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Review Article

CARBON DIOXIDE IN VASCULAR IMAGING AND INTERVENTION

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Abstract

Angiography with iodinated contrast agents is bound up with the risks of contrast-induced nephrotoxicity and hypersensitivity, which led to the idea of using carbon dioxide (CO_2) gas as a negative contrast medium to eliminate these drawbacks. During the last decade, refinements and experiences have proved carbon dioxide digital subtraction angiography (CO_2-DSA) to be an accurate, safe, and clinically promising vascular imaging modality, with the advantages of no hypersensitivity and no nephrotoxicity as well as minimal patient discomfort. In this article, we have reviewed the history, physical and chemical aspects, techniques, and pathophysiologic changes with the use of CO_2-DSA as well as some clinical trials. Applications of CO_2 gas in vascular interventions and other imagings, and the advantages and limitations of using CO_2 gas in DSA are also discussed.

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Although angiography with iodinated contrast agents is the gold standard for examining vascular abnormalities, it carries some risk of contrast-induced nephrotoxicity and hypersensitivity. Acute renal dysfunction has been reported in 11.3% of patients undergoing arteriography, and in up to 62% of patients with a prior history of abnormal renal function (10, 23) (Table 1). Severe hypersensitivity associated with iodinated contrast agents occurs in approximately in 1 of 1 000 angiographic studies (1, 35) and death due to hypersensitivity is estimated to occur in between 1 of 12 000 and 1 of 75 000 procedures (1, 11). These drawbacks of the iodinated contrast agents have led to the search for other materials, among which carbon dioxide (CO_2) gas seems essentially to eliminate the previously known contrast medium-induced risks.

History

Early animal studies have demonstrated the relative safety of CO_2 versus air as a negative contrast medium in the coronary arteries, carotid arteries, and pulmonary circulation without untoward reactions (6–8, 13, 28). Use of CO_2 in the 1960's for detecting pericardial effusions demonstrated its minimal human toxicity (6). During the 1970's, some reports described the value of injecting CO_2 into the femoral arteries for treatment of severe ischemic disease of the lower extremities (2). In 1982, HAWKINS (15) reported favorable results using CO_2-DSA imaging of visceral and extremity circulations in 20 patients. Since then, several reports, concerning the techniques and pathophysiologic effects as well as clinical applications, have established the role of CO_2 gas as a negative contrast medium in angiography (7, 12, 26, 33, 34, 43). Today, CO_2-DSA has become a new and promising technique, which provides accurate and useful vascular images with minor risks (Figure).

Physical and chemical properties of CO_2

CO_2 is colorless, odorless, and noncombustible, and is usually in the form of gas over liquid when shipped in steel cylinders (Table 2). CO_2 gas is not

Table 1

Risk of iodinated contrast medium-induced nephrotoxicity based on serum creatinine level before angiography (modified from HALL *et al. (10))*

Serum creatinine level before angiography	Incidence of acute renal dysfunction after angiography
<1.2 mg/dl (106 µmol/l)	2%
1.3–1.9 mg/dl (115–168 µmol/l)	10%
>2.0 mg/dl (177 µmol/l)	62%

Normal values men 75–105 µmol/l, women 62–90 µmol/l.

Table 2

Physical and chemical properties of vascularly used CO_2 gas

Physical nature:	Colorless odorless noncombustible floats on blood
Chemical nature:	Low osmolality very low viscosity high compressibility highly pure (99.99%)

affected by heat until the temperature reaches about 2 000°C. Humans can breathe air containing less than 10% CO_2 (5, 12).

For vascular diagnostic use, an ideal gas should persist long enough for visualization of vessels and then return to solution quickly enough to prevent systemic hypotension, pulmonary hypertension, bradycardia, and alternating bouts of apnea and hyperpnea (29). CO_2 gas is 20 times more soluble in blood than in oxygen at 38°C and rapidly combines with blood buffers, which facilitates its transport to the lungs in the gaseous state for excretion (28, 34). Sterile, highly pure (99.99%) CO_2 is currently employed for vascular use. It is a nontoxic, highly compressible, very low viscosity (1/400 of iodinated contrast agent), easily injectable, and rapidly absorbable gas (27, 33, 34).

Pathophysiologic changes after CO_2 administration

Intravenous administration. Animal studies have demonstrated that injection of up to 8 cc/kg b.w. of CO_2 gas into either a peripheral vein or a pulmonary vein does not cause gas embolism or significant renal toxicity (15, 16, 28, 29). In an experimental evaluation of the cardiovascular and respiratory effect, investigators injected CO_2 gas into the femoral vein and/or the left ventricle of dogs (29). They found that after i.v. CO_2, right ventricular systolic pressure was elevated and acute systemic hypotension occurred for several minutes. These physiologic changes are due to the gas lodging in the fine pulmonary vessels after leaving the right ventricle, leading to an increase of the pulmonary peripheral resistance and pressure (29). The acute systemic hypotension after i.v. CO_2 is caused by reflexes from the distended right atrium and a decrease of blood flow through the lung to the left heart (29).

Intraarterial administration. Significant neurotoxicity or neurologic deficits were seen in 20 rats after direct injection of CO_2 gas into the carotid ar-

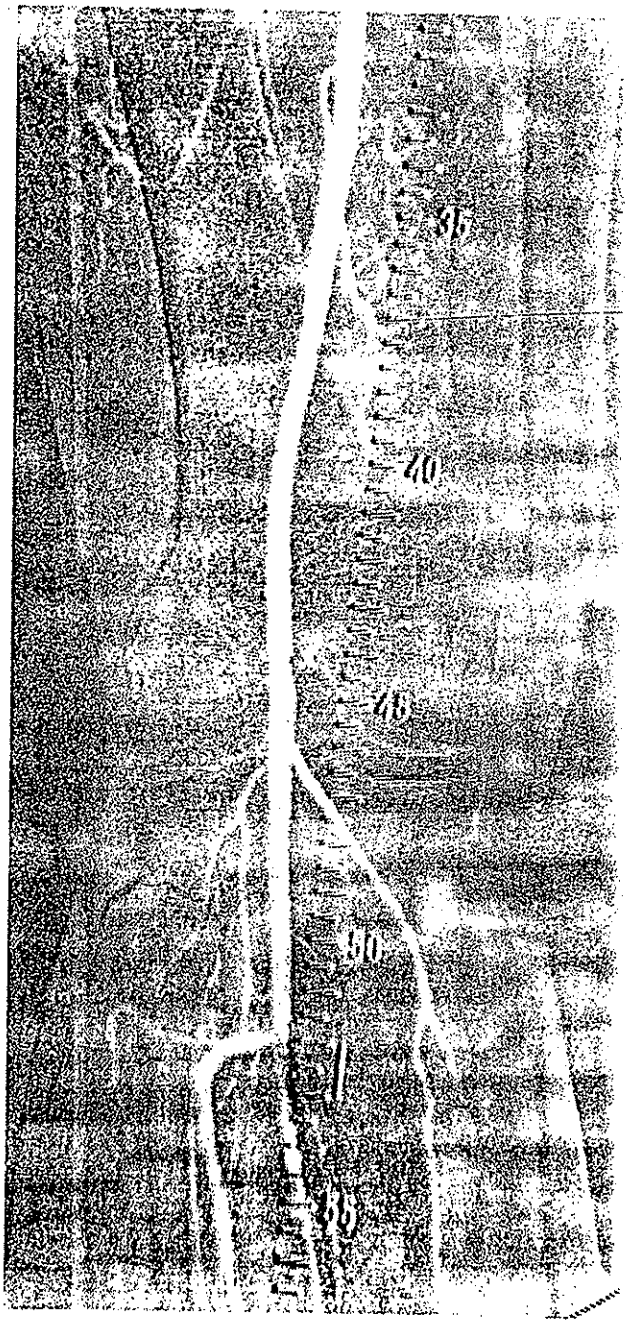

Figure. CO_2-DSA image. CO_2 gas as a negative contrast medium outlines the right popliteal artery.

teries (7). Histologic examination of rat brain tissues revealed multifocal ischemic infarction and disruption of the blood-brain barrier at the endothelial cell membrane (7). The quantity of infarcted cerebral tissue roughly paralleled the amount of CO_2 gas injected (34). However, contrary results have been reported of no neurologic deficit being observed in 14 dogs tested after direct carotid injection (36). Those authors claimed that CO_2 can be used for carotid angiography with a large margin of safety. The discrepancy between the results in rats and in dogs has not yet been clarified (7, 36).

Peripheral arterial injection of CO_2 gas for angiography is safer, because the CO_2 gas must pass at least 1 and usually 2 (including the lung) capillary beds before reaching the coronary or cerebral circulation, which reduces the likelihood of gas embolism (34). A recent study showed that CO_2 gas did not significantly alter the results of blood chemistry studies, complete blood counts, or blood gas studies (4).

One of the principal applications of CO_2 angiography is in patients with renal insufficiency. The effect on renal function of CO_2 gas injection into renal arteries has been carefully investigated in animals, by using radionuclide studies with ^{131}I Hippuran, ^{99}Tc dimercaptosuccinic acid, or/and Hippuran images (16, 17). The serum creatinine level has also been used as an indicator of renal function after CO_2-DSA (12). Nephrotoxicity is usually associated with functional changes, including a decrease in either renal blood flow or glomerular filtration rate, and structural changes in the tubules or glomeruli (17). Some reports have confirmed that although there is a mean decrease of 11.86% in renal blood flow immediately after the CO_2 injection, the flow returns to normal after 24 hours (17). Moreover, unlike ionic and nonionic contrast media, CO_2 gas requires less than 6 seconds to disappear from the major renal arteries and does not cause renal arterial endothelial changes (17).

Clinical trials

To date, at least 17 clinical studies on CO_2 angiography have been published, with approximately 1 000 intraarterial injections for detecting abdominal and peripheral vascular abnormalities, and several thousands of i.v. injections for detecting pericardial effusion (24, 29, 32, 42) (Table 3). Very satisfactory images were obtained in all but 2 cases in which CO_2 gas was used in transjugular intrahepatic portosystemic shunt (TIPS) procedures (31). These 2 failures included inadequate image contrast, a tendency to underestimate the caliber of the hepatic veins, and poor visualization in the region of brisk inflow from other vessels (19, 31).

Indications and contraindications

The main indications for using CO_2-DSA are cases where iodinated contrast media were contraindicated, including patients with renal insufficiency, contrast agent-related hypersensitivity, and congestive heart failure (9, 43) (Table 4). The main contraindication for using CO_2 gas is severe respiratory diseases. Currently, CO_2 gas cannot be used for examining coronary circulation, cerebral circulation, or the thoracic aorta.

Target sites

CO_2-DSA has been clinically performed in the abdominal aorta and in visceral, renal, and extremity

Table 3

Clinical applications of CO_2-DSA

Reference	Cases, n	Target sites	Complications, (n)
15	20	abdomen, extremity	mild abdominal pain (2)
26	9	abdomen, extremity	nausea (3), lower back pain (2)
20	40	extremity	–
39	41	kidney, liver, AV shunt	–
43	40	abdomen, extremity, kidney	tachypnea and tachycardia (1)
34	128	abdomen, extremity, kidney	–
12	24+(700)*	renal bypass	transient colitis and transient extremity mottling (2)*
31	14	TIPS	–
41	31	liver	–
27	12	portal venous system	mild abdominal pain (1)
4	10	abdomen, extremity	vagal episode (1)
9	32	dialysis access graft	transient seizure or loss of consciousness (3)
Total	973		15 (1.5%)

* The 700 cases with 2 complications are cited in reference (12).

Table 4

Indications and contraindications of CO_2-DSA

Indications:	1. renal insufficiency 2. contrast-related allergenic reactions 3. congestive heart failure
Contraindications:	1. severe respiratory diseases 2. examinations of coronary arteries, cerebral arteries, and thoracic aorta

arteries for detecting aneurysms, renovascular hypertension, and extremity ischemia (Table 3). CO_2 gas has also been used during the performance of TIPS (31), in the follow-up evaluation of renal artery bypass (12), for the detection of arterial–venous shunting (AV shunt), including arterial–portal shunting (AP shunt) (17, 38, 40, 41), and for examination of the portal vein (27). These studies showed that DSA with CO_2 provides an image quality comparable to that obtained with iodinated contrast media in the extremities (20), and superior to that obtained with iodinated contrast media in the portal venous system (27). Some authors have suggested that CO_2-DSA may be the best technique for the detection of vascular shuntings in patients with hepatocellular carcinoma, since CO_2 gas clearly reveals AV or AP shunts which cannot be observed in conventional angiography or DSA with iodinated contrast media (39, 41). Recently, some investigators used CO_2 gas to evaluate dialysis access grafts of the arm, and confirmed that estimation of the degree of venous anastomotic stenosis was higher with CO_2 gas than with ionic contrast media (9). Moreover, CO_2 gas bubbles have been injected intraarterially during dynamic contrast-enhanced ultrasound examination for detecting hepatocellular carcinoma and hepatic hyperplasia (14, 21, 22).

Equipment and techniques

Injection. Injection of CO_2 in CO_2-DSA can be performed either manually or automatically. For manual injection, 35 or 60 cm^3 plastic syringes are filled from a medical grade CO_2 gas tank after flushing with CO_2 4 to 6 times and then attached to the catheter (15, 26, 31, 33, 39, 41). A standard mechanical injector can be also used for CO_2 angiography, with two 3-way stopcocks which allow a closed system of CO_2 delivery (6). Two years ago, a prototype of a dedicated CO_2 gas arterial injector was developed at the University of Florida (12, 34). This injector is equipped with multiple check valves that ensure a controlled delivery of CO_2 gas volume and prevent the intraluminal "explosive effect" caused by preceding compression of the CO_2 gas.

Other investigators have created a CO_2 spray mini-injector and a personal computer-controlled CO_2 injector (33). By comparing these 2 injection systems in dogs, they concluded that both injectors provided good visualization of both large and small arteries. The spray mini-injector is said to be more appealing because it is easier to handle and does not require any preparation (33).

Catheters. As one of the advantages of using CO_2 gas in angiography, microcatheters can be used in the procedures, which minimizes vascular trauma (7, 14). Usually, the standard 1.00- to 1.67-mm straight or shepherd's crook catheters with an end-hole are used for examining femoral and popliteal as well as tibial vessels, while the 1.00- to 1.67-mm pigtail catheters with side-holes are used for abdominal and pelvic arteries (43). The catheters are introduced via either a femoral or an axillary artery puncture. Care must be taken to avoid introduction of atmospheric air during connection of the angiographic catheter to the CO_2 injector or syringe, and to ensure that the cylinder from which the CO_2 gas is loaded does not contain water. CO_2 gas combined with water can produce carbonic acid, with potential side effects in patients (34).

Injection volume and flow. When using a mechanical injector, 50 to 70 cc of CO_2 gas are usually delivered at a rate of 140 cc/s for aortic or renal arterial studies, while 20 to 40 cc at 40 cc/s are used for peripheral arteries (12, 34). When using a manual injector, CO_2 gas should be rapidly injected with total volume of 15 to 75 cc of CO_2 gas, at 15 to 35 cc/s flows for the aorta and larger arteries and at 12 to 16 cc/s flows for selective injections (15, 26, 39, 43). In TIPS procedures, very rapid, nearly instantaneous injection of a relative large volume of CO_2 gas is necessary to yield good image quality (31). For i.v. injection, CO_2 gas in doses of 100 to 200 cc has been used clinically without complications for detection of pericardial effusion (3, 24, 30, 32, 42).

Digital subtraction technique. By application of CO_2 gas and digital subtraction technique, high-quality arteriographic images can be obtained of the abdominal aorta and of visceral, renal and leg arteries. Usually, the imaging speed is set at 3 to 6 exposures/s (43), although up to 30 frames/s have been used in CO_2-DSA for special purposes (26). Occasionally, the quality of the final picture can be improved by using postprocessing with a "stacking" software program for compiling multiple digital images into a single composite image (12, 34).

Patient's position. Since CO_2 gas is extremely buoyant, the patient's position is critical during CO_2 angiography. If the area of interest is higher

Table 5

Choice of patient's position for target vessels during CO_2-DSA

.rget vessels	Patient's position
Lower extremity arteries	elevation of lower extremity
Aortic origin of renal arteries	prone or decubitus
Abdominal visceral arteries	supine

than the injection site, good perfusion of CO_2 gas can be achieved (12, 15). Elevation of the lower extremities increases flow of CO_2 gas into the distal segments of the arterial tree. The prone or decubitus position in renal angiography takes advantage of the posterior location and posterolateral aortic origin of the renal arteries. The supine position enhances imaging of the celiac, superior mesenteric, and inferior mesenteric arteries (17, 43) (Table 5).

Some authors have mentioned that if the kidney is vertically orientated, a period of approximately 2 minutes after injection is required for CO_2 gas to clear from the cortex of the kidney. In contrast, when the kidney is positioned horizontally, the CO_2 gas completely clears from the kidney in approximately 30 seconds (34). Therefore, these authors recommended returning the patient to a prone position between CO_2 injections immediately after filming in a lateral decubitus position.

Other considerations. After an overnight fast, the patients should be given an i.v. bolus injection of glucagon (0.5 mg) before CO_2-DSA to decrease the effects of bowel gas motion (12, 34). The glucagon dose can be repeated up to 3 times (26). If large volumes of CO_2 gas are required, pH and PCO_2 as well as PO_2 should be closely monitored during the whole procedure of CO_2-DSA, especially in patients with respiratory diseases (15).

Complications

No significant discomfort or complications occurred in any of the publications concerning CO_2-DSA. Insignificant complications included mild abdominal or lower back pain in 5 cases (15, 26, 27), nausea for up to 30 minutes in 3 cases (26), tachypnea and tachycardia in 1 case (43), a vagal episode in 1 case (4), transient ischemic colitis in 1 case after injecting a total volume of over 2000 cc of CO_2 gas into the aorta, and transient lower extremity mottling in 1 case after multiple injections of CO_2 gas during the lower extremity runoff evaluation (12). During CO_2 imaging of dialysis access grafts, 3 patients suffered from transient seizures or loss of consciousness due to CO_2 gas refluxing retrogradely into the brachial artery back to the subclavian and vertebral arteries (9). These mild complications occurred in about 1.5% of patients (Table 3). Some patients experienced a slight feeling of warmth in the abdomen or in the lower extremities, or a "pins and needles" sensation in the feet lasting 5 to 10 seconds (15, 26).

Application of CO_2 gas in vascular interventions and other imagings

Apart from its use as a negative contrast medium in angiography, CO_2 gas has been employed in some vascular interventional techniques and ultrasound (US) angiography.

Endovascular laser recanalization. In 1990, with an experimental circulation model, we investigated the possibility of CO_2 as a negative contrast medium for directly monitoring the laser recanalization procedure using a roentgen-ray positive sapphire probe (45). The whole recanalization progress was clearly visualized with digital fluoroscopy road mapping. Our previous study also demonstrated that CO_2 gas perfusion facilitated more effective and safer ablation of human atheromatous plaques than did saline perfusion, even though the latter is usually infused in clinical laser angioplasty when using the sapphire probes (45). The greater laser ablation efficiency was related to 1) better insulation by CO_2 gas than by saline, resulting in a stronger photothermal effect of laser heat-tissue interaction; 2) more effective removal of blood from the laser irradiation site by CO_2 gas perfusion; and 3) better penetration of direct laser light through CO_2 gas than through saline (37, 44).

Endovascular angioscopy. Angioscopy is an adjunctive diagnostic modality for differentiating thrombus, dissection, and atheroma, and for monitoring the response to therapy. However, angioscopy requires a blood-free field for adequate visibility. The compressibility and low viscosity of CO_2 enable easy delivery through the very small angioscopic flush channel. Therefore, some authors have investigated the possibility of using CO_2 gas as a flush medium for angioscopy (25, 46). They confirmed that CO_2 gas infusion provides adequate blood displacement for excellent quality angioscopic viewing, superior to that obtained with saline infusion. The reason for this is that CO_2 gas displaces rather than mixes with flowing blood. The flush volumes of CO_2 gas should not exceed 250 ml per injection at 5-min intervals (25).

TIPS procedure and atherectomy. Other authors have found that CO_2 gas facilitates the accurate stent placement during TIPS procedures by providing better visualization than that obtained with liquid media (31). The explanation may be that the CO_2 gas could be rapidly forced through the tiny

with its prominent advantages of no hypersensitivity, no nephrotoxicity and minimal patient discomfort. Thus, this new technique increases the utility of angiography in patients with vascular disease. Future refinements and experience in CO_2-DSA should result in wider and more varied applications, e.g. in the areas of renal transplantation, endovascular interventions, and combined diagnostic and therapeutic vascular procedures.

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