Carbon Dioxide as an Intravascular Imaging Agent: Review

Bhavik N. Patel, MD,[a] Baljendra S. Kapoor, MD, FSVM,[a] Peyman Borghei, MD,[a] Nemil A. Shah, BS,[b] and Mark E. Lockhart, MD, MPH[a]

Patients with renal impairment and/or contrast allergies pose a challenge with regard to diagnostic evaluations. CO_2 may serve as a suitable alternative intravascular contrast agent in these patients with arteriographic applications, including evaluation of peripheral vascular disease, and venographic applications, such as transjugular intrahepatic portosystemic shunt procedure, to name a few. Unique properties of CO_2, such as low viscosity, lack of an allergic reaction, and renal toxicity, have afforded it its diagnostic capabilities. However, certain properties of CO_2 also pose a technical challenge in terms of its delivery. Although it remains a relatively safe alternative contrast agent, potential adverse effects have been reported and exist.

The association of nephrogenic systemic fibrosis and of contrast-induced nephropathy (CIN) with iodinated contrast media (ICM) in patients with renal impairment has led to an increased interest in the search for alternative intravascular contrast agents, such as carbon dioxide (CO_2). CO_2 is a relatively safe alternative agent in those patients with chronic renal failure or an iodine contrast allergy undergoing angiographic examination. It has proven to be useful in a variety of angiographic applications, such as evaluation of arterial occlusive disease, venography, and arteriovenous fistulography. In addition, it has demonstrated an acceptable diagnostic accuracy comparable to ICM in a majority of cases. In the case of delineating portal vein anatomy in wedged hepatic venography during transjugular intrahepatic portosystemic shunt (TIPS) procedure, it has demonstrated superiority to ICM. However, the delivery of CO_2 can be challenging owing to its unique properties. Although relatively safe, potential adverse effects are well documented. In this article, we review the properties of CO_2, its various arteriographic and venographic applications, delivery, and the potential complications and contraindications associated with its use.

From the [a]University of Alabama at Birmingham, Department of Radiology, Birmingham, AL; and [b]University of Alabama at Birmingham School of Medicine, Birmingham, AL.
Reprint requests: Bhavik N. Patel, MD, Diagnostic Radiology, Department of Radiology, 619 19th Street South, JT N331, Birmingham, AL 35294. E-mail: Bpatel@uabmc.edu.
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Contrast-Induced Nephropathy

Using ICM, there is a risk of CIN in patients with impaired renal function. Although it is widely accepted that the risk of CIN is much greater with high osmolar contrast agents, the differences in the degree of nephrotoxicity between low osmolar contrast media and iso-osmolar contrast media has not been clearly established.[1,2] Although the use of bicarbonate-based volume expansion has shown merit in reducing the risk of CIN, the use of N-acetylcysteine and other therapies has not shown consistent results.[2] Previously, gadolinium had been an alternative agent but increased awareness of nephrogenic systemic fibrosis risks in renal patients has limited its use.[3,4]

CO_2 Properties

Although liquid contrast agents fill the lumen and mix with the blood to create radiographic contrast, CO_2 gas acts by displacing the blood within the vessel being studied, serving as a negative contrast agent because of its low atomic number when compared with iodinated contrast. Digital subtraction techniques then take advantage of the differences in radiographic density between the CO_2 and the lumen wall.[5,6] Despite being heavier than air, the relative buoyancy of CO_2 may lead to incomplete filling, and thus displacement, of blood, leading to a lack of optimal contrast in large-

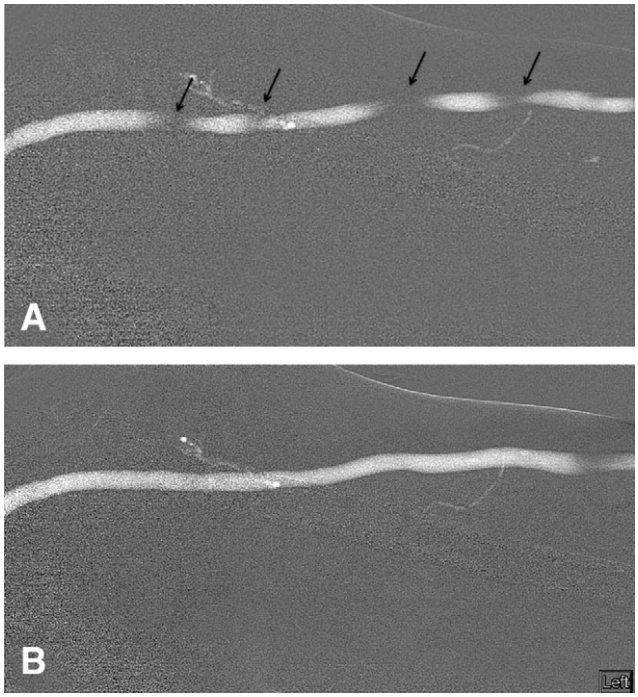

FIG 1. CO_2 venogram. An inadequate volume and column of CO_2 can lead to (A) incomplete displacement of blood leading to the artifacts seen in the image (arrows) compared with an adequate injection (B) where complete visualization is seen.

caliber vessels. This may cause preferential filling of nondependent portions of vessels or preferential filling of various branches based on patient positioning (Fig 1).[5,7] As it is injected, dissolution of CO_2 into blood begins immediately without change in arterial blood gas parameters and systemic removal occurs by way of pulmonary expiration.[8] The low viscosity allowing delivery through small-caliber catheters, lack of nephrotoxicity, lack of an allergic reaction, and low cost are features making CO_2 a useful alternative contrast agent.[5,7,9]

Arteriographic Applications

The earliest application of CO_2 was in visualization of hepatic and portal veins and diagnosing pericardial disease.[10-14] Hawkins first reported the use of CO_2 as an arterial contrast agent in 1982.[15] Aside from the head, neck, and thorax, CO_2 may be used as a contrast agent in virtually any other angiographic diagnostic application.[8]

Atherosclerosis and Arterial Occlusive Disease

CO_2 has been shown to provide diagnostically useful images in the evaluation of peripheral arterial disease, owing its advantages to its low viscosity, affording it the ability to show small collateral branches, stenotic vessels, and the distal reconstituted vessel (Fig 2).[5,8] Several studies have reported the use of CO_2 as an alternative contrast agent with an acceptable diagnostic quality in lower limb peripheral arteries located above the knee (Figs 3 and 4).[16-18] One experimental study showed that in densitometric evaluation of stenosis, CO_2 was occasionally superior to ICM in evaluation of a 50%-70% area of stenosis.[16] However, imaging of infrapopliteal vessels using CO_2 has not been reported to show such favorable results,[5,18,19-21] but selective catheterization in proximity to the vessel being evaluated may yield better results. Another potential limitation of CO_2 arteriography includes an overestimation of stenosis. Because of the dissolution of CO_2 in blood on injection, vessels with slow flow may not be adequately visualized and this lack of contrast may lead to an overestimation of the degree of stenosis.[8] In addition, an overestimation of vessel diameter by CO_2 when compared with intravenous ultrasound as a reference standard has been reported, thereby limiting accurate intervention planning, such as determination of proper stent size. The elastic nature of the vessel wall and expansile properties of CO_2 were attributed as the likely reasons for this behavior.[22]

CO_2 angiography may also be used to evaluate abdominal aortic aneurysms. However, the high buoyancy and inadequate displacement of flowing blood in such a large-caliber vessel may lead to incomplete visualization of the entire lumen if a sufficient column of CO_2 is not used. In addition, the dependent renal arteries may not be well visualized in the supine position. Although the nondependent preference of CO_2 limits filling of the renal and lumbar vessels, CO_2 can provide information regarding involvement of anterior branches, such as the superior mesenteric artery (Fig 5).[6-8] Thus, although the buoyancy of CO_2 allows evaluation of a proximal mesenteric stenosis, visualization of the distal mesenteric vessels is better with iodinated contrast agents.[8] CO_2 has also been successfully used as a contrast agent during endovascular repair of aortic aneurysms to confirm adequate deployment of the endostent.[23] A retrospective study comparing outcomes between 100 patients undergoing endovascular aortic aneurysm repair with ICM versus intravascular CO_2 showed no significant difference in outcome. However, increased fluoroscopy time associated with CO_2 was

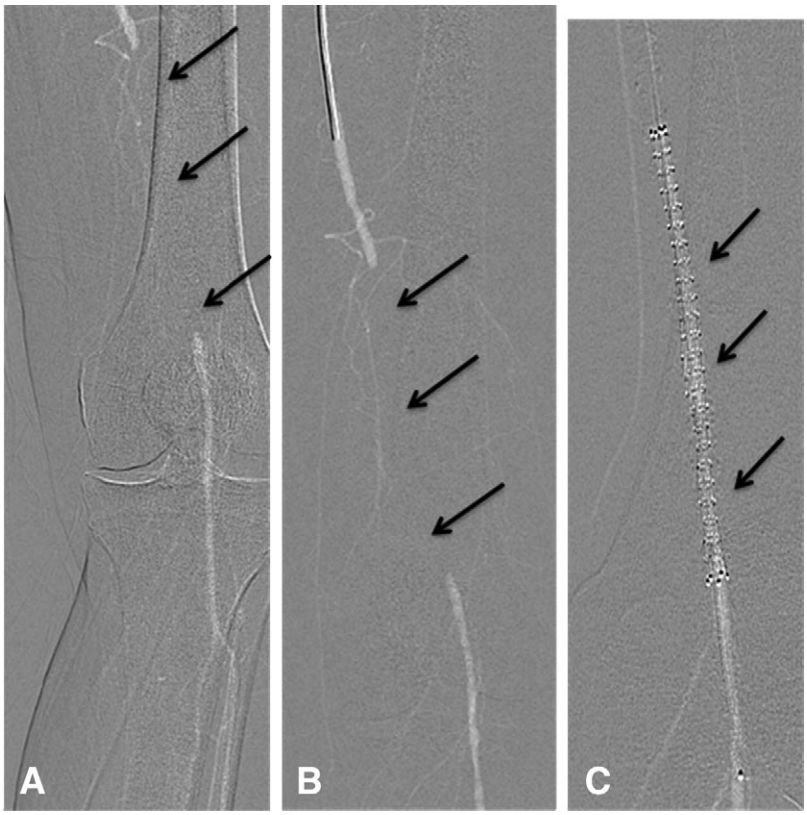

FIG 2. A 55-year-old female with type 2 diabetes, hypertension, and renal dysfunction presented with a left foot ulcer. (A, B) CO_2 arteriography demonstrated complete occlusion of the mid-distal superficial femoral artery (arrows) with subsequent angioplasty and (C) stent placement (arrows).

identified, most likely secondary to the technical challenges associated with CO_2 delivery.[24]

Renal Transplant and Renal Artery Evaluation

CO_2 angiography has also been used to evaluate patients with renal artery stenosis secondary to atherosclerosis or intimal hyperplasia in cases of renal transplantation (Fig 6). Caridi et al were able to adequately visualize the renal vessels using simple maneuvering techniques, such as placing patients in the lateral decubitus position.[25-27] When compared with iodinated contrast, an 83% sensitivity and 99% specificity with an overall accuracy of 97% of CO_2 in evaluating renal stenosis has been reported.[28] A positive predictive value of greater than 90%, and in 1 study up to 100%, have been reported.[28,29] Additionally, a prospective study of 123 patients revealed no correlation of nephrotoxicity and the amount of CO_2 injected.[30] Although these figures do not equal the diagnostic capabilities of ICM, CO_2 may have a role in appropriate settings. CO_2 has also been reported to demonstrate anastomotic stenosis, diffuse arterial disease related to chronic rejection, and arteriovenous fistulas after a renal transplant biopsy (Fig 7).[31,32] Thus, in patients with renal impairment, initial imaging may be performed with CO_2 followed by a smaller, reduced load of ICM to confirm the findings.

Venographic Applications

Venography

Similar to arteriography, wide applications of CO_2 as a contrast agent have been developed for patients with renal disease or an allergy to iodinated contrast media undergoing venography. One such application is CO_2 vena cavography to guide placement of inferior vena cava (IVC) filters. Dewald et al demonstrated a high success rate of CO_2 venography for IVC filter placement with visualization of venous anomalies in all cases and visualization of thrombus in an approximate 78% of cases.[33] The estimation of the IVC diameter carries a reported accuracy of approximately

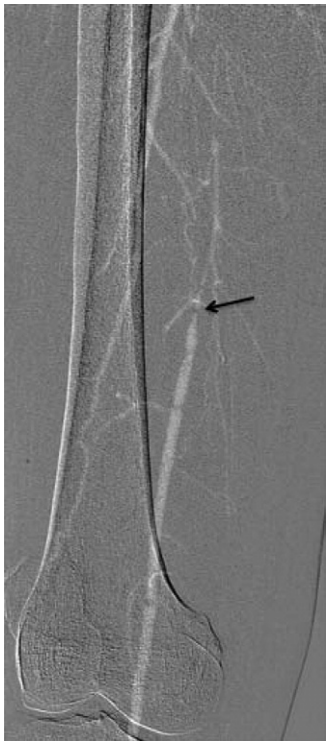

FIG 3. CO_2 arteriography demonstrates a focal occlusion (arrow) of the superficial femoral artery.

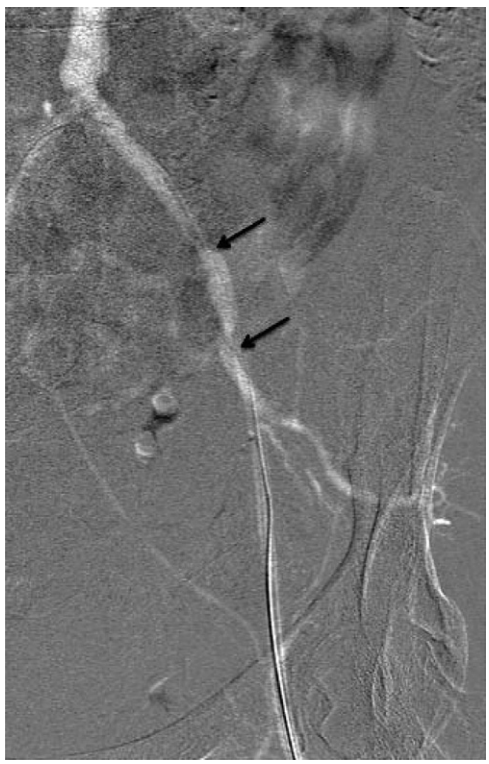

FIG 4. CO_2 arteriography demonstrates atherosclerotic plaque at the aortic bifurcation and areas of stenosis involving the left common iliac artery (arrows).

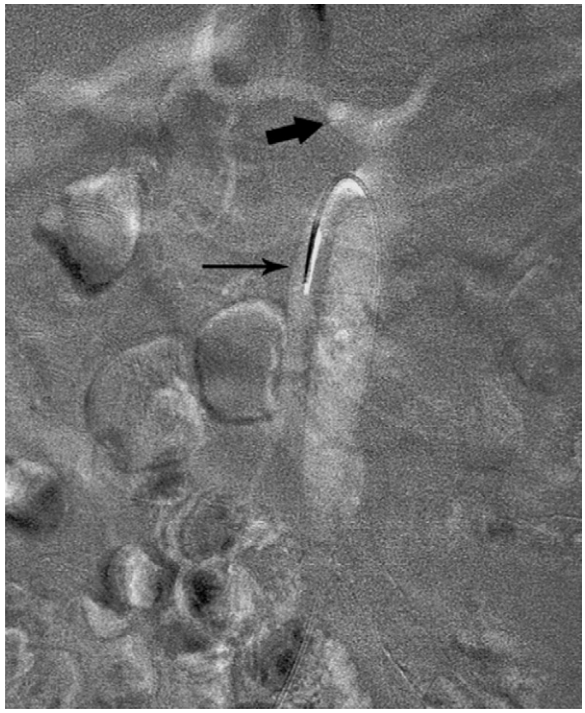

FIG 5. A 58-year-old female with a gastrointestinal bleed. Technetium-99m pyrophosphate-labeled RBC scan showed active gastrointestinal bleeding in the superior mesenteric artery distribution. Supplemental CO_2 was used due to renal dysfunction. CO_2 arteriography did not show any active bleeding but did show adequate visualization of the superior mesenteric artery (thin arrow) and the celiac axis (thick arrow).

97%. The reported accuracy of CO_2 venography in the identification of the renal veins varies depending on whether a dynamic series of images is used or a single static image. Filling defects in the IVC from the renal inflow of unopacified blood affords the dynamic images a higher success in the identification of the renal veins.[34,35] However, the dependent location of the left renal vein may limit its visibility. Other applications include upper arm venography to guide placement of peripherally inserted central venous catheters and preoperative upper extremity venography for hemodialysis access fistulas.[36,37]

Perhaps the utility of CO_2 as an alternative contrast agent is no better demonstrated than in the visualization and identification of portal vein anatomy in wedged hepatic venography during a TIPS procedure (Fig 8). CO_2 has been shown to be superior in identifying and delineating portal vein anatomy compared with iodinated contrast media due to its low viscosity, allowing it to easily traverse through the hepatic sinusoids.[38-40] Sensitivity rates for opacification of the right and left portal veins have been

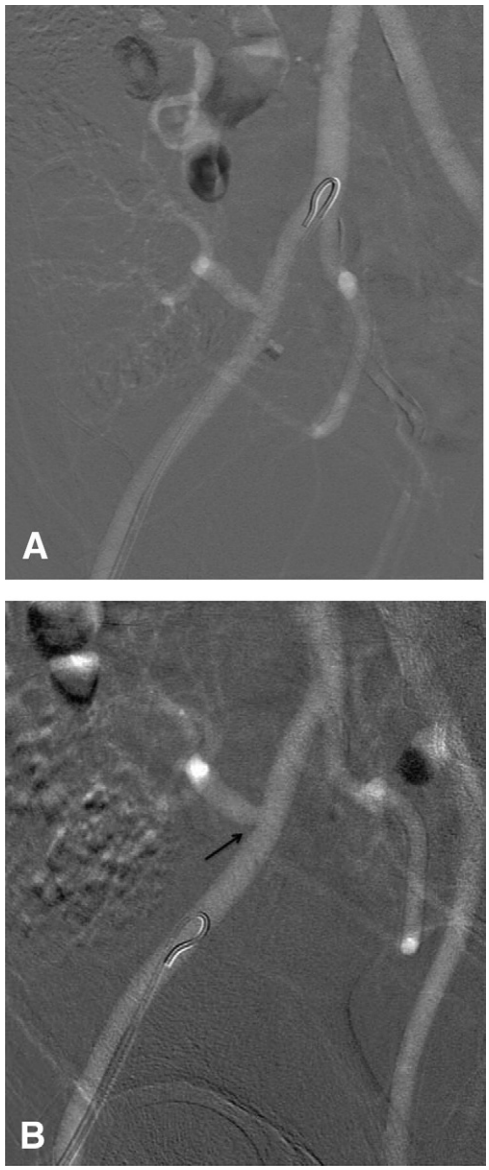

FIG 6. Renal transplant evaluation shows the (A) iliac arteries and the (B) right renal transplant arterial anastomosis (arrow) in adequate detail.

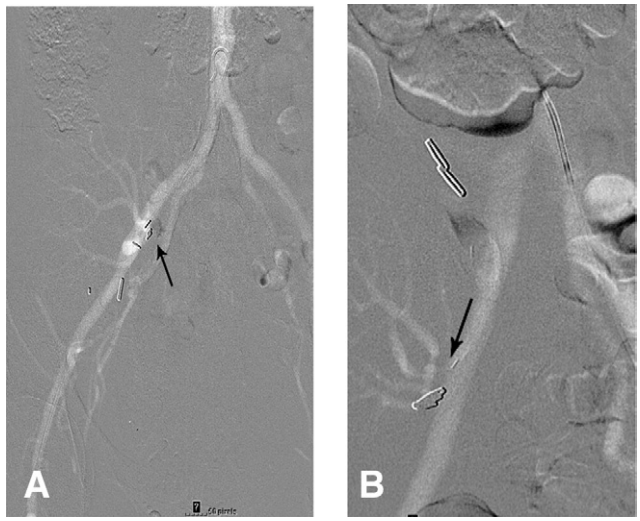

FIG 7. A 37-year-old male with renal allograft dysfunction. CO_2 arteriography in this renal transplant patient shows (A) the allograft renal artery anastomosed to the right internal iliac artery (arrow) and a (B) focal renal arterial stenosis (arrow). This was subsequently confirmed with iodinated contrast.

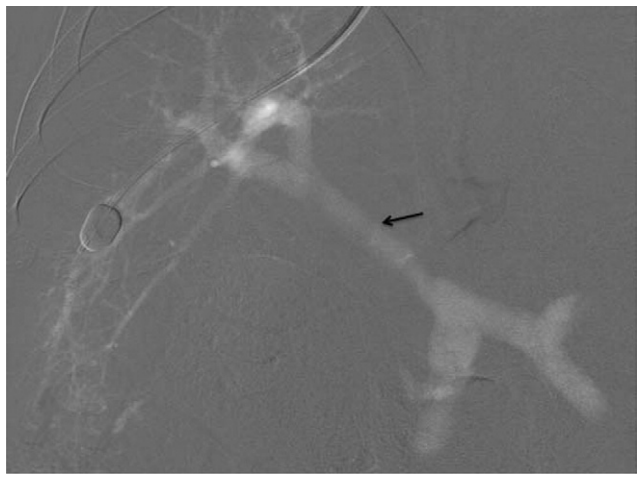

FIG 8. Wedged hepatic venography during TIPS procedure delineates the portal vein well (arrows).

reported as high as 94%.[41] In addition, the portal vein bifurcation can also be easily identified, helping guide the transhepatic puncture during TIPS.[8] Hawkins et al reports a technique whereby a 21-gauge needle is directly advanced into the liver parenchyma and CO_2 is injected to allow identification of the portal vein.[42] One must be careful not to abort a case in a false appearance of cavernous transformation caused by filling of hepatic lymphatic vessels.[43] Although it was initially reported that indirect arterial portography would still provide a better visualization of varices, recent experimental studies with CO_2 wedged arterial splenoportography have shown promise in visualization of gastric varices associated with splenic vein occlusion.[44,45] In addition, the anastomotic site can also be evaluated with CO_2 portography in patients with a hepatic transplant (Fig 9).

Arteriovenous Fistulography

The venous anastomosis of an arteriovenous fistula may be evaluated with CO_2 with a reported sensitivity, specificity, and diagnostic accuracy of 94%, 58%, and 75%, respectively (Fig 10). When compared with

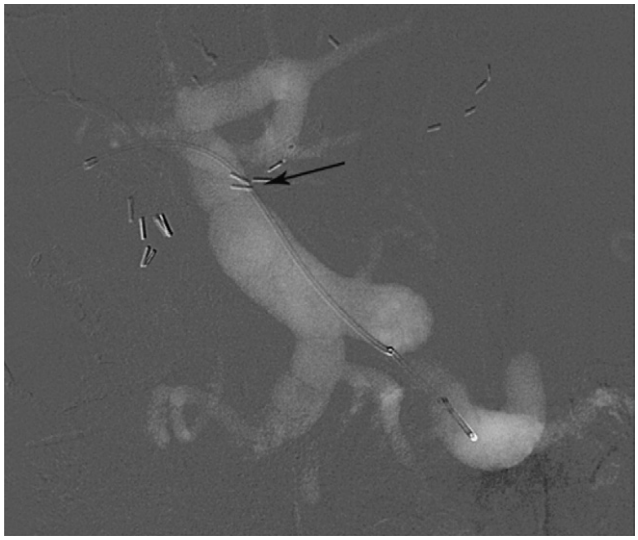

FIG 9. A 64-year-old female status post liver transplant presented with recurrent ascites and acute renal failure with a clinical suspicion of portal vein anastomotic stenosis. CO_2 portography shows no stricture at the anastomotic site (arrow).

iodinated contrast, CO_2 has a tendency to overestimate the degree of stenosis.[46] However, care must be taken not to reflux CO_2 into the arterial system during upper extremity fistulography to avoid potential neurologic damage, such as infarction.[8,46]

Delivery

Although there are unique properties of CO_2 that afford it certain advantages to be used as an alternative contrast agent, there are other unique properties that pose a technical challenge in delivering the agent. The colorless, odorless, and compressible nature of CO_2 requires the special attention needed in handling and injecting CO_2.[8] Many methods for injection of CO_2 exist, including handheld syringes and plastic bag systems as well as dedicated injectors (Fig 11).[47]

Hand injection can be associated with potential complications, including delivery of an unknown volume. In addition, an "explosive delivery" of the gas has also been commonly described as a potential complication of hand injection occurring when the catheter used to inject CO_2 has fluid within it. With fluid in the catheter, a large force is required to expel the fluid from the catheter. The CO_2 is compressed against the fluid-catheter interface and once the fluid has exited the catheter, a sudden expansion of the CO_2 gas occurs, resulting in an "explosive delivery."[7,8,48] In an effort to allow controlled injection of CO_2 and prevent an "explosive delivery," a 3-mL syringe may be used to forcefully expel the fluid from the catheter using a 1-way valve before contrast administration.[8,48]

Because of Boyle's law (the inverse relationship of pressure and volume in an ideal gas), small volumes of gas delivered from pressurized CO_2 tank will expand to a large volume when exposed to atmospheric pressure or the patient's arterial pressure. Thus, the catheter should not be directly attached to the tank in an effort to prevent "explosive delivery." A syringe may be used to draw a volume of CO_2 and subsequently connect to the patient's intravascular catheter. However, a syringe connected directly to and under the pressure of the CO_2 tank will contain an indeterminate volume of CO_2 gas, which can potentially result in an excessive dose of CO_2 being delivered into the patient. Thus, previously it was thought that syringes could be transiently opened to room air and atmospheric pressure to prevent "explosive delivery." To prevent air contamination when the syringe is opened to room air, it was previously hypothesized that because CO_2 is heavier than air, the syringe should not be held upright (tip to the ground) as it may exit the catheter and be replaced by the lighter air. However, this was disproven and it was determined that inverting the syringe has no effect on air contamination. In fact, air contamination occurs because of diffusion when the syringe is open to ambient air, irrespective of the syringe position. Thus, there was a dilemma, as it was known that to prevent delivering an unknown volume of CO_2, and preventing "explosive delivery," the patient's catheter could not be directly connected to the pressurized tank and using a syringe carried the risk of air contamination. To solve this technical predicament, a plastic bag delivery system was found to allow a controlled volume of delivery and reduce air contamination.[7,8,47,48]

Many safe injection systems have been described, including plastic bag delivery and automatic and mechanical injectors that do not pose the aforementioned problems.[8,19,48-50] However, some of these delivery systems can be complex and cumbersome for the operator, leading to modification of previously described systems.[51]

Contraindications and Complications

Although CO_2 is a relatively safe contrast agent, potential adverse effects have been reported. Earliest studies with intravenous CO_2 in the study of pericar-

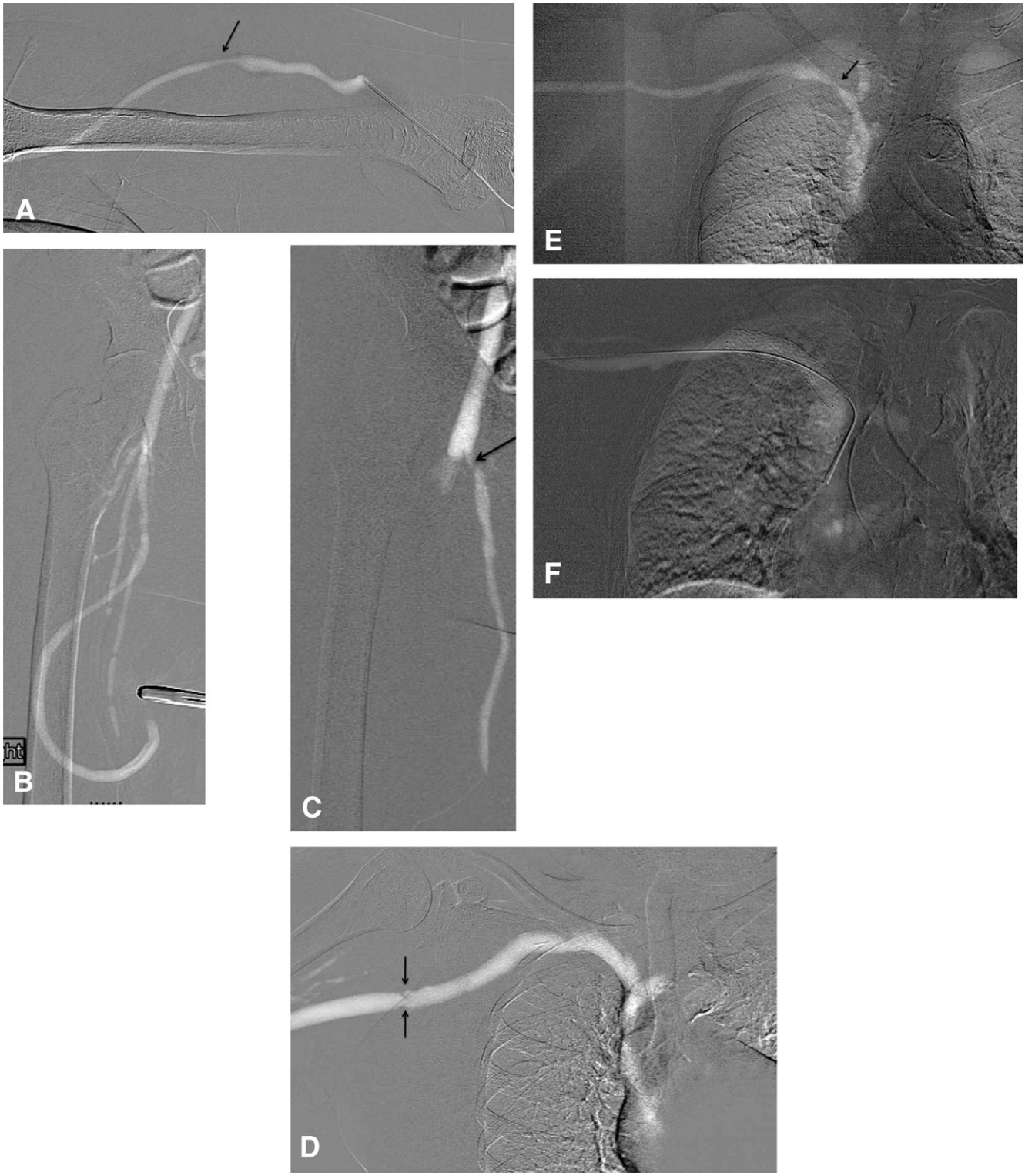

FIG 10. CO_2 arteriovenous fistulography shows (A) stenosis within the right upper extremity graft (arrow). Arterial (B) and venous (C) limbs are demonstrated with a focal stenosis at the venous anastomosis (arrow). A venous valve (arrows) is demonstrated on the central venography (D). A focal central stenosis (E, arrow) with subsequent stenting (F) is shown.

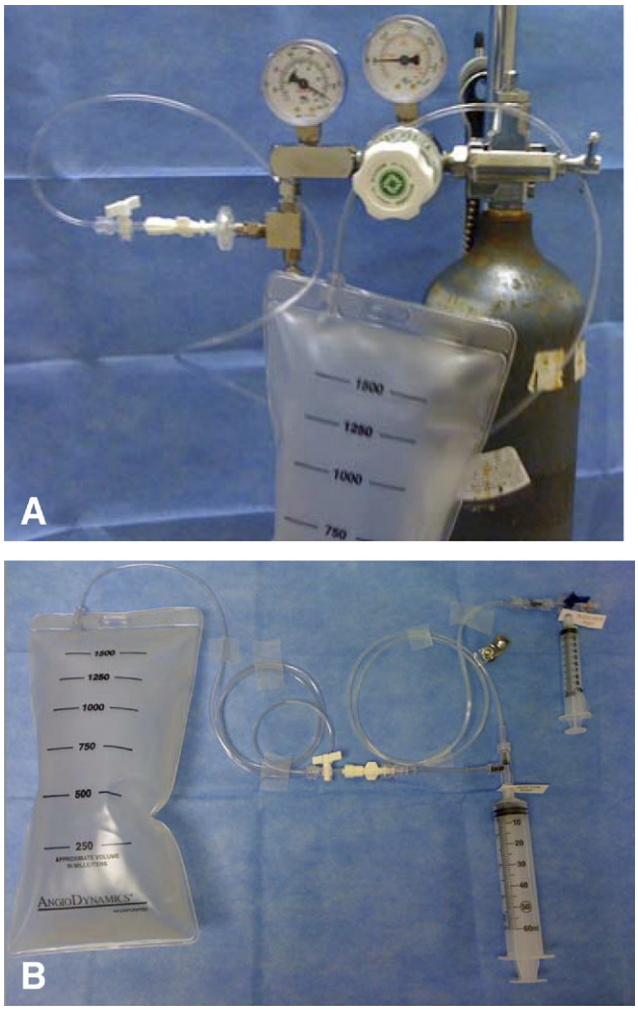

FIG 11. CO_2 delivery system with (A) a bag (AngioDynamics, Latham, NY) attached to a standard medical pressurized CO_2 tank and (B) the handheld syringe apparatus. (Color version of figure is available online.)

dial effusion carried no associated complications.[5,11] In addition, gas embolism is not a known complication of CO_2 venography or arteriography.[5,52]

It seems most of the potential adverse effects of CO_2 are related to the "vapor lock" phenomenon. This results when CO_2 gas is trapped and obstructs normal blood flow, usually in cases where excessively large volumes are injected or adequate time is not allowed between serial injections to allow clearance of the CO_2 gas.[53] The "vapor lock" phenomenon is also responsible for right heart failure during venography due to obstruction of blood flow by CO_2 when excessive volumes are used or adequate time between injections is not allowed. Similarly, transient ischemic colitis and a case of transient mesenteric ischemia have also been reported after CO_2 angiography secondary to "vapor lock" phenomenon.[5,54]

An experimental study in dogs revealed an 11.9% transient decrease in renal blood flow with return to baseline in 24 hours. There was no dose-dependent effect and no histologic evidence of damage was present unless the kidney was positioned vertically, which would require a longer time to cortically clear the gas.[55] This relates to the buoyancy of CO_2 as it can become trapped in a nondependent organ or vessel, such as renal transplants and mesenteric vessels. In addition, slow dissolution may result in tissue ischemia. For example, in the evaluation of abdominal aortic aneurysms, trapped CO_2 can lead to the presence of nitrogen from tissues exchange and subsequent embolization of insoluble nitrogen can lead to ischemia.[5,56] Therefore, allotting adequate time in between serial injections to allow clearance, changing positions to allow trapped gas to be cleared, and using low volumes of gas can avoid these potential adverse effects. Although a recommended maximum arterial injection volume of no greater than 100 mL and a maximum intravenous injection dose of 50 mL have been reported, it is likely that a higher total volume can be used so as long as small doses at a time are delivered and time is allotted between serial injections.[7,8]

Other reactions, such as nausea and vomiting, have been reported after CO_2 injection when compared with iodinated contrast injection.[30] In addition, a fatality has also been reported after CO_2 arteriography, in which a patient suffered from livedo reticularis, rhabdomyolysis, and intestinal infarction. The authors concluded an interarterial injection in a patient with impaired cardiac function as the likely mechanism.[56] With regard to CO_2 hepatic venography during TIPS, wedged techniques have been reported to be associated with hepatic lacerations as opposed to the balloon occlusion method.[57]

Although no alteration in blood gas levels has been reported from the use of CO_2, the use in patients with severe respiratory disease or chronic obstructive pulmonary disorder where CO_2 may not be readily cleared is cautioned. Although CO_2 contrasted studies have been performed without any adverse effects reported, some have recommended frequent arterial blood gas checks during the procedure as well as using a conservative volume of CO_2 and an increased time between injections in these patients.[5,8,53]

CO_2 should not be used for cerebral angiography as mixed results regarding neurotoxicity have been reported. Neurotoxicity and dose-dependent neurologic damage, including infarction and blood–brain barrier disruption, have been demonstrated in animal studies,[58] while other studies showed no such effects.[59]

Despite these reported potential adverse effects, CO_2 is largely and relatively safe with only 1 complication of transient colonic ischemia in a study of 800 patients and only 7 cases of complications in a study of 1200 patients.[8,53] For these reasons, arterial studies should be limited to below the diaphragm. Additionally, intravenous injections into the IVC should be avoided in patients with a patent foramen ovale.

Conclusions

CO_2 can serve as a suitable alternative intravascular contrast agent, especially in patients with renal failure or an iodine contrast allergy. It demonstrates an acceptable diagnostic accuracy in most applications, and in the case of TIPS, even superior to ICM. Although CO_2 is relatively safe as an intravascular agent, it does come with a technical challenge with regard to its delivery as well as a few potential adverse effects.

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