

Review article

Carbon dioxide (CO₂) digital subtraction angiography: 26-year experience at the University of Florida

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Abstract. Although the vascular system is presently being imaged by multiple high technology modalities, contrast angiography continues to be the gold standard; however, severe complications rarely occur. During the last 25 years (in over 1400 patients), CO₂ has proven to be extremely safe (no allergy or renal failure). However, it is imperative to understand CO₂'s physical properties and potential dangers. Recently, CO₂ is being routinely utilized not only because of safety, but for detection of minute amounts of bleeding, better collateral filling, and for most interventional procedures since unlimited volumes of CO₂ can be injected between the catheter and guidewire. Presently, safe, reliable and "user-friendly" delivery systems are now commercially available. CO₂ DSA images are now nearly comparable to iodinated contrast, and improvement in DSA images are evolving, including "stacking" software.

Key words: Contrast – Carbon dioxide (CO₂) – Digital subtraction angiography

Introduction

Iodinated contrast angiography continues to be the gold standard for vascular imaging, although significant advances in ultrasound, CT, and MR imaging may supplement, or even replace contrast angiography in the future. Angiography with iodinated contrast is the imaging modality of choice for performing interventional vascular procedures, and frequently is used for nonvascular intervention. The newer nonionic contrast agents have demonstrated a lower overall complication rate; however, renal failure and occasionally fatalities still occur [1].

Carbon dioxide (CO₂) does not cause renal failure or allergic reactions. Because of its "low density," adequate

imaging was not feasible until the development of digital subtraction angiography (DSA). The DSA equipment now produces images comparable to iodinated contrast. Moreover, CO₂ also occasionally provides information that cannot be obtained with iodinated contrast. Because of carbon dioxide's buoyancy and low viscosity (a) collateral arteries are better demonstrated [2, 3], (b) arteriovenous shunting can be observed in tumors and arteriovenous (AV) malformations [2–4], (c) tumors that appear avascular with iodinated contrast may demonstrate vascularity with CO₂ [2, 3], (d) minute amounts of arterial bleeding can be visualized [5], and (e) the portal vein can be consistently visualized with either wedge or parenchymal injections of CO₂ [6, 7].

At our institution, CO₂ has become invaluable in interventional procedures, since unlimited volumes of CO₂ can be injected for long, complex procedures and its low viscosity permits injection between a guidewire and a catheter, obviating the need to remove the guidewire for test injections.

History

Carbon dioxide was first used in radiology to demonstrate retroperitoneal structures in 1914 [8]. It was used intravenously in the 1950s for the detection of pericardial effusion [9–11]. Bendib et al. reported 1600 cases in which 100–200 cc of CO₂ were injected in an antecubital vein for the detection of pericardial effusion without complications [12]. In the 1960s Hipona et al. introduced CO₂ for the evaluation of the inferior vena cava (IVC) as well as the hepatic veins [13], and Hallin used it for coronary endarterectomy [14]. It was also injected into the fetal peritoneal cavity for intrauterine transfusions [15].

In 1971 we began using CO₂ as an arterial contrast agent with cut-film subtraction techniques, delivering it with a hand syringe. The photographic subtraction techniques were time-consuming and, in general, suboptimal; yet, occasionally diagnostic studies were obtained.

With the acquisition of DSA in 1980, CO₂ imaging became much more reliable [16]. To date, we have used CO₂ in over 140 laboratory animals and in over 1400 patients, with diagnostic images being obtained in the majority of cases. Initially, our indications for CO₂ were renal failure and allergy. Currently, we are utilizing CO₂ in any area where iodinated contrast material is injected, with the exception of the arterial cerebral circulation.

Similarly, CO₂ "bubbles" have been used since the early 1970s for ultrasonic vascular imaging [17]. In 1978 Lantz et al. reported using CO₂ intra-arterially for the therapy of peripheral vascular disease [18]. We have used CO₂ for "clear" angioscopic viewing without the danger of fluid overload [2, 19]. Carbon dioxide has been routinely used in laparoscopy for many years [20].

Presently, several dedicated injectors have been developed [3, 21, 22], and a hand delivery system using a plastic bag reservoir is also commercially available [23].

Safety

Before CO₂ was used in the 1950s for pericardial effusion, multiple animal studies were obtained, which demonstrated only minimal transient changes in PCO₂, PO₂, blood pH, etc., even with large doses [10, 24, 25]. We recently have repeated these experiments because of recent interest in CO₂ venography. We examined 20 swine while in the supine position, injecting incrementally increasing doses of CO₂ (from 0.2 cc/kg up to 6.4 cc/kg) [26]. Imaging was obtained with DSA, and PO₂, PCO₂, blood pH, SaO₂, central, pulmonary, and systemic pressures were obtained at 1, 3, 5, and 10 min after increasing doses of CO₂. The animals were examined in the supine and both right and left lateral decubitus positions. At 0.8 cc/kg (equivalent of 80 cc/average-size patient), no significant changes in any of the parameters were noted in any position. There was a profound increase in pulmonary artery pressure and decrease in systolic pressure when a very large dose (6.4 cc/kg) was delivered, as would be expected. (All recovered from this massive dose, except one animal.) The study demonstrated that the animal could tolerate moderate IV doses in any position.

Although the swine study demonstrated the safety of injecting relatively large volumes of CO₂, clearly the most dangerous aspect of CO₂ imaging is the possibility of inadvertent delivery of massive amounts. In the 1970s, we injected 1000–2000 cc of CO₂ intravenously in three dogs, which promptly died apparently secondary to displacement of the blood from the right heart, vapor lock, and ischemia [3]. Aortography in ten dogs with injections of 50–100 cc of CO₂ demonstrated renal veins and IVC, which suggested either pre-capillary shunting or flow through the capillary bed [3]. Therefore, it is important not to inject excessive volumes into either arteries or veins, since in both cases the right heart can be flooded, resulting in the patient's death.

Another important safety issue is inadvertent injection of room air. A closed delivery system should elimi-

nate this potential lethal complication (see Delivery systems); however, we attempted to reduce this potential complication by fluoroscopically noting the rate of disappearance of the gas in the heart. To determine if pure CO₂ is being delivered, swine were placed in the left lateral decubitus position and 5 cc of CO₂ were delivered, which disappeared from the right atrium in 1–2 min. When room air was injected, the air remained for as long as 10 min. We recommend (because of two cases of transient cardiac arrest where 20 cc of room air was inadvertently injected) fluoroscopy of the pulmonary artery (PA) after the first IV injection, since CO₂ "traps" in the anterior PA in the supine position. If the gas remains in the pulmonary artery for over 20–30 s, the patient should be placed in the left lateral decubitus position and the CO₂ delivery system checked for any possible air contamination.

Although there are no reports of CO₂ causing renal failure or significant exacerbation of renal failure when only CO₂ was injected, we initiated a canine study and two retrospective human studies to address the issue of possible renal toxicity. Potential renal toxicity was evaluated in 14 canines in which selective injection of large amounts of CO₂ were made every 2 min with a dedicated injector [27]. Nuclear medicine studies were obtained pre- and post-CO₂ injections and histology [light, electron, and scanning electron microscopy (SEM)] was obtained 4 days after CO₂ was injected. There was a transient decrease in arterial flow, but no functional changes were noted. Scanning electron microscopy of the endothelium adjacent to the catheter tip was completely normal. There were no significant histological changes with the exception of one animal where minimal acute tubular necrosis was noted. In that animal, the kidney was in a nondependent position, directly above the catheter, predisposed for CO₂ trapping and possible ischemia. In our recent unpublished retrospective study of arteriography in 25 transplanted and 20 reimplanted renal arteries, no persistent increase in creatinine occurred with CO₂.

For renal transplant angiography, because of the anterior position of renal transplants, the amount of CO₂ should be limited and more time allowed between injections to permit absorption of potentially trapped CO₂.

The buoyancy of CO₂ also caused some concern for possible hepatic toxicity. A rabbit study demonstrated no significant hepatic toxicity [28]. Early in our experience, we were fearful that CO₂ cerebral injections or reflux into the cerebral circulation may cause neurotoxicity. To explore this possibility we injected very large volumes of CO₂ into the aortic arch, carotids, and vertebral arteries of canines, with head elevation of approximately 45° [15]. We noted no hemodynamic or neurological changes. Likewise, Shifrin et al. [29] with canines, and M. A. Bettman (pers. commun.) with rabbits also used cerebral injections of CO₂ without evidence of significant neurological, hemodynamic, or histological changes. Similarly, M. B. Plich has used CO₂ in hundreds of patients with congenital heart disease, etc., without complications (pers. commun.). Our earlier experience in rats showed that selective cerebral injections

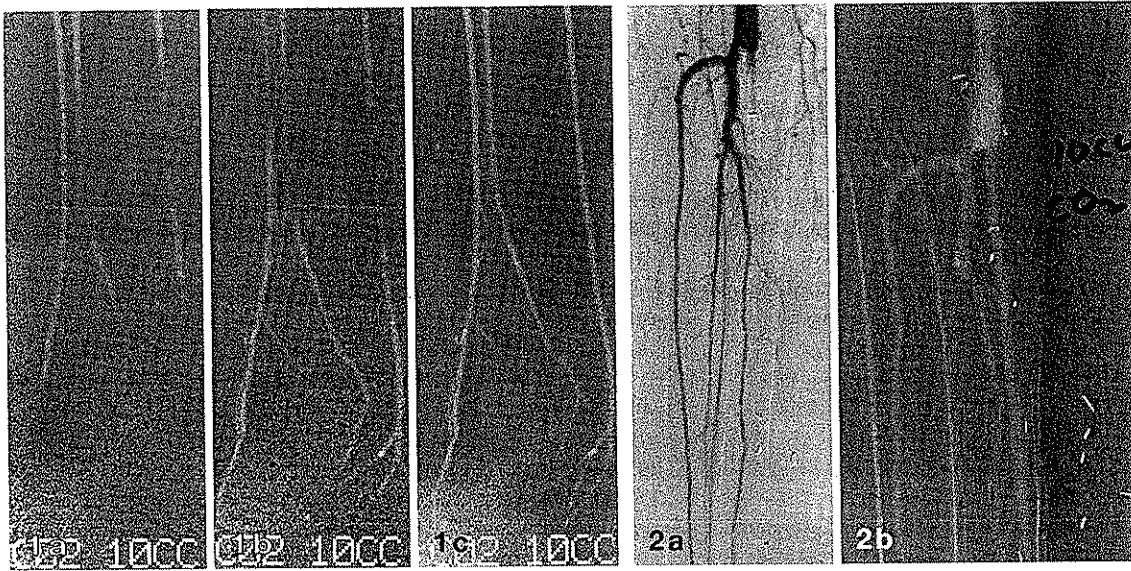


Fig. 1. Lower leg angiogram using stacking software adds **a, b** multiple segments of CO₂ into a **c** single diagnostic composite image

Fig. 2. a Arteriogram of popliteal-posterior tibial graft with 15 cc of nonionic contrast demonstrates pseudo-occlusion of the graft. **b** 10 cc of CO₂ with foot elevated 15° shows a widely patent graft. Ninety-five percent stenosis seen (not shown) at distal anastomosis caused static column of blood which filled only with the buoyant CO₂

of CO₂ caused strokes and disruption of the blood-brain barrier [30]. However, it is uncertain whether this was the result of excessive volume of gas (0.5–1.5 cc), explosive delivery, or air contamination. Recently, we have found that when the gas is transferred in a syringe from the CO₂ cylinder to the gas chromatography analysis unit that the sample is always contaminated with 1–2 cc of room air. This strongly suggested that the rats received a significant amount of room air since a closed system was not used.

Although the majority of animal studies have suggested that CO₂ may not be neurotoxic, we strongly feel that cerebral arterial circulation should not be exposed to CO₂ until primate studies verify the absence of neurotoxicity. Since the rat study demonstrated neurotoxicity, we examined ten dogs after 100 cc of CO₂ were injected into the aorta in the prone position to evaluate for possible spinal cord toxicity. No neurological deficits were noted by a canine neurologist.

Unique chemical and physical properties of CO₂

The high solubility of CO₂ (20 X more than O₂) permits safe intravascular injections. Carbonic anhydrase catalyzes CO₂ and H₂O to form carbonic acid, which rapidly dissociates into the H⁺ and bicarbonate (H⁺ → HCO₃⁻). Bicarbonate moves into the plasma where it quickly dissolves. The reverse occurs to release CO₂ gas into the alveoli [31]. It is not known if CO₂ (in the gaseous phase) enters the pulmonary capillaries during venous injec-

tions; however, if the partial pressure of the gas is high on the capillary side of the alveolus, the extremely diffusible CO₂ gas should very rapidly cross the membrane into the alveolus. We have performed large IVC injections in rats and pigs and selective pulmonary artery injections (ongoing study), which showed no gas in the pulmonary vein of a left atrium, suggesting that massive volumes (equivalent to 600 cc in humans) of CO₂ are eliminated by the lungs in one pass.

Even though CO₂ DSA images are frequently identical to those obtained with iodinated contrast, the physical properties obviously are different. Iodinated contrast medium mixes with blood, whereas CO₂ displaces blood. For iodinated contrast, the density of the image can be improved by either increasing the injection rate or the concentration of iodine. The contrast is then eliminated from the vascular system by glomerular filtration. Carbon dioxide is imaged by displacing the blood and the differential density of the gas compared with the surrounding tissues is recorded with DSA. If the blood is totally displaced, additional CO₂ will not improve the imaging, but will simply reflux into unwanted areas. When blood is totally displaced by CO₂ the image can only be improved by DSA enhancement.

The dilution of iodinated contrast by collateral flow frequently renders nondiagnostic studies. Carbon dioxide, on the contrary, forms small gas "packets," which cannot be diluted by collateral flow, permitting accurate imaging of the distal circulation if these "packets" are added together with DSA software ("stacking"; Fig. 1).

Buoyancy

The extreme buoyancy of CO₂ has both advantages and disadvantages. Position of the patient will greatly affect filling of various organs. Using the analogy of injecting helium into a hollow tree: (a) if the tree is inverted the distal branches will not fill; (b) if the tree is lying on its side the upper or nondependent branches will readily fill; or (c) if the tree is in a normal position, all the distal

branches will easily fill. During CO₂ injections elevating the area of interest always improves filling, and occasionally vessels that are not visualized with iodinated contrast are easily filled with CO₂ (Fig. 2). In conditions of slow flow (especially in the lower extremities), we elevate the extremities 15–20° with the distal vessels filling the majority of the time. If there is good arterial flow, it is not absolutely necessary to elevate the area of interest. In a retrospective study of 30 patients with significant atherosclerotic disease, we compared filling of the popliteal artery and the trifurcation with the legs flat and elevated [3]. The majority of these studies below the knee were nondiagnostic with the patients flat, and all were diagnostic with the feet elevated. Injecting CO₂ in a pulsatile flow model, Song et al. [32] has shown that the larger vessels fill much better with elevations of 15°.

Buoyancy is also important in vessels that originate from the aorta. The anterior vessels [celiac, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA)] always fill well, even with minimal amounts of CO₂ (10 cc with cross-table DSA imaging). The renal arteries are more difficult to fill since they course in a posterior (dependent) direction. The nephrogram is not normally seen since the buoyancy of CO₂ inhibits distal filling. In our animal nephrotoxicity study [29], we obtained a good nephrogram in a single dog when the kidney was vertically oriented. It has been speculated that when filling the distal vessels, CO₂ will not reach the capillary level because of its rapid dissolution [4]. We have noted that if an adequate amount of CO₂ is injected, the majority of the time the distal vessels are well filled. The low density of CO₂ does not produce as dense a stain as iodinated contrast; however, occasionally a faint capillary phase is seen. The left renal artery tends to originate more posteriorly, which frequently requires elevation of the left side. The renal artery like the celiac, SMA, and IMA can be seen more reliably if the left side is elevated and imaged with cross-table lateral DSA. If either renal artery is not adequately filled, selective injections are performed.

Although the buoyancy improves filling in many situations, it can also be a disadvantage. For example, if an inadequate amount of aortic CO₂ is delivered, it will layer anteriorly and the lumbar arteries will not be visualized. It can also potentially trap in nondependent areas, such as the celiac, SMA, IMA, and distal extremities (if they are elevated), etc. Likewise, during venous injections in the supine position, CO₂ has the property to trap in the anteriorly located pulmonary artery. Fortunately, CO₂ is safe since in most cases, if it does trap, it dissolves rapidly (usually within 10–20 s). However, if injections are made very rapidly not allowing time for dissolution, or the CO₂ traps in a large cavity [abdominal aortic aneurysm (AAA)], a “vapor lock” condition may ensue, which could possibly cause ischemia. We have experienced four potentially serious complications, which, we believe, were all secondary to trapping [33]. In a large abdominal aneurysm, ten injections of 200 cc of CO₂ resulted in severe diarrhea of 8-h dura-

tion. It was speculated that the CO₂ trapped in the distal aorta, and since the IMA is nondependent, the colon was ischemic during the duration of the CO₂ injections. In two additional patients, a CT obtained 24 h after the CO₂ study demonstrated a small amount of gas in the anterior convexity of the aneurysm. Since pure CO₂ is believed to always dissolve in 15–20 s, we speculated that because of differential partial pressures, the oxygen and nitrogen in the blood diffuses into the CO₂ bubble. The CO₂ dissolves, leaving the less soluble oxygen and nitrogen. We suggest that in any area where CO₂ traps that either the position should be changed to free the CO₂, or several minutes should elapse between injections to permit absorption. Fortunately, we have experienced no other complications related to trapping of CO₂ in abdominal aneurysms, etc.

Three transient cardiac arrests were also believed to be secondary to gas trapping. An inadvertent injection of a massive amount of CO₂ flooded the right heart and resulted in a transient vapor lock with bradycardia, hypotension, and elevated ST segments [33]. When the patient's position was changed from the supine to the left lateral decubitus, the parameters normalized. There were two other cases, in these instances using hand injection, where 20 cc of room air was believed to be inadvertently injected, resulting in a vapor lock in the right heart. Again, both of these patients recovered when they were placed in the left lateral decubitus position. We initially speculated that the CO₂ syringe might have been contaminated with room air. Cho [34] recently has shown that if the stopcock of a 20-cc syringe filled with CO₂ inadvertently remains open for 1 h, 68% of the volume is replaced by room air. This occurs secondary to the extreme diffusion of CO₂ and the difference in concentration (99.5%) of CO₂ in the syringe compared with 0.03% CO₂ in room air. The air rushes into the open stopcock at a rate of 0.2 cc/s. Because of this extremely rapid gas exchange, a gas “leak proof” closed system must be employed to prevent this potentially lethal complication.

Delivery systems

Although CO₂ has been used in radiology in the vascular systems since the early 1950s, difficulty in delivery has limited the number of investigators. The CO₂ is supplied in cast iron cylinders. The gas in the CO₂ cylinders are compressed to very high pressures (actually in a liquid state), many of which are several decades old and may contain water, rust, methane, etc. We strongly recommend using a disposable CO₂ cylinder which has been individually examined for purity (Custom Medical Devices, Gainesville, Fla.). The pressure is reduced with a gas regulator. If the regulator malfunctions, extreme volumes of CO₂ can be delivered very quickly. If a syringe is filled with the cylinder and regulator, the loaded volume is difficult to determine. If a 100-cc syringe is filled from the tank with the regulator set at 44.1 mmHg, the syringe will contain 400 instead of 100 cc. The regulator's indicator shows pressure above 1 atmosphere

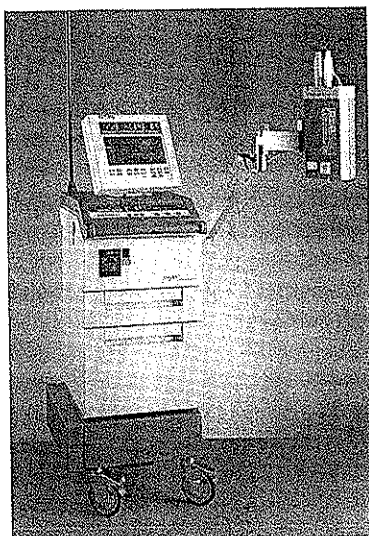


Fig. 3. Dedicated CO₂ injector with incorporated patient monitor, automated saline flush system, and an optional liquid contrast delivery system

(14.7 mmHg); therefore, $14.7 + 44.1 = 4$ atmospheres; $4 \times 100 \text{ cc} = 400 \text{ cc}$. If the stopcock is opened to the atmosphere, the excess amount of CO₂ will escape and equilibrate to one atmosphere; thus, the syringe will contain only 100 cc.

By bench testing, we found that when delivering 100 cc through a 4-F catheter over 4 s, 95 % of the CO₂ gas is delivered in the last 0.5 s [3]. If the syringe is filled with the regulator set at 44.1 psi, the syringe now contains 400 cc and is delivered "explosively" at a rate of over 760 cc/s. We believe that the mechanism for explosive delivery is compression of CO₂ in the catheter and syringe against the resistance generated by clearing the more viscous saline or blood from the catheter. At the instant the liquid exits the catheter the compressed gas rapidly expands, resulting in inconsistent "explosive" delivery (increased discomfort and potential reflux into unwanted area). After the liquid is removed, the gas flows relatively unimpeded through the catheter. Therefore, clearing the catheter of fluid before the bolus is injected will result in a controlled nonexplosive delivery.

Initially, we delivered CO₂ by hand with a 50-cc syringe. We later utilized a standard mechanical angiographic injector, which proved to be more consistent but still resulted in explosive delivery. During the past 15 years, we designed four different hand-held and dedicated computer injectors, which were safer but still resulted in inconsistent, "explosive" delivery. Other injectors have been developed in Europe [21, 22]. A dedicated computer-controlled CO₂ injector (AngioDynamics, Glens Falls, N. Y.) which safely delivers CO₂ in a controlled, nonexplosive manner is now commercially available (Fig. 3) in most countries other than the United States (because of Food and Drug Administration constraints).

The latest commercially available injector purges the saline from the catheter before the bolus of CO₂ is in-

jected. It also incorporates four internal transducers and one external transducer, which aborts the injection if there are any high- or low-pressure events and prevents delivery of excessive volumes. This is a fail-safe closed system with special rubber O-ring fittings which eliminates any possibility of air contamination. The injector has a high-speed valve, which injects more CO₂ during systole and less during diastole to deliver CO₂ in a more uniform manner. It also includes an automated closed saline system with a submicron filter and multiple one-way check valves to prevent reflux of blood into the system. The saline flushing stops during CO₂ injection and automatically resumes at the termination of injection. The in-line transducer provides constant intravascular pressure monitoring and ensures accurate delivery during systole and diastole. The injection rates and total volumes are programmed into the computer, which delivers the precise volume of CO₂ for each specific catheter. A mass flow meter measures the flow rates and volumes and displays them on a liquid crystal screen at the termination of each injection. The injector has been used in over 1000 cases in the United States, Europe, and Australia.

Since the dedicated injector is not approved by the U.S. Food and Drug Administration, we attempted to develop a hand delivery system, which incorporated principles learned from the dedicated injector.

A near fatal complication occurred during a hand injection when at least 1000 cc of CO₂ were inadvertently delivered into the venous system when the CO₂ cylinder was connected to the catheter. Fortunately, because of the extreme solubility of the gas, the patient recovered uneventfully. However, this prompted the development of a plastic bag which is coupled to a fluid management system (AngioDynamics, Glens Falls, N. Y.) with multiple one-way "check" valves. The 1500-cc bag (pressure atmosphere = 760 mmHg) contains less than 1500 cc, if the bag remains flaccid (pressure of 1 atmosphere = 14.7 psi = 760 mmHg). The CO₂ must be aspirated from the bag, which incrementally collapses. The multiple "check" valves permit rapid delivery and prevents reflux of blood into the catheter after the catheter has been cleared with CO₂. The plastic bag system eliminates the possibility of delivering excessive volumes; however, there is still a danger of air contamination. This occurred in two cases, one in which 20 cc were injected during a TIPS procedure, resulting in transient cardiac arrests. We know of another similar case where one of the ports was left open and air was aspirated.

Use of small catheters

Although we have used 3- and 4-F catheters for over 20 years with iodinated contrast, the extremely low viscosity of CO₂ permits easy delivery at very high flow rates and volumes. Flow rates of over 75 cc/s are possible with 3-F catheters or fine needles. Carbon dioxide can be used with any catheter; however, the "halo" catheter (AngioDynamics, Glens Falls, N. Y.; a spiral config-

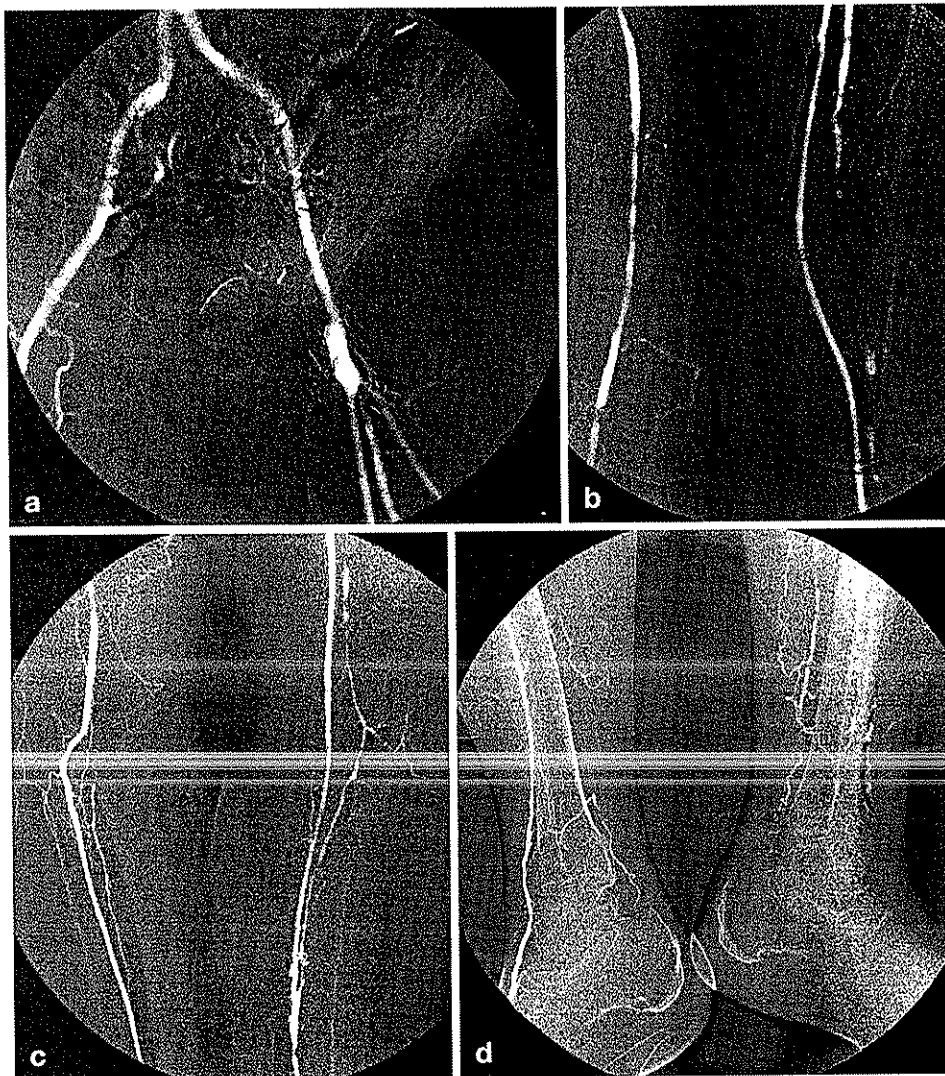


Fig. 4a-d. Runoff arteriogram with 4-F catheter. **a** Patent graft with 95% stenosis at origin of superficial femoral artery. **b** 90% stenosis of distal right superficial femoral artery. **c** Single vessel runoff on right (anterior tibial artery) with patent graft to left posterior tibial artery. **d** Bilateral feet (40 cc of CO₂) demonstrating good dorsalis pedis artery on right with no distal vessels seen in left foot. Selective left common femoral artery with 30 cc of CO₂ and nitroglycerin demonstrated more unnamed collaterals in foot, but no major arteries

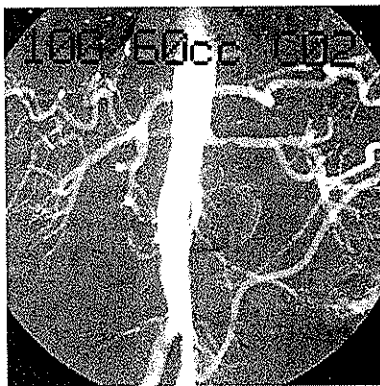


Fig. 5. Aortogram with 60 cc of CO₂ obtained after runoff demonstrates patent right renal stent, 30% stenosis of proximal left renal artery, and large artery of Drummond

uration catheter with side holes placed along the inner curvature of the spiral) will deliver CO₂ as a bolus without "breakup" into segments [32]. A pigtail catheter tends to cause CO₂ to "breakup" into more segments. We frequently use a 4-F SOS Omni (AngioDynamics, Glens Falls, N. Y.), which functions as a pigtail catheter; however, it has the advantage of easily catheterizing the contralateral iliac artery.

Although the halo catheter seems to deliver CO₂ more homogeneously, it was developed to reduce possible intimal damage. We demonstrated the safety of CO₂ jets by comparing iodinated contrast to CO₂ in a delicate gelatin block flow model. The CO₂ produced no damage at an injection rate of 200 cc/s, whereas iodinated contrast caused severe damage to the model at 12 cc/s with a pigtail catheter. Although CO₂ injections are extremely safe, in the event that an endhole catheter would inadvertently become wedged, we prefer placing a single small side hole near the tip of the catheter to serve as a safety valve.

Suggested injection procedures and rates for safe and reliable delivery

1. Use a closed system; however, never attach the CO₂ cylinder to the catheter.
2. Initially inject small volumes of CO₂. Nonexplosive delivery produces little or no sensation, and therefore less motion. Increase volume appropriately according to size of vessel.

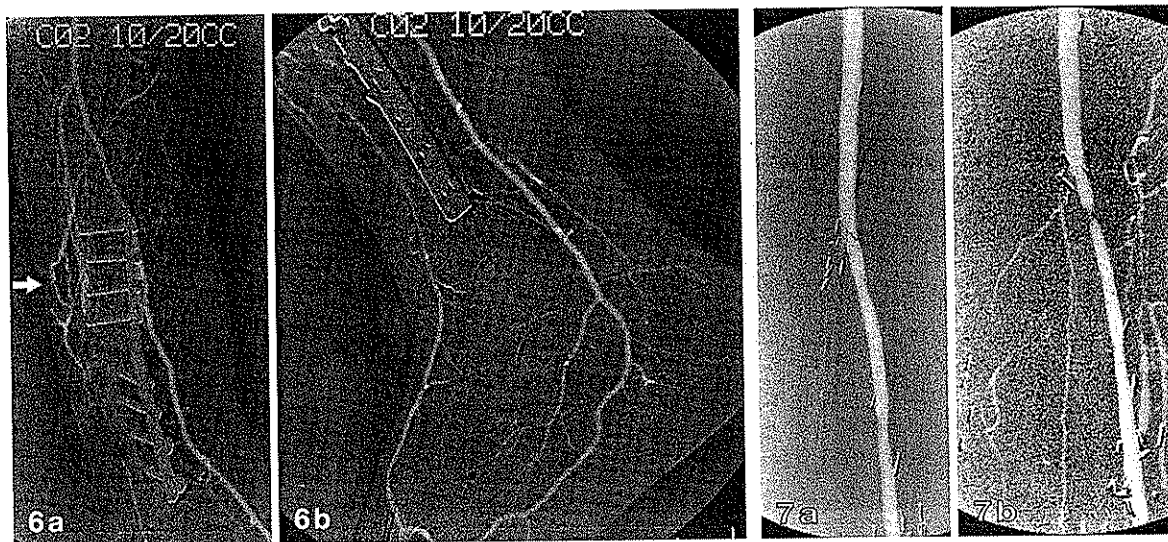


Fig. 6a, b. Common iliac injection of 20 cc of CO₂ demonstrating occlusion of anterior tibial artery with good filling of the pedal arteries (arrow). Imaging with Toshiba 1024 × 1024 with 60-ms exposure

Fig. 7a, b. Patient status post femoral-posterior tibial graft with claudication and Doppler findings suggesting high-grade graft stenosis. **a** Thigh angiogram with 10 cc nonionic contrast demonstrates an apparently normal graft. **b** CO₂ (10 cc) angiogram with 4-F catheter placed at aortic bifurcation demonstrates 80% graft stenosis. Note filling of native vessels. Patient became asymptomatic after balloon angioplasty

3. Wait 2–3 min between injections to allow potentially trapped CO₂ to dissolve.
4. If the area of interest is located below the injection site (lower), position area of interest above catheter (i.e., renals; elevate right and left flank). In poor flow condition elevate feet 10–15°.
5. Use a catheter with at least one sidehole for safety.

The following is suggested for aortogram and runoff studies:

1. Perform runoff first to allow patient to become acclimated to CO₂ injections.
2. Inject 20–40 cc/s for total of 20–40 cc with catheter above aortic bifurcation (Fig. 4).
 - a. Film pelvis, both thighs, knees, lower legs, and feet with above flow rates. Lower legs and feet may require higher volumes (60 cc). Also, if stacking is not available longer injections cause less “breakup” of CO₂.
 - b. Aortogram requires higher injection rates to displace blood (100–120 cc/s for a total of 50–60 cc; Fig. 5). Lower rates and volume (60 cc/s for a total of 30–40 cc) may be adequate and cause less sensation and nausea.
 - c. If filling below the knee is suboptimal, do selective common femoral artery injections: maneuver catheter into contralateral femoral artery (“over-the-hill”); retract catheter in ipsilateral common femoral artery; or place a 3- or 4-F catheter in contralateral common femoral artery. Elevate extremity 10–15° and inject 100–150 g of nitroglycerin intra-arterially before injection

CO₂; selective injections of celiac, renal, SMA 10–20 cc/s for a total of 10–50 cc/s.

Venous injections

Injection rates for superior vena cava and inferior vena cava are 40–80 cc/s for a total of 20–60 cc. For peripheral veins inject 5–10 cc/s for a total of 20–40 cc. Always image the pulmonary artery immediately after the first injection to rule out air contamination. Pure CO₂ should dissolve in 15–30 s.

CO₂ imaging

Although imaging was adequate with the very first commercially available DSA unit (Philips DVI 1, 256 × 512 matrix, Philips, Eindhoven, The Netherlands), the newer 1024 × 1024 units produce images with considerably improved resolution. Unfortunately, there has been little or no effort directed toward optimizing imaging for this low-density contrast. Presently, the equipment is fine-tuned for only iodinated contrast. Recently, when using a Toshiba unit (Toshiba Corp, Nasu, Japan), we increased the exposure time from 10 to 60 ms and have noted a considerable improvement in contrast. Many of the images (including small distal vessels) are comparable with iodinated contrast (Fig. 6).

In the past, if a segment of CO₂ demonstrated poor contrast, it was felt that an inadequate amount of CO₂ was delivered. Since CO₂ does not mix with blood and will not become diluted, if a small bubble of CO₂ is poorly seen it is not due to poor delivery, but to poor imaging. We would recommend that if the imaging is poor, the manufacturer’s applications person should be contacted and modify the exposure times, acquisition maps, etc.

Another significant advance has been the addition of the “stacking” program [3]. This is similar to maximum opacification; however, rather than adding the positive pixels, multiple negative pixels are integrated into a single-composite image. If the CO₂ “fragments” or a small

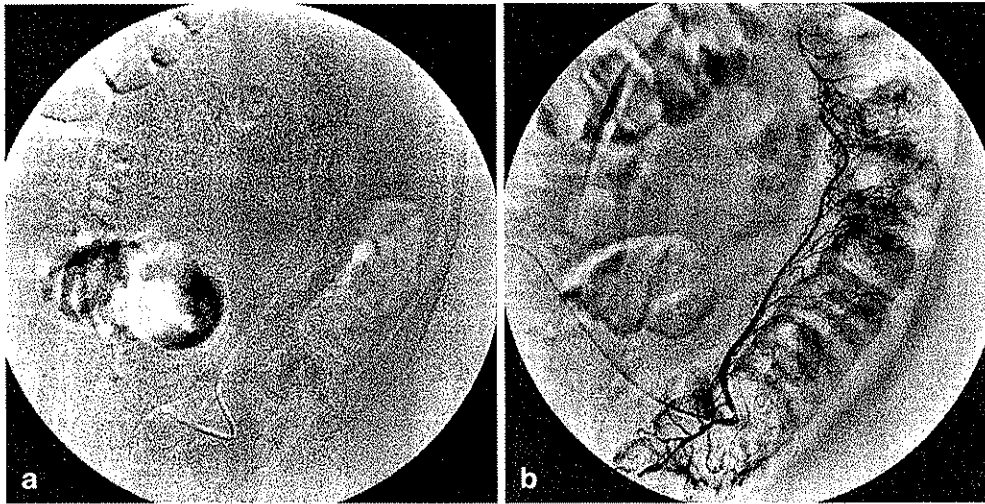


Fig. 8. **a** Bleeding diverticulum of sigmoid colon demonstrated after 10 cc of CO₂ injected via 4-F catheter placed in distal inferior mesenteric artery. **b** DSA and cut film with nonionic contrast failed to demonstrate bleeding site

amount of CO₂ is delivered, the segments can be added together to produce a single diagnostic film. This has reduced injection rates in the lower extremities from 30 cc/s for a total of 90 cc/s to as low as 5–10 cc/s for a total of 10–20 cc/s. Injecting small amounts of CO₂ nonexplosively produces no sensation, thus decreasing the motion difficulties inherent to DSA.

Diagnostic efficacy of CO₂ DSA

Multiple publications have demonstrated the diagnostic efficacy of CO₂ [4–7, 35–43]. Since the physical properties of CO₂ gas are quite different from liquid contrast, a learning curve is usually required for proper interpretation.

If the blood is totally displaced from the artery and imaging is optimal (no motion, etc.), interpretation of anatomy and lesions is identical to iodinated contrast.

If the vessel is only partially filled (top only) a mild stenosis may appear high grade and a lesion or a vessel originating from the dependent portion may be completely missed. This occurs primarily in large vessels such as the aorta or IVC. Several authors report overestimation of stenosis [6, 39]. If an inadequate amount of CO₂ is injected, overestimation of the stenosis does occur. However, we believe that when CO₂ is properly delivered it may detect more lesions than iodinated contrast (Fig. 7).

In a larger vessel, or even in medium-size vessels when an inadequate amount of CO₂ is delivered, cross-table lateral or oblique imaging should be obtained, the position of the patient should be changed to fill another segment of the artery, and the catheter should be placed as close as possible to the lesion to improve the filling.

Our surgeons (independent of radiology) retrospectively reviewed 115 patients who underwent CO₂ angiography for evaluation of peripheral vascular disease [41]. Carbon dioxide alone produced correct diagnoses in 92 % of the cases. Carbon dioxide plus a small amount of iodinated contrast resulted in the correct diagnosis in 100 % of cases. Eighty-eight of these patients had either

allergy or increased creatinine. No increase in creatinine was noted in any of the patients who presented with renal insufficiency. At that time, the failures in the study were primarily due to suboptimal filling below the trifurcation. With improvements in imaging and delivery and the addition of vasodilators (100–150 g nitroglycerin), presently the feet can be imaged in over 95 % of the patients. We have also noted that because of its low viscosity and buoyancy, CO₂ frequently will fill distal vessels when iodinated contrast material does not. In cases with Leriche's syndrome or similar occlusions, iodinated contrast may be diluted by collateral flow and result in nondiagnostic images. Since CO₂ is nonviscous and does not mix with blood, it easily crosses small collaterals, fills distal vessels without dilution, and by using "stacking" diagnostic images can be obtained.

If one area of the CO₂ study fails due to patient motion or buoyancy of the gas, etc., small amounts of iodinated contrast can be used to supplement the diagnosis. Carbon dioxide and iodinated contrast should be complementary, since they each have different properties. If only a small amount of iodinated contrast is required in patients with renal failure, the risk of renal damage is only slightly increased.

Detection of arterial bleeding

Recently, detection of arterial bleeding has become a very important additional indication for CO₂ [5, 44–46]. In a relatively large number of patients, CO₂ has dramatically demonstrated bleeding sites not seen with iodinated contrast (Fig. 8). Hashimoto has used CO₂ in 62 patients, demonstrating the bleeding site in 52 % of cases with CO₂ and only 20 % with iodinated contrast material [45]. It is believed that the mechanism for this improved visualization is primarily due to the low viscosity, which permits the CO₂ to readily flow through the small tear in an artery as compared with the very viscous iodinated contrast. In addition, CO₂ is compressed in the artery and when it flows into the lower pressure periarterial location, the CO₂ expands. Since the CO₂ is

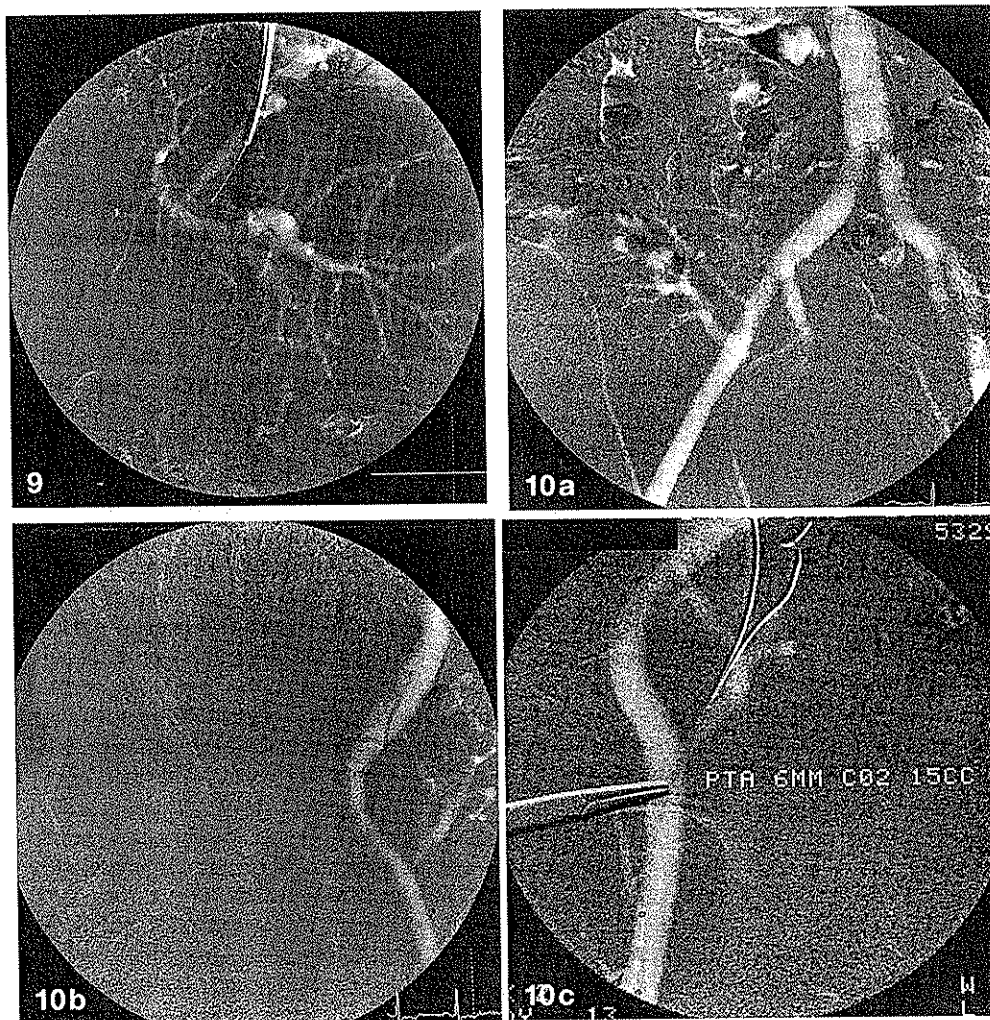


Fig. 9. Portogram obtained during TIPS procedure by injecting 20 cc CO₂ through a transjugular 21-gauge needle embedded in the liver parenchyma

Fig. 10a-c. A 50-year-old renal transplant patient with renal failure and hypertension. **a** Frontal projection of pelvis (20 cc of CO₂) demonstrates apparently normal transplant arterial anatomy. **b** After six separate CO₂ injections, a steep oblique projection demonstrates stenosis of the anastomosis to the external iliac artery. Because of early renal bifurcation, two guidewires were placed across the stenosis and the lesion was balloon dilated. **c** Injection between guidewire and angioplasty catheter shows no residual stenosis

not diluted by blood in the extravasated area, it is more readily imaged as compared with iodinated contrast, which may be diluted to the extent that it is not imaged. The lack of capillary staining with CO₂ is extremely important in organs that densely stain with iodinated contrast (such as stomach, spleen, kidneys, etc.), since the stain may obscure the bleeding site.

We also recommend using both CO₂ and iodinated contrast in trauma patients, even though the iodinated contrast demonstrates a bleeding site. In several cases we have seen no bleeding with iodinated contrast and multiple bleeding sites with CO₂. If "missed" bleeding arteries are not embolized, then life-threatening bleeding may recur. Also, after the bleeding site is identified, CO₂ is helpful in adequately demonstrating the anatomy if small tracker-type catheters are used. Hawkins et al. [46] and Hashimoto [45] have noted that after embolization with coils and gelfoam, etc., the bleeding site may still be seen with CO₂, but not with iodinated contrast. After suspected "complete" embolization, we usually wait 20-30 min and repeat the CO₂ injection. Usually with more clotting, CO₂ will not flow through the occluded artery.

Low viscosity improving AV shunting

In cases of hypernephromas and hepatomas, we have seen immediate shunting through the tumor into the renal or portal veins, respectively. In hypernephromas, we frequently see immediate filling of the IVC, which is helpful in evaluating tumor thrombus invading the IVC. Takeda et al. [4] originally described shunting into the portal veins of patients with liver tumors. Miyazono et al. [43] reported 12 cases with good visualization of the portal vein, injecting 25-35 ml of CO₂ into the hepatic artery with a 3-F microcatheter. It is of interest that only eight patients had hepatocellular carcinoma, two had metastatic disease, one gallbladder cancer, and one cirrhosis. The authors felt that the shunting occurred through the anastomosis between the hepatic artery and portal vein known as the peribiliary or periportal plexus, which has been demonstrated in rats. We have seen shunting into the portal vein with tumors; however, we have only occasionally seen the portal vein in patients without hepatocellular carcinoma. With arterial injection of CO₂, visualization of the portal vein may occur more often with a more "explosive type" delivery.

We have reliably imaged the portal vein with intraparenchymal injections of CO₂ (usually 20 cc in 0.5 s) for

(a) TIPS procedure [7], (b) embolization of the portal vein, (c) portal vein sampling, or (d) as an adjunct to percutaneous cholangiography. We have also visualized the portal vein by advancing a 25-gauge needle into the spleen and injecting 20 cc of CO₂ [47].

Multiple AV fistulas secondary to trauma, and occasional shunting in atherosclerotic peripheral vascular disease, have been noted that were not seen with iodinated contrast. M. Maynar (pers. commun.) has seen AV shunting in many patients undergoing high-volume CO₂ distal "runoff" studies.

CO₂ for TIPS

For TIPS procedures, CO₂ has proven to be more helpful than iodinated contrast [6, 7]. We prefer using a fine-needle system, placing the 21-gauge needle into the hepatic parenchyma in the area where the portal vein should be located. With the use of a Tuohy-Borst fitting and a 20-cc syringe, 20 cc of CO₂ are forcefully injected through the 21-gauge needle into the hepatic sinusoids with immediate opacification of the portal system (Fig. 9). Multiple injections in several projections will verify the relative position of the needle to the portal target. After the needle enters the suspected target and the 0.018-inch guidewire is advanced, the Tuohy-Borst fitting is tightened and multiple injections of 20 cc of CO₂ are made between the guidewire and the needle in various projections to ascertain the exact entry point of the needle. If the guidewire is in an unwanted target (peritoneal cavity, bile duct, or hepatic artery), the fine needle is simply removed and repeat passes are made. After a safe portal entry site is verified, the tract between the portal vein and the hepatic vein can be tested with the Tuohy-Borst fitting by retracting the needle slowly and first injecting CO₂, and "double checking" by injecting iodinated contrast using a 1-cc syringe. After the tract is dilated, injection of CO₂ between the guidewire and the stent catheter ascertains the location of the stent before it is deployed. Previously, Hawkins et al. [7] and Rees et al. [6], have made wedged hepatic venous injections to obtain a portogram; however, we have seen three cases where extravasation into the peritoneal cavity occurred. Semba et al. [48] report one fatality and Rees et al. [6] report a complication with the wedged position. We have injected CO₂ through a fine needle into the liver parenchyma in a large number of cases without complications.

Interventional procedures

There are two major advantages of CO₂ for interventional procedures as opposed to iodinated contrast agents [3, 49]. Since we believe the CO₂ is eliminated by the lungs in a single pass, unlimited quantities of CO₂ can be injected. This is particularly helpful during long, complex interventional cases where a large amount of contrast agent may be required. In canines, 100 cc of CO₂ can be injected every minute for hours

without adverse effects [24]. In patients, if several minutes are allowed between injections, there is no maximum total dose of CO₂.

The second important property of CO₂ is its low viscosity which permits injections between the guidewire and the catheter or between the needle and the guidewire. This is extremely helpful during the majority of complex procedures because the guidewire never has to be removed. For example, in renal PTA (Fig. 10), CO₂ will verify the intraluminal location of the guidewire after the stenosis has been crossed. Also, CO₂ (10–30 cc) can be injected between the PTA catheter and the guidewire, and the CO₂ will reflux into the aorta to verify the correct location before the balloon is inflated. Iodinated contrast can be injected with a tuberculin syringe. However, because of the low volume, only the distal branches will be seen. After the stenosis is dilated, the PTA catheter can be retracted to the origin of the renal artery and CO₂ can be injected with the wire remaining across the lesion. This ability to inject between the guidewire and the catheter has been extremely helpful for the placement of renal stents. Again, as with renal angioplasty, multiple injections can be made to accurately place the renal stent. Carbon dioxide is particularly helpful in distal extremity angioplasty, since with below-the-trifurcation angioplasties and "over-the-hill" angioplasties CO₂ can be injected between the guidewire and the catheter, producing excellent images without using an excessive amount of contrast or requiring additional catheter or sheath placement, etc.

High pressure is required to inject the CO₂ between the guidewire and the catheter. If a 1-cc syringe is used, the CO₂ will simply compress. At least a 20-cc syringe is required. Also, because CO₂ compresses, it may not exit from the catheter for 5–10 s. After the first injection, subsequent injections are much easier to deliver with minimal delay.

Carbon dioxide has been extremely helpful for embolization, since large volumes can be injected through microcatheters, and we have also noted that more tumor vessels fill with CO₂ than with iodinated contrast, thus making the embolization more complete with CO₂ imaging.

More recently, CO₂ has been used for venography [26, 50, 51]. It is useful in the venous system to place Hickman catheters, translumbar Hickman catheters, IVC filters, balloon dilatation, and stent placement of the subclavian vein [44].

For venous injections, CO₂ fills collaterals better, is not diluted by other collaterals, and flows much faster than iodinated contrast. We use CO₂ very cautiously in dialysis fistula, since Ehrman et al. [39] reported several cases of seizures, etc., when either CO₂ or air-contaminated gas apparently refluxed into the cerebral circulation. If CO₂ is delivered nonexplosively in minimal volumes, we feel it is safe to use on the venous side of the dialysis grafts.

We also use CO₂ for nonvascular procedures (biliary, urinary, abscess, fistula). For nephrostomy we inject 10–20 cc of CO₂ into the renal pelvis with a 25-gauge needle [52]. With the patient in the prone position the CO₂

"floats" into the posterior calyx, which creates an easy target. We also use a blunt puncture needle since it pushes arteries aside and is less likely to cause bleeding.

Contraindications

Because of the possibility of neurotoxicity [28], the cerebral arterial circulation should never be exposed to CO₂.

Relative contraindications

Carbon dioxide should not be used in the venous circulation or arterially if a large AV fistula is suspected in the presence of a right-to-left intracardiac shunt. If this exists and a CO₂ venous examination is absolutely necessary, small amounts of CO₂ may be safe if the patient is placed in the left lateral decubitus position allowing CO₂ to trap and dissolve in the right atrium.

Carbon dioxide should not be used with nitrous oxide anesthesia [53]. Nitrous oxide which is saturated in the soft tissues will diffuse into the CO₂ bubble, increase its volume, and dilute the CO₂. Therefore, the potential exists for routine safe volumes to be more prone to cause a vapor lock phenomena.

The present authors and others [6] have used CO₂ cautiously in patients with severe chronic obstructive pulmonary disease (COPD); however, we recommend decreasing the volume per injection and increasing the interval between injections. We have obtained blood samples in at least ten patients with COPD after multiple injections (total volume 3–500 cc), with only one patient demonstrating a slight decrease in pH. In these patients we normally inject less than 70 cc every 4–5 min, which is minimal when compared with the normal metabolic release of 200 cc per minute in a resting adult. With exercise, the amount can increase 4–5 times and is rapidly eliminated with increased ventilation. PCO₂ remains unchanged. Carbon dioxide should not be a problem unless a patient has severe COPD with increased PCO₂ and cannot respond by increased ventilation.

Summary

Presently, the dedicated delivery system delivers CO₂ very safely without chance of air contamination, excessive volumes, explosive delivery, etc. We would strongly recommend not using hand injection directly from the CO₂ cylinder since air contamination can readily occur and explosive delivery is more difficult to eliminate. Imaging has improved and will improve considerably more when the manufacturers optimize imaging of the low density contrast. The safety and advantages afforded by its buoyancy, low viscosity, and low cost have provided advantages for not only patients with renal failure and allergy, but for routine diagnostic and interventional procedures.

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