Review Article

CARBON DIOXIDE IN VASCULAR IMAGING AND INTERVENTION

XIAOMING YANG, HANNU MANNINEN and SEppo SOIMAKALLIO

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 (CO₂) gas as a negative contrast medium to eliminate these drawbacks. During the last decade, refinements and experiences have proved carbon dioxide digital subtraction angiography (CO₂-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 CO₂-DSA as well as some clinical trials. Applications of CO₂ gas in vascular interventions and other imagnings, and the advantages and limitations of using CO₂ gas in DSA are also discussed.

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 6.2% of patients with a prior history of abnormal renal function (10, 23) (Table 1). Severe hypersensitivity associated with iodinated contrast agents occurs in approximately 1 of 1000 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 (CO₂) gas seems essentially to eliminate the previously known contrast medium-induced risks.

and pulmonary circulation without untoward reactions (6–8, 13, 28). Use of CO₂ 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 CO₂ into the femoral arteries for treatment of severe ischemic disease of the lower extremities (2). In 1982, HAWKINS (15) reported favorable results using CO₂-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 CO₂ gas as a negative contrast medium in angiography (7, 12, 26, 33, 34, 43). Today, CO₂-DSA has become a new and promising technique, which provides accurate and useful vascular images with minor risks (Figure).

History

Early animal studies have demonstrated the relative safety of CO₂ versus air as a negative contrast medium in the coronary arteries, carotid arteries.

Physical and chemical properties of CO₂

CO₂ is colorless, odorless, and noncombustible, and is usually in the form of gas over liquid when shipped in steel cylinders (Table 2). CO₂ 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))

<table>
<thead>
<tr>
<th>Serum creatinine level before angiography</th>
<th>Incidence of acute renal dysfunction after angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.2 mg/dl (106 μmol/l)</td>
<td>2%</td>
</tr>
<tr>
<td>1.3–1.9 mg/dl (115–168 μmol/l)</td>
<td>10%</td>
</tr>
<tr>
<td>&gt;2.0 mg/dl (177 μmol/l)</td>
<td>62%</td>
</tr>
</tbody>
</table>

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

Table 2

Physical and chemical properties of vascularly used CO₂ gas

<table>
<thead>
<tr>
<th>Physical nature:</th>
<th>Colorless odorless noncombustible floats on blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical nature:</td>
<td>Low osmolality very low viscosity high compressibility highly pure (99.99%)</td>
</tr>
</tbody>
</table>

affected by heat until the temperature reaches about 2000°C. Humans can breathe air containing less than 10% CO₂ (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). CO₂ 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%) CO₂ 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 CO₂ administration

Intravenous administration. Animal studies have demonstrated that injection of up to 8 cc/kg b.w. of CO₂ 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 CO₂ gas into the femoral vein and/or the left ventricle of dogs (29). They found that after i.v. CO₂, 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. CO₂ is caused by reflexes from the distended right atrium and a decrease of blood flow through the lung to the left heart (29).

Intravascular administration. Significant neurotoxicity or neurologic deficits were seen in 20 rats after direct injection of CO₂ gas into the carotid ar-

Figure. CO₂-DSA image. CO₂ 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 CO₂ 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 CO₂ 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 CO₂ gas for angiography is safer, because the CO₂ 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 CO₂ 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 CO₂ angiography is in patients with renal insufficiency. The effect on renal function of CO₂ gas injection into renal arteries has been carefully investigated in animals, by using radionuclide studies with 131I Hippuran. 99mTc dimercaptosuccinic acid, or/and Hippuran images (16, 17). The serum creatinine level has also been used as an indicator of renal function after CO₂-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 CO₂ injection, the flow returns to normal after 24 hours (17). Moreover, unlike ionic and nonionic contrast media, CO₂ gas leaves within 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 CO₂ angiography have been published, with approximately 1000 intraaerial 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 CO₂ gas was used in transjugular intrhepatic 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 CO₂-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 CO₂ gas is severe respiratory diseases. Currently, CO₂ gas cannot be used for examining coronary circulation, cerebral circulation, or the thoracic aorta.

Target sites

CO₂-DSA has been clinically performed in the abdominal aorta and in visceral, renal, and extremity

Table 3

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases, n</th>
<th>Target sites</th>
<th>Complications, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>20</td>
<td>abdomen, extremity</td>
<td>mild abdominal pain (2)</td>
</tr>
<tr>
<td>26</td>
<td>29</td>
<td>abdomen, extremity</td>
<td>nausea (3), lower back pain (2)</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>extremity</td>
<td>-</td>
</tr>
<tr>
<td>39</td>
<td>41</td>
<td>kidney, liver, AV shunt</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>40</td>
<td>abdomen, extremity, kidney</td>
<td>tachypnea and tachycardia (1)</td>
</tr>
<tr>
<td>34</td>
<td>128</td>
<td>abdomen, extremity, kidney</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>24+700*</td>
<td>renal bypass</td>
<td>transient colitis and transient extremity mottling (2)*</td>
</tr>
<tr>
<td>31</td>
<td>14</td>
<td>TIPS</td>
<td>-</td>
</tr>
<tr>
<td>41</td>
<td>31</td>
<td>liver</td>
<td>mild abdominal pain (1)</td>
</tr>
<tr>
<td>27</td>
<td>12</td>
<td>portal venous system</td>
<td>vagal episode (1)</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>abdomen, extremity</td>
<td>transient seizure or loss of consciousness (3)</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>dialysis access graft</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>973</td>
<td>-</td>
<td>15 (1.54%)</td>
</tr>
</tbody>
</table>

* The 700 cases with 2 complications are cited in reference (12).
Table 4

Indications and contraindications of CO₂-DSA

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
<th>1. renal insufficiency</th>
<th>2. contrast-related allergic reactions</th>
<th>3. congestive heart failure</th>
<th>1. severe respiratory diseases</th>
<th>2. examinations of coronary arteries, cerebral arteries, and thoracic aorta</th>
</tr>
</thead>
</table>

arteries for detecting aneurysms, renovascular hypertension, and extremity ischemia (Table 3). CO₂ 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 CO₂ 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 CO₂-DSA may be the best technique for the detection of vascular shunts in patients with hepatocellular carcinoma, since CO₂ 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 CO₂ gas to evaluate dialysis access grafts of the arm, and confirmed that estimation of the degree of venous anastomotic stenosis was higher with CO₂ gas than with ionic contrast media (9). Moreover, CO₂ gas bubbles have been injected intraarterially during dynamic contrast-enhanced ultrasound examination for detecting hepatocellular carcinoma and hepatic hyperplasia (14, 21, 22).

Injection and techniques
Injection of CO₂ in CO₂-DSA can be performed either manually or automatically. For manual injection, 35 or 60 cm³ plastic syringes are filled from a medical grade CO₂ gas tank after flushing with CO₂ 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 CO₂ angiography, with two 3-way stopcocks which allow a closed system of CO₂ delivery (6). Two years ago, a prototype of a dedicated CO₂ 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 CO₂ gas volume and prevent the intraluminal “explosive effect” caused by preceding compression of the CO₂ gas.

Other investigators have created a CO₂ spray mini-injector and a personal computer-controlled CO₂ 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 CO₂ 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 CO₂ injector or syringe, and to ensure that the cylinder from which the CO₂ gas is loaded does not contain water. CO₂ 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 CO₂ 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, CO₂ gas should be rapidly injected with total volume of 15 to 75 cc of CO₂ 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 CO₂ gas is necessary to yield good image quality (31). For i.v. injection, CO₂ 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 CO₂ 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 CO₂-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 CO₂ gas is extremely buoyant, the patient’s position is critical during CO₂ angiography. If the area of interest is higher
### Table 5

<table>
<thead>
<tr>
<th>Target vessels</th>
<th>Patient's position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity arteries</td>
<td>elevation of lower extremity</td>
</tr>
<tr>
<td>Aortic origin of renal arteries</td>
<td>prone or decubitus</td>
</tr>
<tr>
<td>Abdominal visceral arteries</td>
<td>supine</td>
</tr>
</tbody>
</table>

than the injection site, good perfusion of CO₂ gas can be achieved (12, 15). Elevation of the lower extremities increases flow of CO₂ 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 CO₂ gas to clear from the cortex of the kidney. In contrast, when the kidney is positioned horizontally, the CO₂ gas completely clears from the kidney in approximately 30 seconds (34). Therefore, these authors recommended returning the patient to a prone position between CO₂ 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 CO₂-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 CO₂ gas are required, pH and PCO₂ as well as PO₂ should be closely monitored during the whole procedure of CO₂-DSA, especially in patients with respiratory diseases (15).

### Complications

No significant discomfort or complications occurred in any of the publications concerning CO₂-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 CO₂ gas into the aorta, and transient lower extremity mottling in 1 case after multiple injections of CO₂ gas during the lower extremity runoff evaluation (12). During CO₂ imaging of dialysis access grafts, 3 patients suffered from transient seizures or loss of consciousness due to CO₂ 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 CO₂ gas in vascular interventions and other imaging.**

Apart from its use as a negative contrast medium in angiography, CO₂ 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 CO₂ 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 CO₂ 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 CO₂ 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 CO₂ gas perfusion; and 3) better penetration of direct laser light through CO₂ 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 CO₂ enable easy delivery through the very small angioscopic flush channel. Therefore, some authors have investigated the possibility of using CO₂ gas as a flush medium for angioscopy (25, 46). They confirmed that CO₂ gas infusion provides adequate blood displacement for excellent quality angioscopic viewing, superior to that obtained with saline infusion. The reason for this is that CO₂ gas displaces rather than mixes with flowing blood. The flush volumes of CO₂ gas should not exceed 250 ml per injection at 5-min intervals (25).

**TIPS procedure and atherectomy.** Other authors have found that CO₂ 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 CO₂ gas could be rapidly forced through the tiny
REFERENCES


36. Shifrin E. G., Puch M. B., Verstandig A. G. et al.;


