

Carbon Dioxide Digital Subtraction Angiography: Expanding Applications and Technical Evolution

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Although several noninvasive techniques now exist for vascular imaging, including MR imaging, three-dimensional CT, and color-flow and duplex sonography, the gold standard to which these techniques are compared remains catheter angiography. Cut-film and digital subtraction angiography (DSA) using iodinated contrast material are the standard methods by which vascular imaging is performed. However, despite the development of low-osmolar contrast agents, premedication regimens, and careful patient selection, adverse reactions to contrast material, including idiosyncratic reactions and contrast-induced nephropathy, continue to occur in a small number of patients [1–3]. Carbon dioxide (CO₂) was developed as an alternative to iodinated contrast material to avoid these problems [4]. Once the behavior of intravascular gas, the methods of safe delivery, and the principles of successful imaging are understood, the use of CO₂ as an intravascular contrast agent during DSA allows accurate imaging with little risk. Recent advances in delivery systems, postprocessing capabilities, and its extension to new vascular interventional procedures have greatly expanded the usefulness of CO₂ angiography in both diagnostic and interventional vascular radiology.

In the 1950s, IV-injected CO₂ was first used to diagnose pericardial effusions [5–7], and a decade later it was used to evaluate the portal venous and hepatic venous systems [8, 9]. The use of CO₂ in the peripheral and visceral arterial circulation was pioneered by Hawkins in the 1970s [4]. He originally used the cut-film subtraction technique and hand injection, but later moved to DSA and standard mechanical injectors. Until recently, the development of CO₂ angiography has focused

primarily on diagnosis in the peripheral and visceral arterial circulation. Currently, the use of CO₂ as an intravascular contrast agent is being extended to other parts of the circulation and to newly developed interventional techniques.

Behavior of CO₂ in the Vascular System

When iodinated contrast material is injected intravascularly, it begins to immediately mix with blood, with the resulting increase in radiographic density depending on the flow and volume of blood, the rate and volume of contrast injection, and the degree of contrast dilution. An increase in density is generally achieved by increasing the injection volume and/or rate. Conversely, intravascular CO₂ initially maintains a gas/liquid interface. The decrease in radiographic density is due to temporary displacement of blood by the gas. A rapid injection rate, rather than a large injection volume, is needed to quickly displace blood and completely fill the vessel. Although there is no clinical evidence that higher injection rates do not damage vessels, an upper limit exists for each vessel above which no improvement in image quality occurs [10]. If too small a rate is used, the gas tends to float on the blood, thereby incompletely filling the lumen of the vessel. The result is underestimation of vessel diameter and nonvisualization of nondependent structures, which may inaccurately suggest a stenosis or occlusion.

The fate of intraarterially injected CO₂ depends in part on the volume injected. After it is injected, CO₂ immediately begins to dissolve in the blood. Small volumes, such as 10 ml,

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may actually dissolve before the gas reaches the area being imaged. Dissolution is accentuated by slow blood flow, which increases the time of contact between blood and gas. For this reason imaging of the distal extremities may lead to overestimation of occlusive disease. Increasing the volume usually allows adequate visualization. The dissolved CO₂ is expired by the lungs in a one-pass fashion. Even large volumes injected intravascularly result in no changes in arterial pH, pCO₂, and pO₂ (Bettmann MA, et al., presented at the Radiological Society of North America meeting, November 1993), suggesting that the blood can absorb and the lungs expire large amounts of gas.

Gas Delivery and Imaging Principles

CO₂ is a colorless, odorless, compressible gas requiring unique methods of handling and injection. Pure medical grade CO₂ should be used, and we recommend disposable cylinders, as reusable cylinders may corrode from accumulation of water vapor. Hand-injection is the simplest method for delivery, but the compressibility of the gas may result in an unpredictable and explosive delivery [11]. A 3-ml syringe of CO₂, attached in series to a 50-ml syringe of CO₂, is used to clear the catheter of fluid before injecting the main bolus. A small syringe is used because greater pressure can be generated. Once the fluid in the catheter is cleared it is much easier to inject a large syringe (50 ml) of CO₂. However, this method can initially be cumbersome, as several stopcocks must be turned quickly in the correct sequence for a successful injection. In addition, a maximum of approximately 50 ml can be injected manually at one time. Standard contrast injectors may be used instead, and a larger volume may be delivered, but as they are not closed systems the risk of room air contamination is high [11]. Because CO₂ is heavier than room air, the tip of the injector syringe must be kept pointed up while room air is purged from the syringe and CO₂ is loaded. Once the desired volume is loaded, the syringe is briefly opened to atmosphere with the tip up. If it is not, more than the desired volume of gas may be injected because of the compressibility of the gas.

Injection rates and volumes vary depending on site of injection, area of interest, and underlying vascular disease. Representative rates and volumes are given in Table 1. The buoyancy of CO₂ may be an advantage, for instance in obtaining lateral images of the mesenteric artery origins (Fig. 1) and in evaluating aortorenal bypasses or renal transplants (Fig. 2). Elevation of dependent structures of as little as 15° or 20° can produce significant improvement in imaging. We routinely elevate the legs to improve imaging of the tibial vessels, and roll the patient with the side of interest up when imaging the renal arteries. We have found no specific catheter design to be advantageous as far as image quality is concerned, although the low viscosity of CO₂ allows us to routinely use 3- and 4-French catheters.

Similar to all techniques using DSA, imaging with CO₂ is improved if all motion during image acquisition is kept to a minimum. We sedate our patients as little as possible so they can completely suspend respiration. Bowel peristalsis can be eliminated with IV glucagon. Image quality may be further improved by using postprocessing functions including pixel shifting, remasking, edge enhancement, and image summation.

Many of the problems unique to CO₂ delivery have been solved with the development of a dedicated CO₂ injector (AngioDynamics, Glens Falls, NY) [11]. This investigational

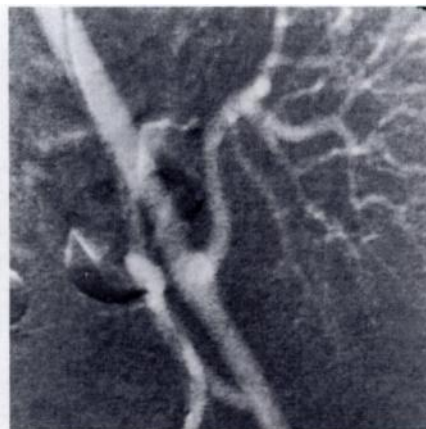
TABLE 1: Representative CO₂ Angiography Injection Parameters^a

Type of Study	Rate (ml/sec)	Volume (ml)
Abdominal aortogram	100–150	75–100
Pelvic arteriogram	40–60	40–60
Leg arteriogram	10–20	20–40
Dialysis fistula	10–20	20–40
Arm venogram	10–20	25–50
Vena cavagram	50–100	40–50
Renal transplant	10–20	10–20
Mesenteric arteriogram	10–20	20–30
Direct portography	50–100	40–50

^aMeasured at 1 atm of pressure.



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Fig. 1.—76-year-old man with renal insufficiency and possible acute bowel ischemia. Cross-table lateral CO₂ aortogram shows mild stenosis of celiac axis (*arrow*).

Fig. 2.—29-year-old man with a left iliac fossa renal transplant and nonhealing wound on left foot. CO₂ arteriogram before revascularization of left leg shows normal inflow to transplant.

device delivers pure, dry CO₂ via a closed system, thus reducing the risk of room air contamination. All patients give informed consent before the use of this investigational device. The catheter size and length, and injection rate and volume are entered by the operator. The injector delivers this bolus more accurately and reliably than any other method. Between injections the catheter is conveniently flushed automatically.

Clinical Uses

Arterial Applications

CO₂ may be used as an intravascular contrast agent, except in the thorax, head, and neck, in any situation in which angiography is needed for diagnosis or to guide percutaneous therapy. Owing to the prevalence of atherosclerotic disease involving the abdominal aorta, its branches, and the arterial supply to the lower extremities, CO₂ arteriography is most commonly used at our institution for the evaluation of arterial occlusive disease in the abdomen and legs.

Approximately 20% of our patients require CO₂ angiography, many of whom are specifically referred to us for this procedure because of renal insufficiency or a history of previous reaction to iodinated contrast material. In those patients with iliac, femoral, or popliteal disease, diagnostic information necessary for revascularization may be obtained with little or no iodinated contrast material (Fig. 3). The low viscosity of CO₂ allows filling of even very small collateral branches with reconstitution of distal vessels. When compared with iodinated contrast material in the same patient, CO₂ is highly accurate in depicting the level and severity of disease as well as the distal runoff [12]. However, in some diabetics with poor tibial vessel runoff, CO₂ tends to overestimate disease because of dissolution of the gas associated with slow flow in the diseased tibial vessels. In these cases, we supplement the CO₂ study with small volumes of low-osmolar iodinated contrast material. This allows more accurate determination of the status of the distal vessels for possible bypass procedures. Compared with the pain and burning sensation sometimes accompanying the use of iodinated contrast material, our patients only occasionally feel a tingling sensation when CO₂ is used.

Mesenteric arterial stenosis is well demonstrated on cross-table lateral studies because of the buoyancy of the gas, although imaging of distal mesenteric vessels, even with selective injections, is not as accurate as with iodinated contrast material. Renal artery stenosis is a common indication for CO₂ arteriography because of its association with azotemia. The number and location of renal arteries, and the presence of a stenosis, can be determined (Fig. 4), although we usually obtain a limited, focused iodinated contrast arteriogram for balloon sizing before angioplasty. As there is some evidence that contrast-induced nephropathy is related to the volume of contrast material used [13, 14], we believe we are lessening the chance of nephropathy by performing the vast majority of the study with CO₂.

Abdominal aortic aneurysms may also be studied with CO₂ arteriography (Fig. 5). The relationship of the aneurysm to the renal arteries can usually be determined, although in very ectatic aortas it may be difficult to displace blood adequately enough to fill the dependent renal arteries. Any associated mesenteric stenosis is well documented, again because of the buoyancy of the gas. Evaluation of the runoff in these patients may be complicated by the gas pooling in the aneurysm [15]. In these patients, catheters can be placed in both external iliac arteries, and excellent runoff studies are then usually obtained, as these patients uncommonly have occlusive peripheral vascular disease.

We have noticed a striking difference between iodinated contrast material and CO₂ in the evaluation of patients with gastrointestinal hemorrhage or those who have sustained trauma. In some instances, ongoing hemorrhage is seen only with CO₂. Owing to its lower viscosity, CO₂ shows arteriovenous fistulas better than iodinated contrast material does [16]. Similarly, we believe CO₂ allows better detection of active bleeding (Fig. 6).

Venous Applications

In the upper extremity, CO₂ may be used in the evaluation of an arteriovenous fistula or prosthetic hemodialysis graft [15]. The gas demonstrates central venous stenoses and may be used to guide percutaneous therapy (Fig. 7). Because of the

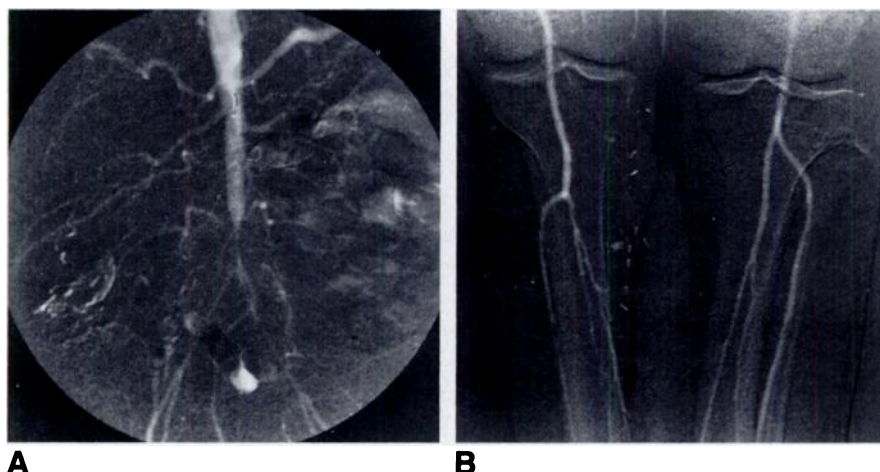
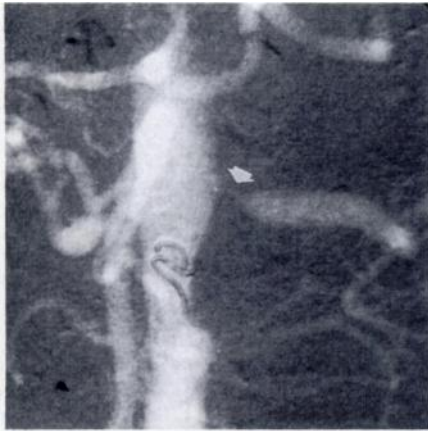


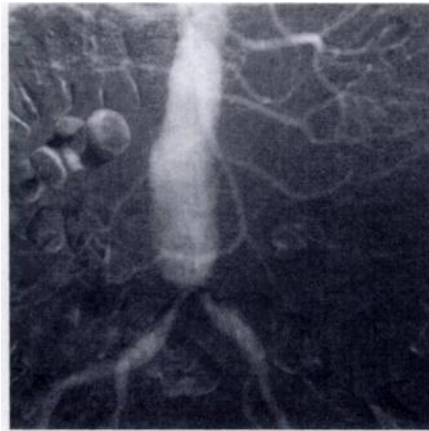
Fig. 3.—55-year-old woman with bilateral hip and leg claudication and history of severe reaction to iodinated contrast material.

A. CO₂ aortogram from left brachial approach shows high-grade long segment stenoses of distal aorta and both common iliac arteries.

B. Excellent runoff to tibial trifurcations was obtained with catheter in upper abdominal aorta.



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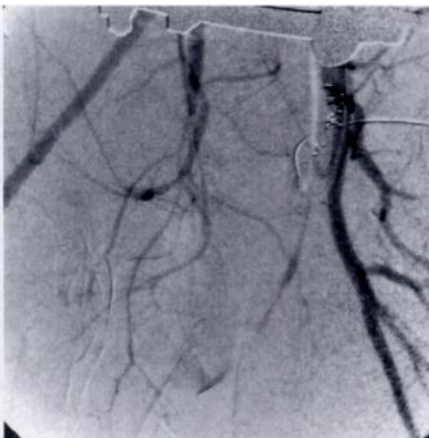
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Fig. 4.—65-year-old woman with hypertension and renal insufficiency. Left anterior oblique CO₂ aortogram shows a high-grade ostial stenosis of left renal artery (*arrow*).

Fig. 5.—54-year-old man with abdominal aortic aneurysm and azotemia. CO₂ aortogram shows infrarenal abdominal aortic aneurysm with bilateral common iliac artery origin stenoses.



A



B

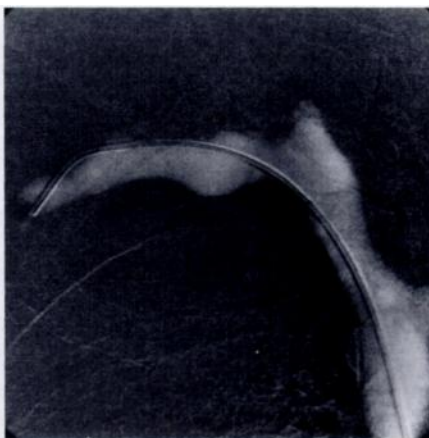
Fig. 6.—20-year-old woman with multiple pelvic fractures and falling hematocrit.

A, Left anterior oblique CO₂ pelvic arteriogram shows two areas of extravasation (*arrows*) and a traumatic arteriovenous fistula (*arrowheads*).

B, Iodinated contrast arteriogram in same projection fails to show these abnormalities.



A



B

Fig. 7.—35-year-old woman with visceral myopathy and history of severe reaction to iodinated contrast material who required long-term IV hyperalimentation.

A, Right subclavian CO₂ venogram prior to placement of central venous catheter shows weblike venous stenosis (*arrow*).

B, Repeat CO₂ venogram after angioplasty shows resolution of stenosis.

possibility of neurotoxicity, caution must be used to prevent reflux of gas back into the subclavian or brachiocephalic arteries and to space the injections if the catheter has been advanced into the feeding artery to avoid ischemia of the

hand. CO₂ venograms of the upper extremity provide accurate information regarding central venous stenosis or occlusion and collateral supply in patients with malfunctioning central lines or presumed venous thrombosis.

We also use CO₂ to perform preliminary venography in patients about to undergo initial central line placement. In our experience, injection of gas into IV lines in the hand tends to be painful. This may be due to the sudden expansion of the gas in the small vein after being compressed in the syringe. Therefore, we recommend injecting into an antecubital vein for venography. Gas in the subclavian vein usually remains visible for several seconds, aiding fluoroscopic cannulation during central line placement. We do not routinely perform venography of the internal jugular or lower extremity veins, as these are accurately evaluated noninvasively.

Inferior vena caval (IVC) occlusion, IVC thrombus, and collateral formation are also well depicted with CO₂ venography. Selective visceral venography is possible, although indirect venography may be performed in selected situations after intraarterial injection (e.g., extension of a renal cell carcinoma into the renal vein). Inferior vena cava filters may be placed under CO₂ guidance [15], although this is not routinely suggested because of possible inaccuracies in caval measurement and subsequent malposition or migration of the filter.

CO₂ has several roles in the placement of transjugular intrahepatic portosystemic shunts (TIPS). Free hepatic venography, wedged hepatic venography, and portography both before and after shunt placement may be performed [17]. Location of hepatic veins can be determined easily with CO₂ because of the buoyancy of the gas. We have also found that CO₂-wedged hepatic venography is particularly helpful in locating the portal bifurcation, thereby aiding the direction of the transhepatic puncture (Fig. 8). We currently routinely use this method of portal vein localization in TIPS procedures. Transhepatic CO₂ portography clearly defines the presence of varices (Fig. 9), although in some cases the left portal vein fills better than the right because of the buoyancy of the gas. Occasionally, late hepatic vein stenoses causing recurrent variceal hemorrhage or ascites are better seen with CO₂ portography than with iodinated contrast

material. These stenoses can then be dilated and stented successfully under CO₂ guidance (Fig. 10).

Safety of Intravascular CO₂

Several early animal studies showed that, compared with room air, even relatively large amounts of CO₂ could be injected IV with no significant changes in hemodynamics or arterial blood gas parameters such as pH, pCO₂, and pO₂ [18–21]. Room air is composed primarily of nitrogen, which does not dissolve readily in blood and therefore may impede blood flow. Because the solubility of CO₂ in serum is approximately 20 times that of room air or oxygen [20, 21], CO₂ dissolves rapidly and is expired by the lungs in a first-pass fashion. However, these early studies also showed that pump failure in the right side of the heart can occur with very large IV volumes, although the volumes needed for even cut-film imaging were well tolerated in both animals and humans.

With the development of intraarterial CO₂ imaging, new issues have had to be addressed, such as the possibility of tissue ischemia due to gas embolism and the question of a direct toxic effect on tissues. The effect of directly injected CO₂ on canine renal flow, function, and histology has been studied [22]. As compared with iodinated contrast material, CO₂ produced no significant difference in renal blood flow or function, and no significant histologic changes were observed, with the exception of acute tubular necrosis in one dog in which the kidney was placed vertically over the catheter during rapid, repeated injections. It was postulated that gas trapping and ischemia occurred as a result of insufficient time between injections, thereby not allowing gas dissolution and reestablishment of parenchymal blood flow. No histologic changes in the renal arteries were seen, suggesting no direct toxic effect by the gas.

The safety of intravascular CO₂ has been demonstrated in several small clinical series as well. No significant changes in

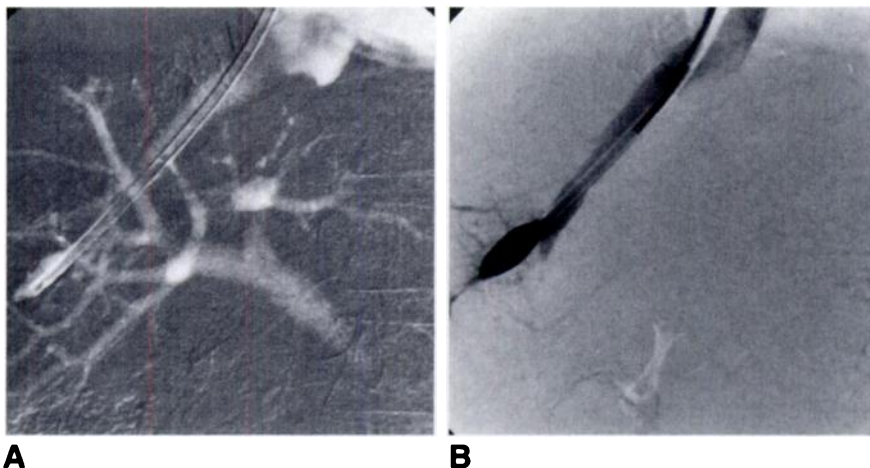


Fig. 8.—45-year-old man with cirrhosis and variceal bleeding refractory to sclerotherapy.
A, Wedged right hepatic CO₂ venogram before transjugular intrahepatic portosystemic shunts (TIPS) procedure with filling of main portal vein and intrahepatic branches.
B, Wedged right hepatic venogram with iodinated contrast material failed to opacify portal venous system.

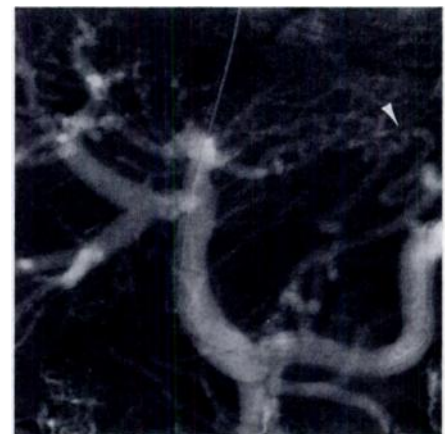


Fig. 9.—75-year-old man with cirrhosis and variceal bleeding. Transhepatic CO₂ portogram shows hepatopetal flow and varices (arrowheads).

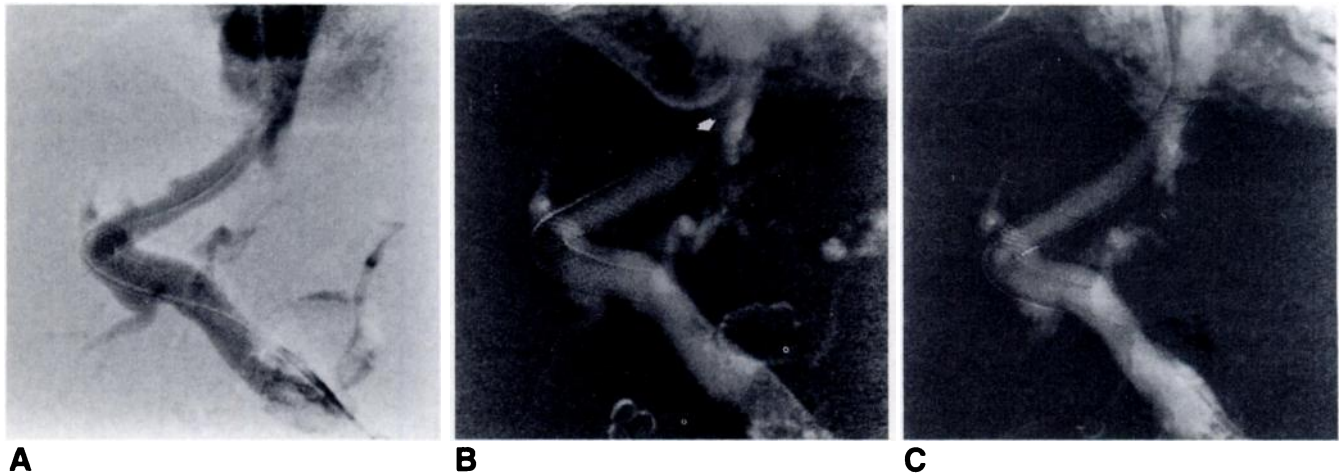


Fig. 10.—69-year-old man with recurrent ascites and 20 mm Hg gradient between portal vein and right atrium 1 year after transjugular intrahepatic portosystemic shunts (TIPS) procedure.

A, Transstent portogram with iodinated contrast material shows no definite stenosis.

B, Transstent CO₂ portogram shows focal stenosis at ostium of right hepatic vein (*arrow*).

C, Repeat CO₂ portogram after additional stent was placed across stenosis with resolution of gradient.

renal function, as reflected by the serum creatinine, were observed when patients who had also received iodinated contrast material were excluded [12, 23–25]. In our large clinical experience with approximately 800 patients, we have seen only one definite complication attributable to CO₂ angiography. Profuse watery diarrhea developed in one patient after angiographic evaluation of an abdominal aortic aneurysm. This patient had received about 2000 ml of CO₂ over a 30-min period, resulting in transient left-sided colonic ischemia as evidenced by characteristic endoscopic changes.

It is not surprising that there have been no reports of urticarial or idiosyncratic reactions to CO₂, as it is a natural constituent of the body. However, patients may experience nausea after the first intraabdominal injection [23]. The cause of this response is uncertain, and it is unpredictable with no known correlation with the patient's disease or presentation, although IV glucagon seems to potentiate it. It may be a visceral reflex-mediated response, as it does not occur in those patients whose examinations are confined to the extremities when all other variables are held constant. We have noticed that the occurrence of nausea may be reduced by initially administering a small-volume injection into the abdomen or pelvis.

Risks of CO₂ Angiography

On the basis of limited animal research, the current major safety concern is the possibility of neurotoxicity to CO₂. Studies performed on rats in which CO₂ was injected directly into the carotid artery showed damage to the endothelial cell membrane on microscopic examination with multifocal ischemic infarction grossly [26]. What effect injection volume or pressure had on these results is uncertain. Subsequent use of CO₂ in thoracic aortography and carotid angiography in canines resulted in no detectable changes on neurologic examinations, electroencephalography, or gross pathologic

specimens [27]. At this time the question of neurotoxicity remains unanswered, and until more work is done to resolve this issue we recommend that CO₂ not be injected intraarterially within the thorax, head, and neck.

The buoyancy of CO₂ must also be considered, particularly in situations in which injected gas may become trapped in a nondependent vessel or organ. Examples include renal transplants, mesenteric vessels, or elevated extremities. In these situations, particularly if blood flow is slow, the gas may become trapped in the vessel. The kinetic energy of the forward blood flow may not be enough to overcome the buoyant force of the gas. Dissolution may slow as a result of saturation of the blood in contact with the gas. If prolonged, this stagnant situation may result in tissue ischemia. Using the smallest volume of gas necessary for imaging, spacing injections apart temporally, and changing the position of the area of concern to allow gas release help avoid ischemia caused by gas trapping. Currently, we do not recommend intraarterial injections larger than 100 ml, and serial injections should be spaced several minutes apart.

During CO₂ venography gaseous CO₂ frequently reaches the right side of the heart and the pulmonary arterial circulation. Care must be exercised not to flood the right side of the heart with gas, which may cause pump failure. We limit individual venous injections to 50 ml or less. Injections should be spaced apart to allow resorption and expiration of CO₂, and fluoroscopy should be used to ensure the complete disappearance of the gas before the next injection. In our experience, careful imaging has failed to detect gas reaching the pulmonary venous circulation, supporting the belief that CO₂ is removed by the lungs in one pass. Although no cases of adverse neurologic complications have been reported in patients with cardiac septal defects, we do not perform CO₂ venography in any patient suspected of having a potential shunt lesion, as the pulmonary capillary bed could be bypassed, allowing gas to reach the intracranial circulation.

Summary

CO₂ has proved to be a safe and effective intravascular contrast agent in most parts of the arterial and venous circulations. A clear understanding of intravascular gas behavior, methods of safe delivery, and the imaging principles particular to this technique should enable accurate vascular imaging while avoiding the risks associated with iodinated contrast material. Minimal or no adjustments in standard angiographic equipment are needed to perform basic CO₂ angiography. However, specialized techniques and equipment have been designed to enhance imaging. Recent expanded clinical uses in both diagnostic and interventional vascular procedures have emphasized the role of CO₂ as an intravascular contrast agent. The remaining question of neurotoxicity currently restricts the use of CO₂ arteriography to the abdomen, pelvis, and extremities. Further research into this problem may someday allow its use in the thoracic and cerebral arterial circulation.

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