has been effectively used in a variety of angiographic procedures. For most arterial studies, CO_2-DSA provides sufficient images for diagnostic as well as therapeutic purposes. In certain situations, to better define the arterial anatomy, small supplemental doses of iodinated contrast are necessary. This amounted to, on average, 10 to 40 mL of contrast for a variety of arterial procedures, whereas for venous procedures, the volumes of supplemental contrast were somewhat greater.

Air trapping in the vasculature with a "vapor lock" phenomenon following the use of CO_2 as an arterial contrast agent can occur.[15-18] Owing to the buoyancy of gas in blood, the gas preferentially fills nondependent vessels. If the forces of buoyancy exceed the kinetic energy of venous flow that promotes clearing of the gas, CO_2 can be transiently "trapped" within the vascular space. The high solubility and rapid absorption of CO_2 minimizes the risk of vapor lock, but large injection volumes in nondependent vessels increases this risk, as does any room air contamination of the gas injected.

This was purported to be the case in a patient with end-stage congestive heart failure described by Rundback et al.[5] Forty-eight hours after a diagnostic CO_2-DSA aortogram that revealed extensive atherosclerotic irregularity of the abdominal aorta, the patient was noted to have livedo reticularis of the buttocks and legs and rhabdomyolysis. The patient's condition rapidly deteriorated, and the patient died 31 days after angiography. Examination of pathologic specimens revealed no evidence of atheroembolization. The authors attributed these findings to delayed clearing of CO_2 gas from the small arteries of the lower extremities and bowel, resulting in tissue ischemia and possibly to a direct vasoconstrictive effect of CO_2 on the microvasculature. There was some concern that the patient's severe cardiac dysfunction also contributed to delayed clearing of CO_2 from the microvasculature.

Vapor lock was also believed to be operational in a patient reported by Spinosa et al[6] who developed abdominal pain after CO_2-DSA. The pain resolved and the patient recovered uneventfully, but colonoscopy visualized patchy areas of ischemic mucosa in nondependent portions of the colon. Caridi and Hawkins[7] have also described 2 patients with symptoms of transient mesenteric ischemia after CO_2-DSA, which they also attributed to vapor lock.

A potential contributor to these above case reports is room air contamination of the injected CO_2. Great care must be exercised to prevent violation of the seal of the delivery system and resultant contamination of the injected gas with room air. Multiple (at least 3) purgings of the system are important to ensure that all room air contamination is eliminated. Early in our experience, we devised an inexpensive, easy-to-use system that was readily assembled from components found in most angiography suites. However, multiple steps were required to transfer CO_2 from the tank to the patient, increasing the potential for room air contamination. Our current technique is a closed system that we adopted in 2005. It requires only 1 step from CO_2 tank to patient injection, thereby minimizing the potential for room air contamination. With this technique, patients' abdominal discomfort and clinical evidence of pancreatitis have decreased significantly. Unfortunately, Angiodynamics has recently decided to stop producing the delivery tubing with 1-way valves, which we believe is important to minimize room air contamination. Other companies are currently interested in manufacturing a similar construct, but regulatory issues and approval may delay its application in clinical practice.

To our knowledge, this is the first series to describe hyperamylasemia and clinical manifestations of pancreatitis following CO_2-DSA. Possible mechanisms have been mentioned above, but the most likely, in our view, is occult room air contamination. Alternatively, pancreatic ischemia could have resulted from emboli associated with the angiographic catheter or atheroemboli originating from existing aortic disease. This appeared to be the case in the one patient who died of suppurative pancreatitis. Whatever the etiology, it is conceivable that an identical process of lesser magnitude was also operational in the 6 patients with transient abdominal pain.

Table 3. Periprocedural Complications, by Procedure

Procedure	Complication	No. (%) (n=61)
Aortography	Puncture site hematoma	8 (13)
	Transient abdominal pain	6 (10)
	Pancreatitis	4 (7)
	Chest pain	1 (2)
	Intimal dissection	1 (2)
	Tachyrhythmia	1 (2)
	Diarrhea	1 (2)
	Dehydration	1 (2)
	Hives	1 (2)
	Severe hypertension	1 (2)
	Seizure	1 (2)
	Death	1 (2)
Renal PTA/stent	Puncture site hematoma	4 (7)
	Acute renal failure	3 (5)
	Tachyrhythmia	1 (2)
Extremity PTA/stent	Puncture site hematoma	2 (3)
	Renal failure	1 (2)
	Intimal dissection	1 (2)
	Compartment syndrome	1 (2)
EVAR	Puncture site hematoma	2 (3)
	Transient paresthesia	1 (2)
	Ischemic colitis	1 (2)
TIPS	Transient hypotension	5 (8)
	Fever	2 (3)
	Nausea	2 (3)
	Aspiration	1 (2)
	Death	1 (2)
TJLB	Nausea	1 (2)
	Fever	1 (2)
	Death	1 (2)
IVC	Death	1 (2)
Hepatic venography	Transient hypotension	2 (3)

Abbreviations: EVAR, endovascular aneurysm repair; IVC, inferior vena cava; PTA, percutaneous transluminal angioplasty; TIPS, transjugular intrahepatic portosystemic shunt; TJLB, transjugular liver biopsy.

Table 4. Comparison of Preoperative and Postoperative Creatinine Values

Before Procedure, mg/dL	Patients, No. (%)	Creatinine Level, mg/dL, Mean (SD)		*P* Value	Patients With Rise in Creatinine Level >0.5, No.	Change in Creatinine Level, Mean (SD)
		Before Procedure	After Procedure			
<1.2	196 (28)	0.9 (0.2)	0.9 (0.3)	.16	5	0.05 (0.3)
1.3-1.9	259 (37)	1.6 (0.2)	1.6 (0.5)	.13	12	0.04 (0.45)
>2	245 (35)	3.1 (1.3)	3.2 (1.6)	.30	27	0.19 (0.91)
Total	700	2.1 (1.2)	2.1 (1.4)	.25	44	

Other steps to minimize visceral complications associated with aortography, especially in patients with significant atherosclerotic plaque, include angiographic catheter placement at the renal arteries to minimize reflux of gas into the nondependent visceral vessels. If visceral vessel imaging is required, the volume of CO_2 injected per imaging run should be no more than 50 mL, and adequate time should be allowed between injections (3 to 5 minutes) to allow for complete absorption of the gas. Changing the patient's position during examination may also promote more rapid clearing of CO_2.

In general, complications were more common following venous therapeutic interventions owing to the preponderance of interventions being TIPS or transjugular liver biopsies in patients with end-stage liver disease and cirrhosis. Another significant source of complications, namely access site hematomas and vessel injuries, were attributable to the angiographic catheter rather than to the use of CO_2 as a contrast agent. Admittedly, less-than-optimal imaging with CO_2-DSA may in some cases have contributed to catheter-related events, particularly when attempting to cannulate a branch vessel. This may have been the case in the one patient who sustained an ultimately lethal hepatic vein injury during a TIPS procedure. The remaining events, most of which were mild and self-limited, are common to any angiographic procedure regardless of the contrast used.

The advantage of CO_2-DSA in patients with renal dysfunction is clearly demonstrated by our 2-decade experience. No significant decline in renal function was found in the overall experience and in patients most at risk (serum creatinine level >2 mg/dL); the average increase in serum creatinine level was 0.2 mg/dL, with only 27, or 11%, experiencing an increase of more than 0.5 mg/dL. This is in contrast to the 62% incidence of renal deterioration and increased overall mortality found in patients with preexisting renal dysfunction that was documented in a large series examining contrast-induced nephropathy at the Mayo Clinic. Consequently, although patient hydration, bicarbonate infusion, and *N*-acetylcysteine have been used in an attempt to mitigate the nephrotoxic effects of iodinated contrast, contrast nephrotoxicity remains an issue.[19,20] Adding CO_2-DSA as a complement to the above strategies markedly reduces the iodinated contrast required and thus the nephrotoxic insult, particularly in aortic, visceral/renal, and lower-extremity arterial studies.

This article details a large, single-institution experience with CO_2-DSA that demonstrates the utility and safety of this technique in a variety of applications. Overall procedure-related mortality was low and comparable with contemporary series using iodinated contrast. Development of renal dysfunction or aggravation of existing renal insufficiency was lessened, suggesting this technique should be used for procedures in which iodinated contrast nephrotoxicity is a concern. The importance of avoiding room air contamination is evident by our experience. Adoption of a closed system appears to be important in avoiding abdominal pain and the rare pancreatitis associated uniquely with this technique.

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