Carbon Dioxide Digital Subtraction Angiography (CO_2 DSA): A Comprehensive User Guide for All Operators

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ABSTRACT: In 1971 during a routine celiac axis injection, 70 cc of room air was inadvertently injected into a patient instead of iodinated contrast. Fortunately, there were no ill effects and despite the use of cut film at the time, Hawkins visualized the celiac axis and its branches as a negative image. Because of this incident, in combination with his previous knowledge of carbon dioxide (CO_2) in venous imaging, he began to study the intra-arterial use of CO_2 in animals. Following the safe, successful use in animals he applied the same principles to humans. Unfortunately, technology lagged behind his genius and the initial imaging was poor. Later, during the 1980s, there was the development of digital subtraction angiography, tilting tables and a safe, reliable CO_2 delivery system. As technology continued to improve, CO_2 evolved into a viable vascular imaging agent. Although used initially for renal failure and iodinated contrast allergy, the many unique properties of CO_2 yielded multiple advantages, which are now used in a multitude of scenarios alone or in combination with traditional contrast. It has now been used with great success in both adults and children for more than 3 decades with only limited reportable complications. Its safe use in children has been described and when performed in this age group the same principles apply as for adults. This paper describes the history and technique of CO_2 angiography for vascular procedures.

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Key words: peripheral vascular disease, abdominal aortic aneurysm, renal failure, contrast medium, new techniques

HISTORY

It wasn't long after the discovery of x-rays by Conrad Roentgen in 1895 that gas was first used as an imaging agent. In 1914 room air was used with radiographs in an attempt to visualize the abdominal viscera and its abnormalities.[1] Less than a decade later room air, oxygen, or carbon dioxide was insufflated in the retroperitoneum to evaluate for masses.[2,3] Because of the problem of air emboli, room air and oxygen were eventually replaced with carbon dioxide (CO_2), the solubility of which is 20 times to 30 times that of O_2.

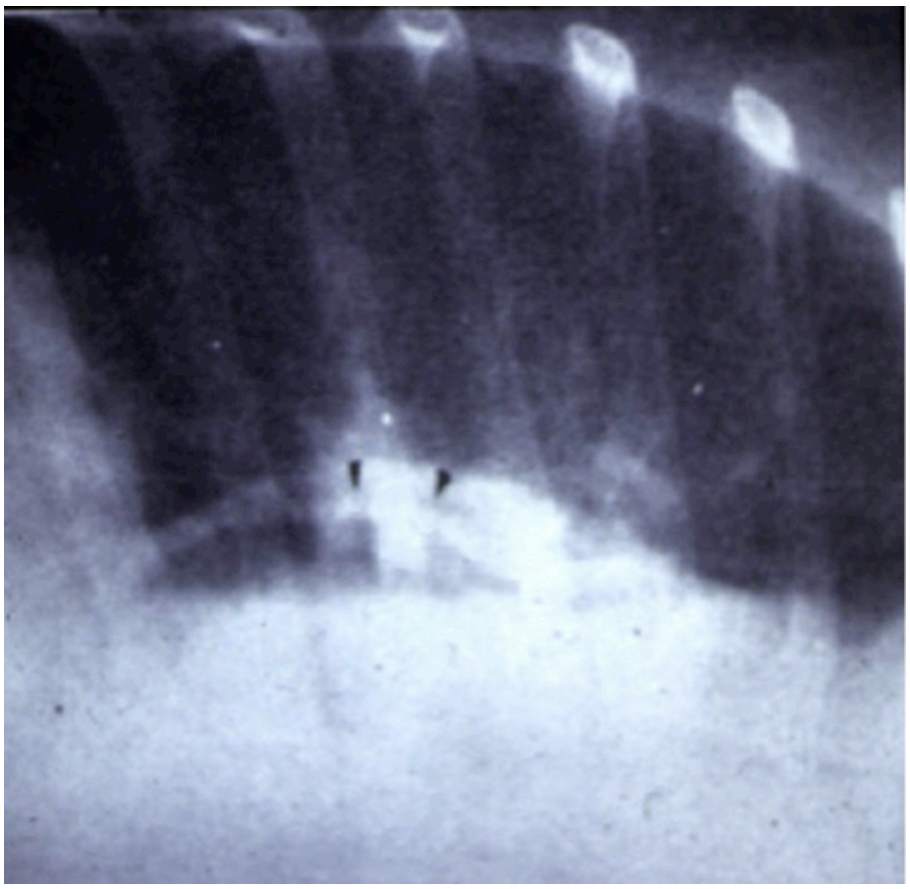


Figure 1. Left lateral decubitus chest x-ray after the administration of intravenous CO_2 for pericardial evaluation. The CO_2 bubble trapped in the nondependent portion of the right atrium is seen as a negative contrast.

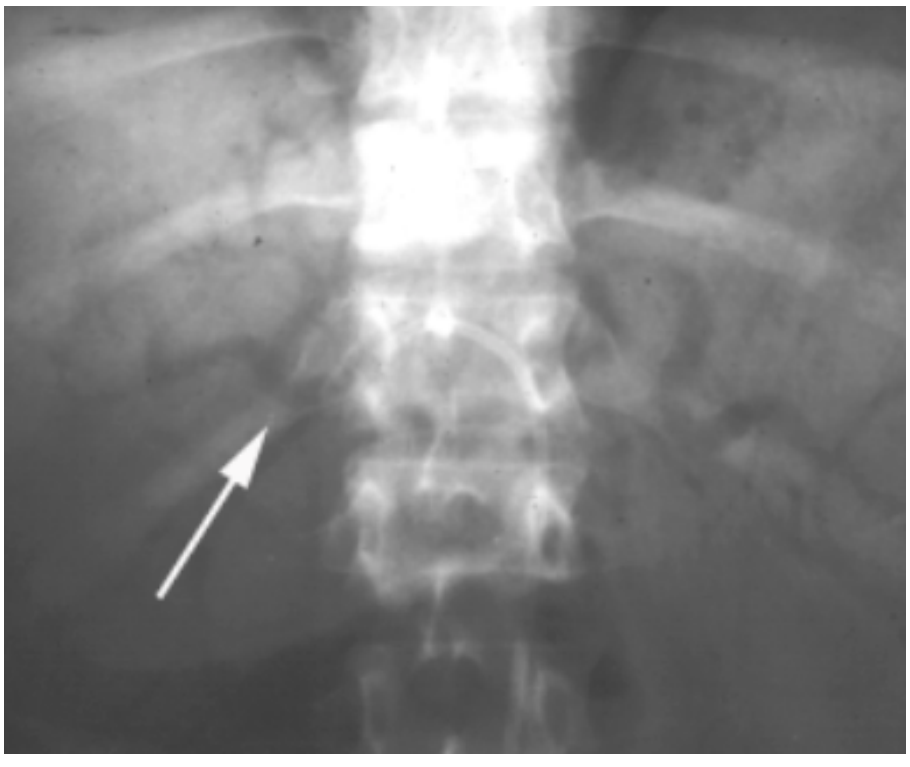


Figure 2. Celiac arteriogram with an inadvertent injection of room air. The branches of the celiac artery are filled with gas. Arrow points to negative image from room air in the celiac circulation.

Extrapolating from Cormak who in 1837 reportedly blew two large breaths into the jugular vein of a horse with no ill effects, CO_2 was later used in the 1950s and 1960s as a venous contrast agent to evaluate for pericardial effusion.[4-7] Patients were placed in the left lateral decubitus position and a cross table lateral x-ray could outline the width of the right atrium. Bendib et al performed 1,600 cases without complications, using a peripheral injection of 100 cc to 200 cc of CO2 to evaluate for pericardial effusion **(Figure 1)**. Additionally in 1969 Hipona reported the safe use of CO2 for the evaluation of the inferior vena cava (IVC).[8]

Subsequently, the biggest advancement in the use of CO_2 as a contrast agent was fortuitous. In 1971 during a routine celiac axis injection, 70 cc of room air was inadvertently injected into a patient instead of iodinated contrast. Fortunately, there were no ill effects and despite the use of cut film at the time, Hawkins visualized the celiac axis and its branches as a negative image **(Figure 2)**.[9] Because of this incident and with his previous knowledge of CO_2 in venous imaging, he began to study the intra-arterial use of CO_2 in animals. Following the safe, successful use in animals he applied the same principles to humans.[10] Unfortunately, technology lagged behind his genius and the initial imaging was poor. Later, during the 1980s, there was the development of digital subtraction angiography, tilting tables, and a safe, reliable delivery system. As technology continued to improve, CO_2 evolved into a viable vascular imaging agent. Although used initially for renal failure and iodinated contrast allergy, the many unique properties of CO_2 yielded multiple advantages, which are now used in a multitude of scenarios alone or in combination with traditional contrast.

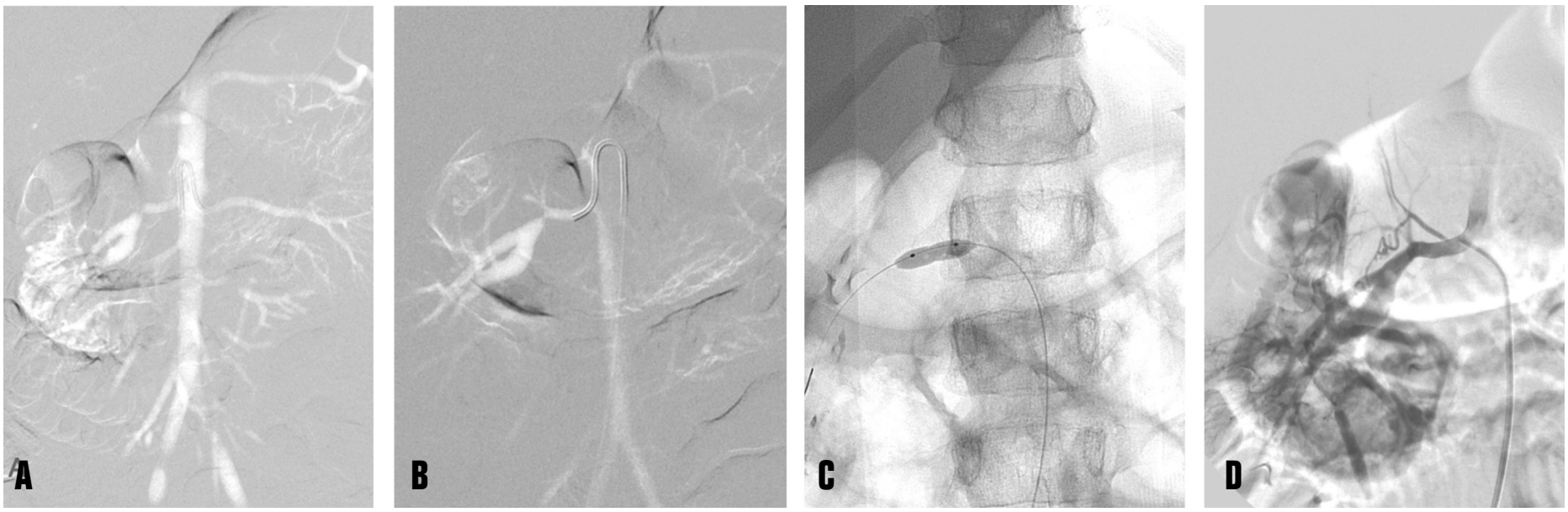


Figure 3. CO_2 renal angiogram and angioplasty in a 6-year-old patient with angiodysplasia. CO_2 aortogram demonstrating right renal artery stenosis (A). Selective right renal angiogram confirming the findings (B). Balloon percutaneous transluminal angioplasty (C). Post angioplasty renal angiogram using dilute iodinated contrast (D).

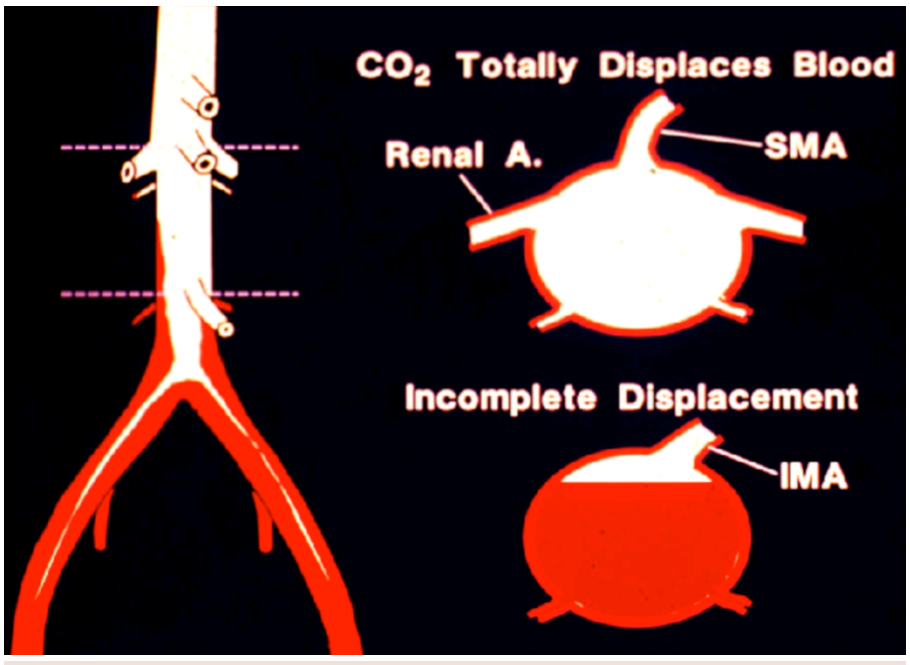


Figure 4. Carbon dioxide (white) will generate a representative image depending on the amount of blood that is displaced.

It has now been used with great success in both adults and children for over three decades with only limited reportable complications. Its safe use in children has been described and when performed in this age group the same principles as the adult apply **(Figure 3)**.[11,12]

PROPERTIES

To use CO_2 appropriately, a basic knowledge of its properties is essential. CO_2 is a nontoxic, nonflammable,

Table 1. Physical Properties of CO_2 and Physiologically Related Gases

	CO_2	O_2	N_2
Molecular weight	42	32	28
Solubility	0.87	0.03	0.016

buoyant, compressible gas that has low viscosity and is produced endogenously at approximately 200 cc to 250 cc per minute. It is a natural byproduct and there are approximately 120 liters of CO_2 stored in the soft tissues at one time.[13] It is transported in the blood to the lungs by three mechanisms: dissolution directly in the blood (7%), bound to hemoglobin (10%), or predominantly carried as a bicarbonate ion (85%) **(Figure 4)**.

Because CO_2 is present endogenously there is no concern for allergy or renal toxicity, which has been confirmed by numerous animal and human studies.[9,10] Its viscosity is 1/400 that of iodinated contrast and it is also highly soluble, roughly 20 times to 30 times greater than O_2. Therefore it is less occlusive than other gases **(Table 1)**. When administered intravascularly, it tends to dissolve within a vessel in 30 seconds to 60 seconds. In intravenous administration it is also removed from the lungs in one pass. If CO_2 persists in a vessel for more than

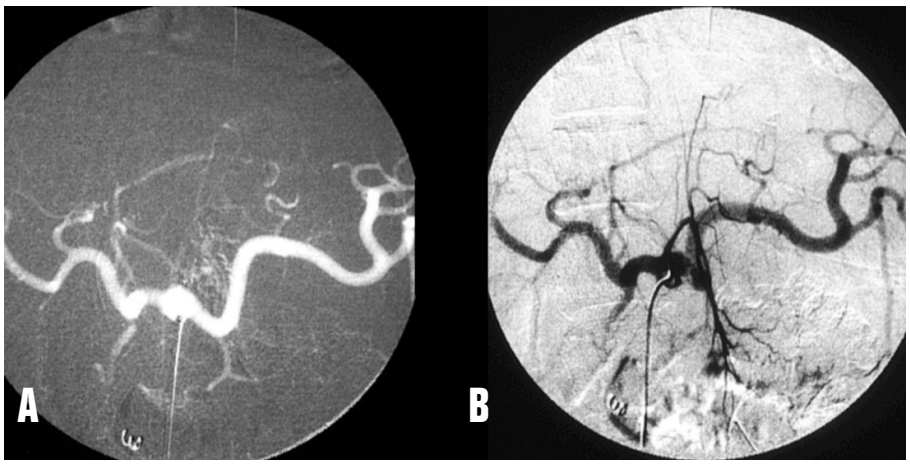


Figure 5. Comparison of CO_2 (A) and contrast (B). Vessels less than 10 mm in diameter yield comparable images.

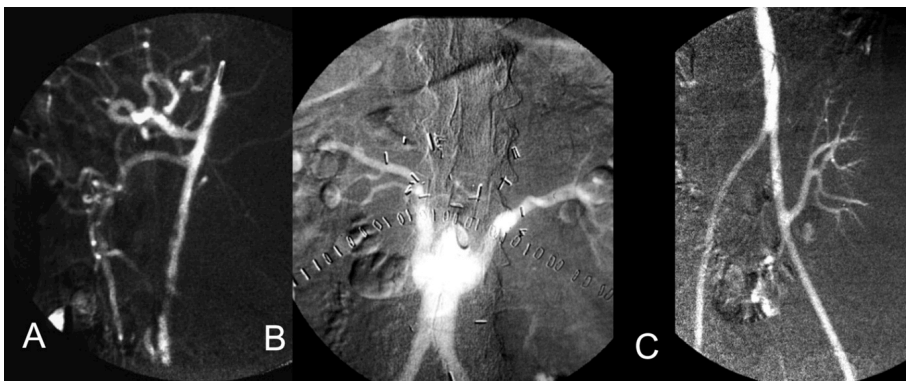


Figure 6. Anterior vessels are well demonstrated by CO_2 digital subtraction angiography (DSA) in the supine position. Superior mesenteric artery and celiac artery (A). Reimplanted renal arteries (B). Transplant renal arteries shown in left posterior oblique projection with the patient in the supine position (C).

30 seconds it is either trapped **(Figure 4)** or there is room air contamination.

As opposed to traditional liquid agents, carbon dioxide does not mix with blood. In fact, CO_2 is lighter than blood and floats anterior to it. To render a representative image it must displace the blood in the vessel. As a result, the vessel is less dense and a negative image is obtained with digital subtraction angiography. The quality and accuracy of the image will depend on the amount of blood displaced by the CO_2 **(Figure 4)**. Typically, smaller vessels, especially those 10 mm or smaller, demonstrate a better correlation with iodinated contrast **(Figure 5)**.[14-16] The difficulty sometimes lies in the much larger vessels where a higher volume of CO_2 is required. Furthermore, once the total volume of blood has been displaced, using a higher volume of CO_2 does not improve the vascular image.

Buoyancy must also be considered when using CO_2. Typically, a gas will rise to the nondependent surface of the vessel. If all blood is not displaced from the vessel it will readily demonstrate the anterior structures but potentially generate a spuriously smaller image of the larger feeding vessel. Again, it is imperative to displace as much blood as possible to generate a comparable image.

Conversely, buoyancy can be used as an advantage when attempting to visualize anterior vessels such as the celiac as well as the superior mesenteric artery (SMA) and inferior mesenteric artery. Where CO_2 is particularly favorable is in renal transplants and reimplanted renal arteries. These vessels are easily demonstrated because of their anterior position. CO_2 has the added advantage that it does not present a risk of renal toxicity in this group of patients who are particularly susceptible to renal insufficiency **(Figure 6)**.[17,18] Conversely, in vessels such as the native renal arteries, the left renal artery lies slightly posterior. In this scenario as well as others where vessels are more posterior, the patient can be placed in the partial decubitus position with the site of interest situated anteriorly. CO_2 will preferentially demonstrate these repositioned vessels.

In addition to its buoyancy, when CO_2 is administered into the vessel via a catheter it has the potential to fragment into random bubbles depending on how it is delivered. In an attempt to avoid this, the catheter should be purged prior to definitive delivery and a continuous, controlled delivery of the volume of choice

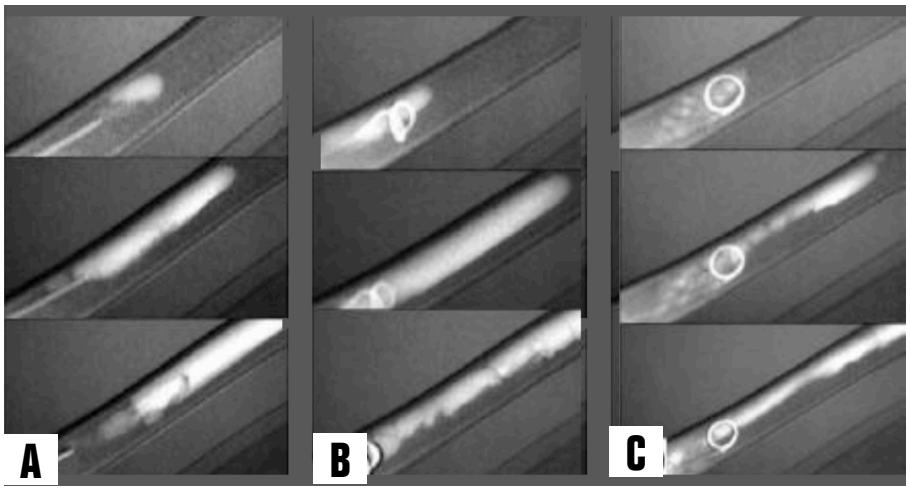


Figure 7. Patterns of gaseous delivery using different types of catheters. Using the end-hole catheter provides the most consistent bolus at the exit of the catheter (A). The halo catheter shows good bolus configuration at the exit site due to the side-hole distribution within the spiral portion of the catheter (B). The pigtail catheter shows a less homogenous gas bolus due to multiple side holes distributed along the distal portion and pigtail of the catheter (C).

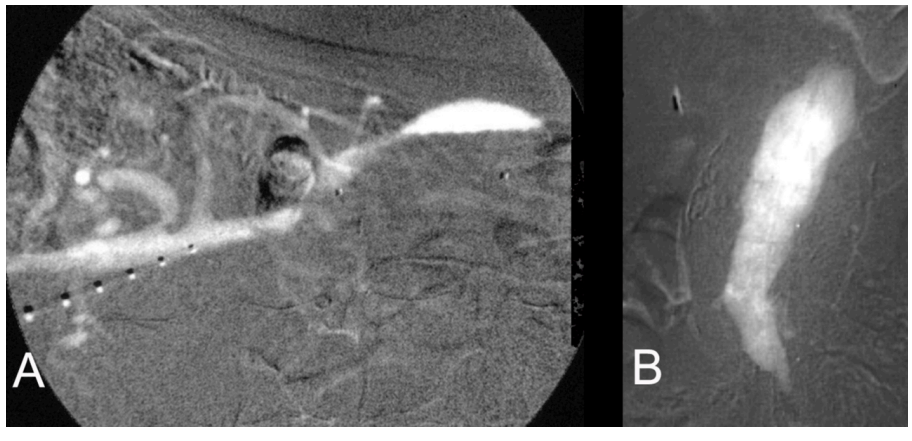


Figure 8. A cross-table lateral abdominal digital subtraction angiography in a supine patient showing a CO_2 bubble trapped in the most ventral part of the abdominal aortic aneurysm (A). Abdominal digital subtraction aortogram in the supine position showing CO_2 gas in the central part of the aortic lumen (B). Because of the gas buoyancy, the intramural thrombus cannot be demonstrated.

should be given. Dr. Cho studied the best catheter to administer a uniform, organized bolus of gas to minimalize the bubbling effect. He found that an end-hole catheter yielded the best results **(Figure 7)**.[19]

Again with respect to buoyancy, there is one instance in which it can be a significant detriment. When a blood gas interface is not present in an anterior structure such as an abdominal aortic aneurysm (AAA), the CO_2 may sit without dissolving and "trap" in that position (Figure 8). This can cause a problem in two different ways. First, if there is an anterior vessel arising from the trapped gas portion of the aneurysm such as the inferior mesenteric artery, it may preclude the flow of blood and potentially lead to ischemia. Secondly, if a bolus of CO_2 is stagnant, more occlusive gases such as N_2 and O_2 will be exchanged into the bolus due to partial pressure differences. Again this could potentially lead to ischemia. If trapping occurs it is usually evident on fluoroscopy or may produce symptoms of pain. It can easily be remedied by repeatedly changing the patient's position to stimulate gas movement. Some operators describe aspirating the gas with a catheter, but the author has not found this useful. Regardless, despite this potential, the reported incidence of this occurrence leading to significant clinical problems is negligible.

Although trapping is exceedingly rare, it can be exacerbated by the administration of excessive volumes of CO_2. An excessive volume can be caused by one exceptionally large volume or multiple smaller volumes delivered repetitively without allowing enough time for the CO_2 to dissolve. As described below a single sizeable bolus-causing trapping is extremely unlikely. The incidence of gas trapping most commonly arises if a typical large tank (usually 3 million cc) of CO_2 under pressure is misconnected to the delivery catheter allowing unfettered flow of gas into the vessel. Regarding repetitive small doses, it is best to wait at least 30 seconds to 60 seconds between injections to allow for CO_2 to be dissolved.

Concerning dose, Cho addressed the effect of various

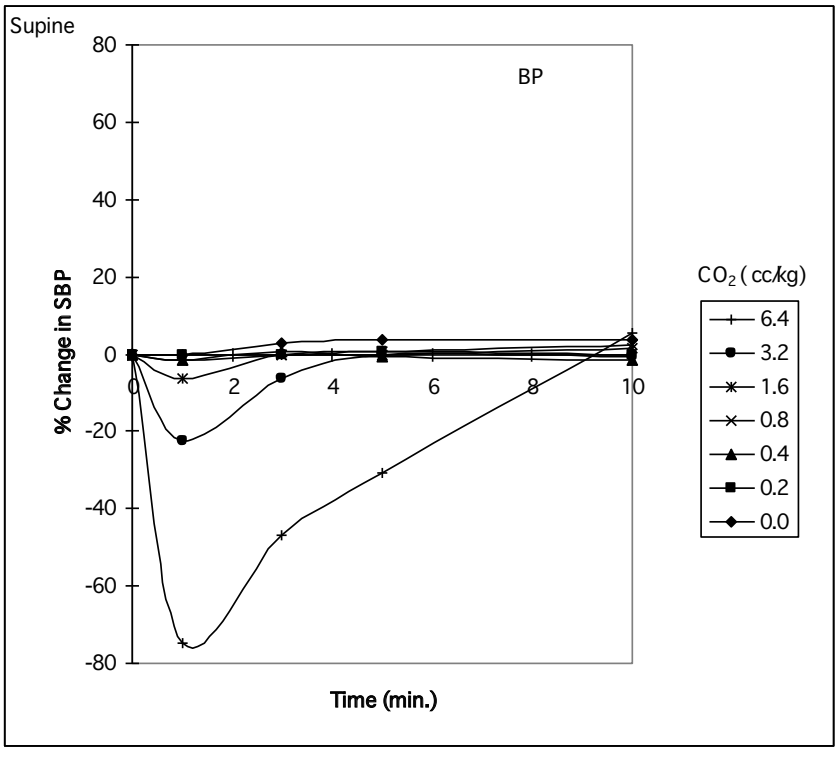


Figure 9. Percentage changes in blood pressure following intracaval injections of ascending doses of CO_2 in swine.

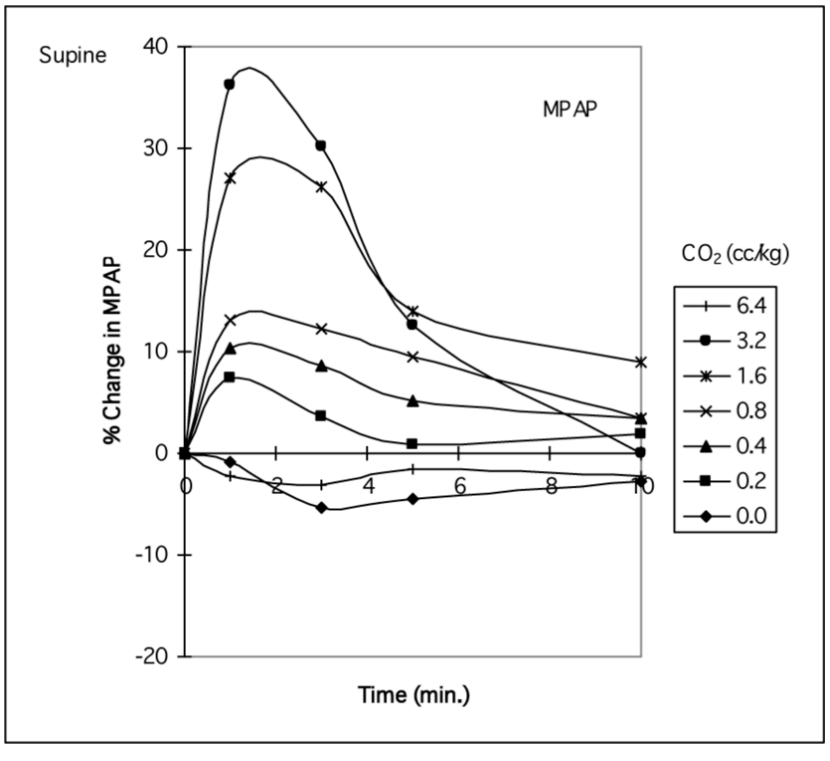


Figure 11. Percentage changes in SaO_2 following intracaval injections of increasing doses of CO_2 in swine.

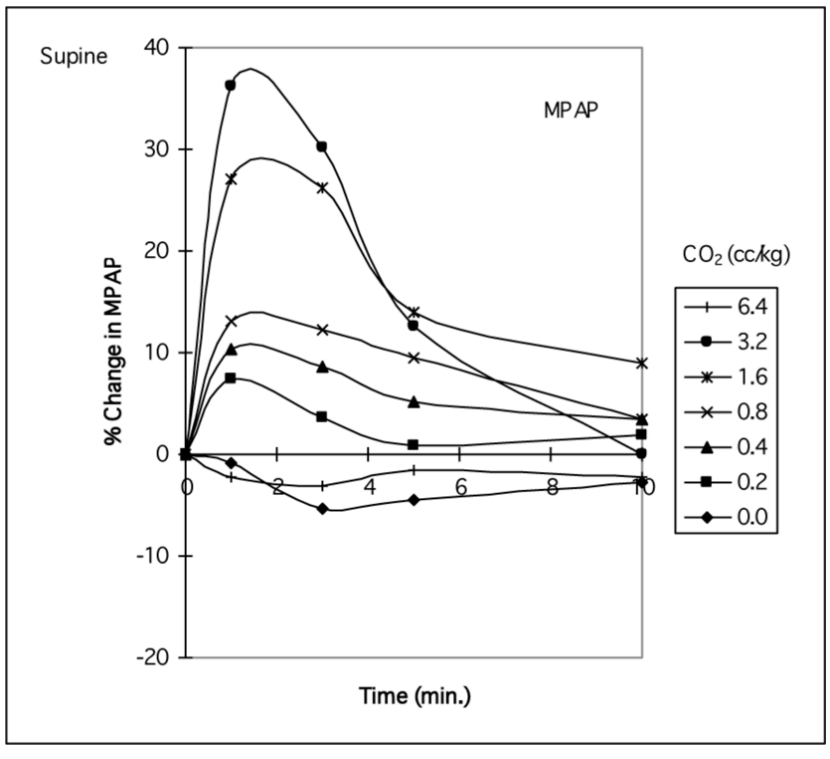


Figure 10. Percentage changes in pulmonary arterial pressure following intracaval injections of ascending doses of CO_2 in swine.

intravenous CO_2 volumes on heart rate, respiration rate, blood pressure (BP), pulmonary artery pressure, arterial blood saturation of O_2, partial pressure of CO_2, partial pressure of O_2, pH, and bicarbonate at 1, 3, 5, and 10 minutes.[19] He concluded that a single dose up to 1.6 cc/Kg resulted in no changes in cardiopulmonary parameters **(Figures 9–11)**.[19] The dose can subsequently be repeated with impunity after 30 seconds to 60 seconds. This amounts to a single dose of 112 cc for a 70-Kg person. That volume is more than necessary for any clinical scenario. Following the study, Cho mentioned a caveat that intravenous CO_2 should be performed cautiously in patients with known pulmonary hypertension.

As with any interventional procedure, patients undergoing CO_2 digital subtraction angiography (DSA) should have routine monitoring of ECG, pulse oximetry BP, respiratory rate, and heart rate. As a safety measure, Cho recommends monitoring BP 1, 2, and 3 minutes after the first CO_2 injection.

Another important divergent property of CO_2 when compared with liquid agents is its compressibility. This compressibility can affect delivery, including volume, in various ways. Because CO_2 is a gas it is extremely

Table 2. Grades of CO_2.	
TYPE	PURITY
Research grade	99.999%
Supercritical fluid chromatography grade	99.998%
Instrument grade	99.99%
Coleman grade	99.99%
Anaerobic grade	99.9%
Medical grade	99.5%
Standard grade	99. 5%

compressible under pressure. A 20-cc syringe can hold a volume of 200 cc if compressed sufficiently. This can affect intravascular injections. Initially, if you are trying to keep the individual dose below the volume causing changes in parameters set forth by Cho, it is imperative to know the amount of CO_2 delivered. Therefore the delivery system should be purged to atmospheric pressure to eliminate the compression and to avoid administering a larger dose than the amount indicated on the syringe.

Additionally, we have found that when a compressed dose is delivered it can be explosive. This type of delivery can expand the vessels, which results in adverse symptoms. In the abdomen symptoms of abdominal pain, urge to defecate and nausea can occur. The veins, which have less media in their walls than arteries, are more susceptible to pain especially when rapidly expanded. It is hypothesized that the vascular stretch receptors are activated with larger volumes and more explosive administration.[20] Aside from causing undue pain to the patient, this pain usually results in motion that significantly degrades the acquired images. Moreover, compression, which can lead to explosive delivery, can cause CO_2 to reflux into inappropriate vessels, potentially resulting in complications. This is especially true of the cerebral vessels in which CO_2 should be avoided. Finally, to completely avoid explosive delivery, the delivery catheter should be purged of saline or blood prior to the definitive dose. Hawkins showed that by not purging the catheter, the CO_2 in the delivery syringe can compress and 95% of the dose is explosively delivered in the last 0.5 seconds.

To recapitulate, for avoiding these rare but potentially untoward events, compressed explosive delivery should be avoided. The delivery system should not be under pressure. Whatever system is being used should be purged to the atmosphere to equilibrium. Following this, the delivery syringe plunger should be gently advanced to purge the diagnostic catheter of saline or blood. Subsequently the appropriate dose can be delivered in a controlled and nonexplosive manner. Note that unlike a liquid contrast syringe, in which a smaller syringe generates more pressure, a larger syringe (usually 20 cc to 35 cc) should be employed with CO_2. If not, the gas may simply compress in the syringe without delivery, especially if the catheter is not purged.

Probably the most significant property of CO_2 and the one that causes the most concern and discourages competent operators from using it is that it is invisible. Because it is invisible, contamination with more occlusive room air is a major concern of many operators. Knowledge of the sources of contamination and how to avoid them is imperative but relatively simple. During the inception of intravascular use of CO_2, Hawkins found that routine, reusable cylinders contained carbonic acid, rust, particulate matter and water.[10] It is essential, therefore, that disposable sources of at least medical-grade CO_2 be utilized **(Table 2)**.

PROPERTIES OF CO_2

- Endogenous
- Invisible
- Nontoxic
- High solubility (29 times that of O_2)
- Low viscosity (1/400 that of iodinated contrast)
- Buoyant
- Compressible
- Nonallergenic
- Non-nephrotoxic
- Not diluted by blood like contrast
- Dissolves rapidly in the blood and is removed by the lungs in one pass

We suggest research grade, which is more pure. Not only does this avoid inappropriate embolization but it also avoids pain for the patient.

Contamination may also result when a syringe of CO_2 is left open to room air. Because of partial pressure differences, room air will enter the syringe and replace the pure CO_2 at the rate of .2 cc per minute. So a 20 cc open syringe will contain 12 cc of room air after an hour. This can be avoided with the use of a closed delivery system that is not open to room air. Delivery systems, especially those that use a bag reservoir, should be purged three times to rid the system of residual room air.

Finally, delivery system connections should be secured, either with glue or luer lock. Loose connections can lead to the aspiration of room air. Some individuals also hypothesize that stopcocks are not impervious to gas introduction with aspiration. Therefore, stopcocks and aspiration should be kept to a minimum.

In summation, contamination can be easily avoided by utilizing medical-grade CO_2, disposable sources (cylinder or cartridge), and a closed, purged delivery system with secured connections, utilizing few stopcocks and minimal to no aspiration. Delivery systems are discussed below.

CONTRAINDICATIONS, CAVEATS, AND DISADVANTAGES

When utilizing gas as an imaging agent the biggest concern is the possibility of embolic occlusion and secondary ischemia. The rapid solubility of CO_2 allows for intravascular use but the coronary, thoracic aortic, and cerebral vessels are less forgiving and delivery into these vessels should be avoided. Likewise, CO_2 should never be delivered in or adjacent to the thoracic aorta especially in the prone position. Theoretically the buoyancy of CO_2 can dissipate into spinal vessels and cause ischemia from embolus or trapping. Although there are literature discussions to the contrary, most operators will avoid direct injections in these sensitive vessels.[21-25] Additionally, because of the tendency of CO_2 to reflux, it is prudent to avoid intra-arterial injections above the diaphragm. Similarly, when imaging dialysis interposition grafts or fistulas, the arterial limb should be examined cautiously. To reduce the possibility of central cerebral reflux the patient can be placed in the Trendelenburg position or a microcatheter can be inserted into the artery and a gentle antegrade angiogram can be performed. In fact it is good practice, regardless of the procedure, to refrain from arterial delivery with the patient's head in the elevated position. Again, this reduces the potential for central reflux into the arterial cerebral and thoracic circulation.

Other clinical scenarios that theoretically predispose a patient to untoward embolization include right-to-left shunts and the combination of pulmonary artery hypertension and a patent foramen ovale. These instances are extremely rare and mostly hypothetical but

operators should be knowledgeable of this possibility. In the patients with known right to left shunts, CO_2 can be safely injected into the venous system with the patient's position right side up (left lateral decubitus) to trap the gas in the right atrium away from the septal defect.

An additional rare contraindication is the use of nitrous oxide general anesthesia when using intravenous CO_2. When using this anesthetic there is the potential for N_2 residing in the soft tissues to diffuse into the CO_2 bubble, causing it to be 5 times to 6 times more occlusive. This potential scenario arises in transjugular intrahepatic portosystemic shunt (TIPS) patients in which CO_2 is used in general anesthesia for the procedure.

A recurrent concern for novice operators is the use of CO_2 in patients with chronic obstructive pulmonary disorder (COPD). Considering the small amounts of CO_2 necessary for imaging compared to endogenous production, it is unlikely that a clinical dose will cause a problem as long as the patient is breathing spontaneously. As a precautionary measure in COPD patients, it is suggested to allow more time between injections. Instead of the recommended 30 seconds to 60 seconds between injections in most routine patients, those with COPD should be increased to 2 minutes to allow for definitive dissolution.

It is important to remember the potential increase in radiation exposure to the operator and the patient when using CO_2 DSA. It is recommended that the frame rate for acquiring CO_2 images approximate 6 per second or more. This is double the frame rate for typical iodinated contrast imaging, which could potentially result in an increase in radiation by a factor of 4. However, this number is difficult to measure exactly because each scenario is different and finding the diagnosis or accomplishing the desired result using CO_2 may decrease the overall necessity for more runs. Finally, the consequences of not using CO_2 DSA may far exceed the potential adverse effects of a slight increase in radiation from CO_2 DSA use. Considering the potential to increase radiation exposure when performing CO_2 DSA, typical radiation protection steps should be employed.

DISADVANTAGES AND CONTRAINDICATIONS FOR GASEOUS CONTRAST

Disadvantages

- Requires a unique gas based delivery system
- Invisible – operator concern for undetected room air contamination
- Patient motion can deteriorate images
- Bowel gas motion can interfere with abdominal imaging
- Obtaining appropriate images may be more labor intensive
- Administration into cerebral, coronary, and thoracic aortic arteries should be avoided

Absolute Contraindications

- Direct or refluxed administration of CO_2 into the cerebral, cardiac, or thoracic aortic arteries
- Use of arterial CO_2 in known right-to-left shunt
- The concomitant use of intravenous CO_2 injections and nitrous oxide anesthesia

In addition to the above contraindications, there are a few minor disadvantages that exist when changing from a fluid-based vascular contrast to carbon dioxide. The primary disadvantage is learning how to employ a gas-based delivery system as opposed to iodinated contrast. CO_2 is invisible, colorless, odorless, and cannot be seen or felt so the comfort level for use is much less than iodinated contrast. The operator must learn and feel confident in the type of delivery system.

Additionally, CO_2 vascular imaging is typically not as dense, and patient motion can seriously affect the final product. Likewise, bowel gas motion can deteriorate

abdominal images. For these reasons and because of the fact that gas properties are much different than traditional liquid agents, rendering diagnostic images and post-processing may be more labor intensive when using CO_2. Reducing patient motion by injecting CO_2 gently without explosive delivery is extremely beneficial. To reduce bowel gas motion some operators use glucagon 1 mg/mL intravenously prior to injection. Using a gastrointestinal compression device to assist in displacing the bowel has been suggested.[25]

ADVANTAGES OF CO_2 DIGITAL SUBTRACTION ANGIOGRAPHY

- Nonallergic
- Non-nephrotoxic
- Can use unlimited total volumes
- Low viscosity (1/400 that of contrast)
  - Improves detection of acute hemorrhage
  - May enhance demonstration of arteriovenous fistula, tumor vessels
  - Easier administration through microcatheters
  - Can be administered around wire in catheter using a Y-connector without losing wire position
  - Portal vein opacification
  - Can be administered via super fine small needles (25-27 gauge) with less invasiveness
  - Central reflux
  - Can demonstrate entire vessel, central and peripheral, to catheter end hole unlike contrast
- Not diluted by blood like contrast
- Inexpensive: 100 cc costs 3 cents
- Although primarily for the vasculature can be used in any luminal structure, e.g. biliary ducts

Nonallergic Quality of CO_2

Because CO_2 is disseminated throughout the body's soft tissues, it is nonallergenic. This advantage is extremely beneficial when an operator is confronted with an emergent intravascular procedure in a patient with a severe allergy to iodinated contrast. Currently most operators utilize low osmolar nonionic contrast which has an incidence of allergic reaction of .7% to 3% and severe anaphylaxis of .02% to .04%.[26-28] Rarely, even with appropriate premedication, breakthrough can occur. One of the classic procedures for this indication is IVC filter placement, particularly when there is no time for classic premedication with prednisone.

In addition to the emergent situation, there are scheduled allergic patients who accidentally are not pretreated or simply forget to take the prep. Often, a scheduled procedure takes a great deal of preparation, travel, and cost, so cancelling would be counter-productive and expensive. CO_2 DSA can be employed in many of these cases to avoid the additional cost and chaos.

Non-nephrotoxic Quality of CO_2

Undoubtedly the best advantage of CO_2 DSA is its lack of nephrotoxicity.[10,29-34] Contrast-induced nephropathy (CIN) is the third leading cause of hospital-acquired renal failure behind decreased renal perfusion and nephrotoxic medications.[35] The incidence of hospital-acquired contrast-induced nephropathy approximates 7%.[36] This is based on the definition of CIN representing an increase of serum creatinine of 0.5mg/dL or a 25% elevation over baseline. This usually begins within the first 24 hours and peaks up to 5 days following the offending incident.

The significance of CIN was underscored by McCullough.[37] He compared individuals who developed hospital-acquired CIN to those who received contrast and maintained stable creatinine. Those with CIN had 5.5 times the incidence (34%) of in-hospital mortality. Those requiring dialysis had even higher rates of mortality. The duration of hospitalization was twice those without CIN accompanied by increased morbidity and cost. In addition, those developing CIN demonstrated chronic effects with increased (2 times) 1- and 2-year mortality. Cardiovascular events were

the leading cause of increased morbidity and mortality in these patients.

Rihal et al prepared a retrospective analysis on approximately 7,500 in-hospital patients, of whom 3.3% developed CIN.[38] The in-hospital mortality was 22% for those developing CIN vs 1.4% who did not. The 1- and 5-year mortality rates were almost 4 times greater in the CIN group. Therefore the risk of death persists long term following discharge. It must be stated that the incidence of CIN in these two groups was all-inclusive and that the incidence of CIN was much higher proportionately in those with underlying renal insufficiency. The majority of patients with CIN do not undergo dialysis. Today with improved iodinated contrast the incidence of CIN requiring dialysis approximates 4% for those with renal insufficiency[39] and 3% for those undergoing percutaneous coronary intervention.[40]

Early animal studies by Hawkins and others showed that CO_2 as an intravascular contrast agent did not affect renal function.[9] Hawkins later went on to demonstrate this in humans as well. Comparing iodinated contrast, gadolinium, and CO_2 in renal insufficient patients, CO_2 was the only agent not demonstrating an elevation in creatinine.[41,42] It should be the first-line imaging agent in patients with renal insufficiency requiring vascular evaluation or intervention. Even if there are limitations to the CO_2 imaging it can be used in conjunction with limited diluted doses of iodinated contrast. Although hydration and cessation of nephrotoxic drugs are helpful, reducing the volume of iodinated contrast is by far the best method for eliminating CIN.[43] CO_2 DSA can usually accomplish this alone or as an adjunct to dilute liquid contrast. Moreover, because of the solubility of CO_2 and the fact that it is eliminated via one pass through the lungs when given IV, there is no limit to the total dose delivered. As a result, unlimited volumes can be given provided that individual doses are given as previously discussed.

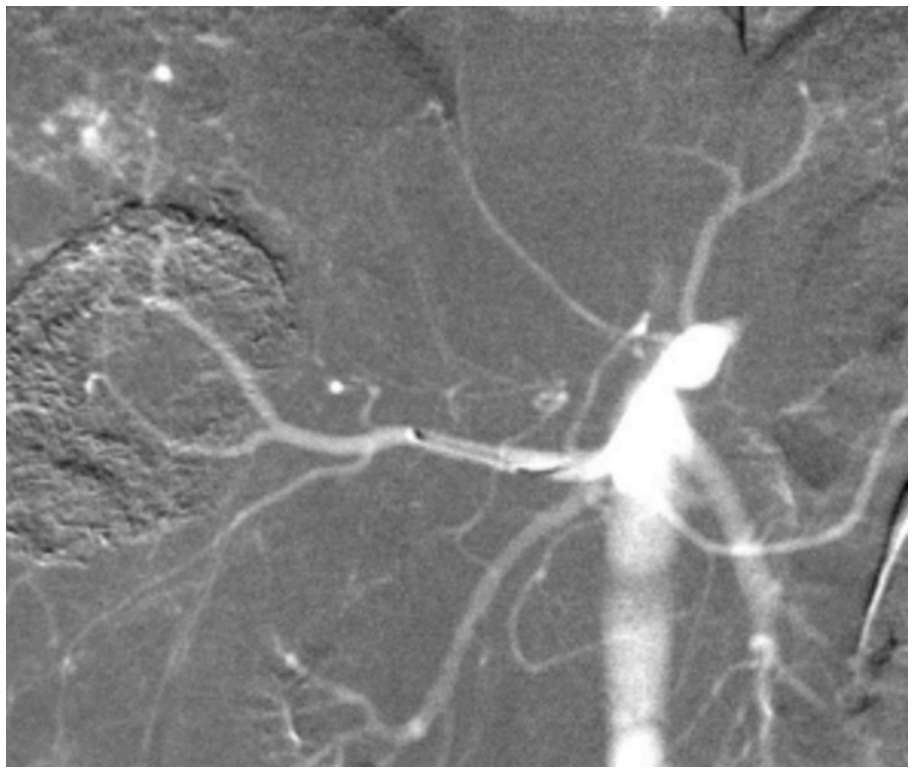


Figure 12. Facile injection of CO_2 using a high-flow microcatheter. Digital subtraction angiogram with the injection of CO_2 into the mid right hepatic artery through a Renegade HI-FLO microcatheter (Boston Scientific) with inner diameter .027″. CO_2 visualized both the distal and proximal hepatic arteries. CO_2 refluxed into the aorta and other aortic branches including the superior mesenteric, left gastric, and inferior phrenic arteries.

Low Viscosity

The viscosity of CO_2 is 1/400 that of iodinated contrast, permitting its delivery through smaller, less invasive catheters and needles. This is advantageous when using microcatheters in which sufficient volumes of thicker contrast may be difficult to deliver. CO_2 can easily be administered in significant doses and has the advantage of central reflux resulting in opacification of the entire vascular structure **(Figure 12)**. As opposed

Figure 13. Selective renal injection into the left main renal artery displaying the renal ostium and the contralateral renal artery origin. CO_2 will display the ostium for proper intervention when necessary.

to CO_2, contrast will only demonstrate distal to the catheter. This is especially useful in procedures such as renal stent deployment in which intervention is central to the catheter tip. The position of the stenosis and ostium can always be visualized using CO_2 reflux **(Figure 13)**.[44]

Likewise, CO_2 can be injected through (ultra fine) needles as small as 27 gauge. These needles are much less invasive and have been used successfully with CO_2 in the liver and spleen as well as peripheral venography **(Figure 14)**. When injected in the splenic and hepatic parenchyma CO_2 will opacify and exit via the low-pressure veins. Considering the size and flexibility of the smaller needle, use in the liver and spleen can be done in the presence of ascites and does not require the correction of an underlying coagulopathy.

Because of its low viscosity, CO_2 can be injected through a catheter with the wire in place using a Y-adapter **(Figure 15)**. This is advantageous when

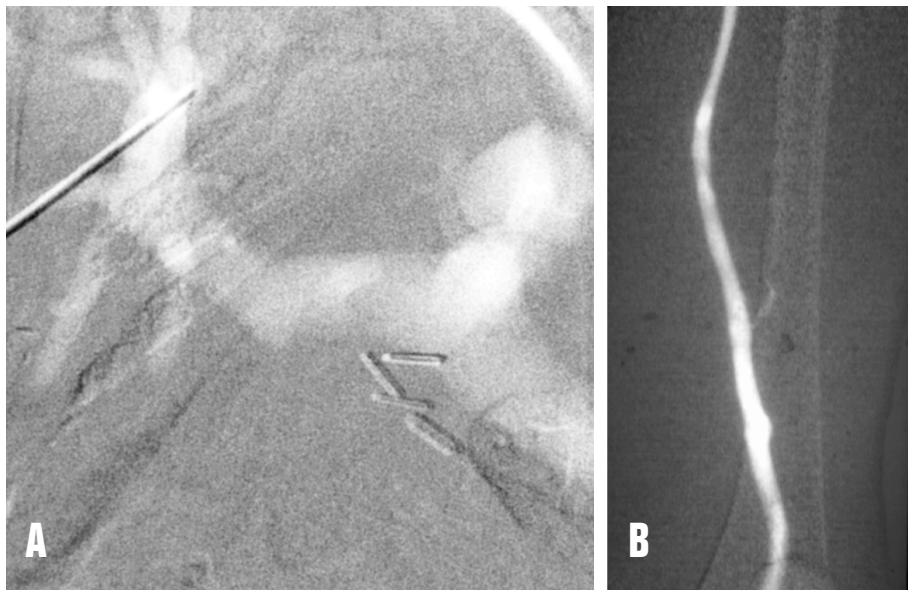


Figure 14. Parenchymal injection of CO_2 demonstrates portal vein (A). Peripheral leg CO_2 venous injection demonstrates femoral vein patency (B).

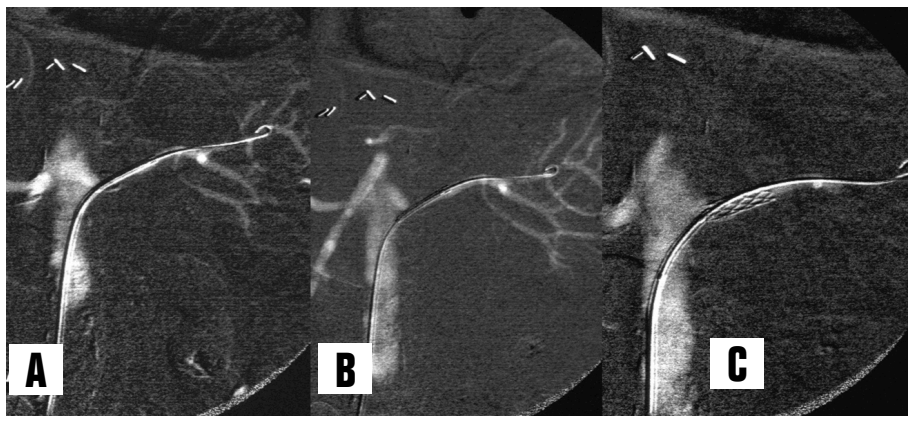


Figure 15. After placing the balloon expandable stent in the stenotic left renal artery, CO_2 is injected between the guidewire and catheter using a Touy-Borst adapter and digital subtraction angiography shows the correct positioning of the stent (A, B). After placement of the stent, CO_2 is injected into the sheath positioned at the proximal stent while the wire is in place. Digital subtraction angiography shows the patent stent in good position.

performing invasive procedures and at times when it is preferable to maintain wire access. The result of the procedure can be assessed while leaving the wire in place. The more viscous contrast would require removal of the wire and loss of access.

Similarly, CO_2 is extremely beneficial in the demonstration of hemorrhage **(Figures 16-18)**.[45-49] It tends to

exit the arterial rent much more readily than its thicker counterpart (described later). Although less consistent this can also be seen with arteriovenous (AV) fistulas and tumor vessels.

Another potential benefit of CO_2 is the fact that it doesn't mix with blood so it is not diluted. This property permits excellent central venous visualization from peripheral injections using small needles **(Figure 19)**.

Finally, one of the biggest advantages of CO_2 is its cost. The typical cost for CO_2 is 3 cents per 100 cc, which is exponentially cheaper than iodinated contrast.

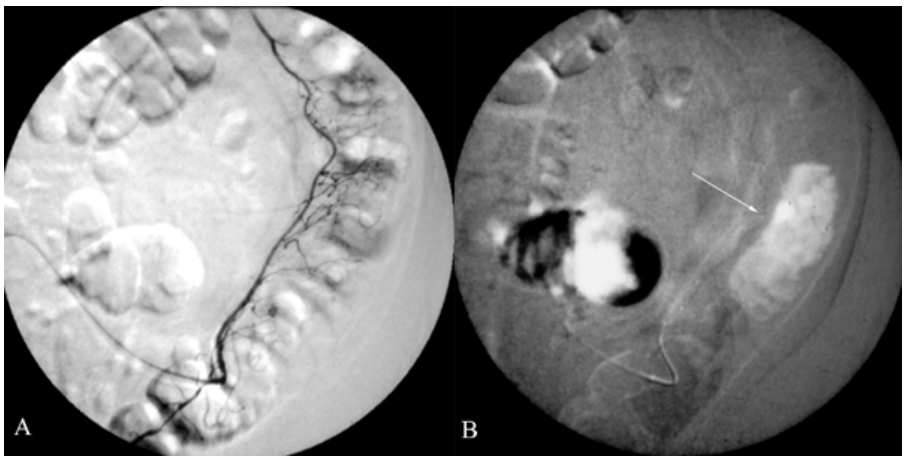


Figure 16. Left colic arteriogram in a patient with massive lower gastrointestinal bleeding shows no active contrast extravasation (A). Repeat arteriogram with the injection of CO_2 shows gas extravasation in the descending colon (arrow) (B).

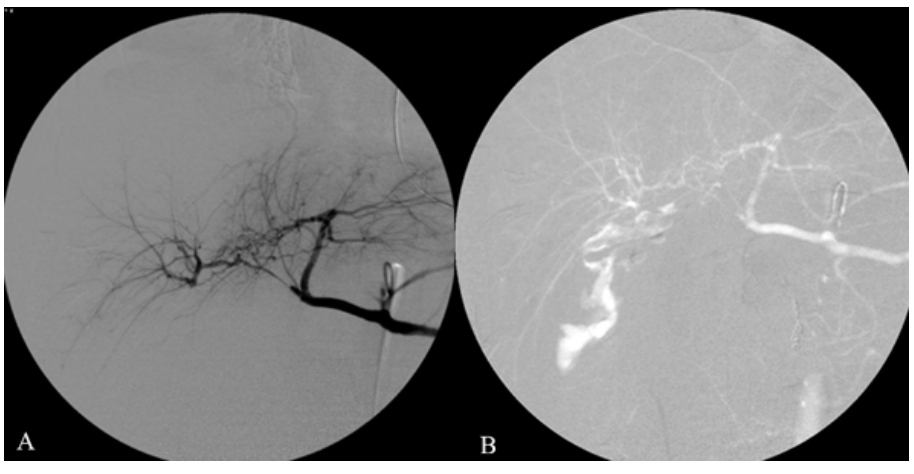


Figure 17. Celiac digital subtraction angiography (DSA) in a patient with liver laceration shows occlusion of the right hepatic artery with reconstitution of its distal branches by collaterals from the middle hepatic artery. No contrast medium extravasation is seen (A). Repeat DSA with the injection of CO_2 shows gas extravasation from the occlusion site of the right hepatic artery (B).

INDICATIONS: ALONE OR AS AN ADJUNCT TO IODINATED CONTRAST ALLERGY

Iodinated contrast allergy is explained above. Emergent patients or those who for a variety of reasons did not receive prednisone prep can use CO_2 DSA if necessary.

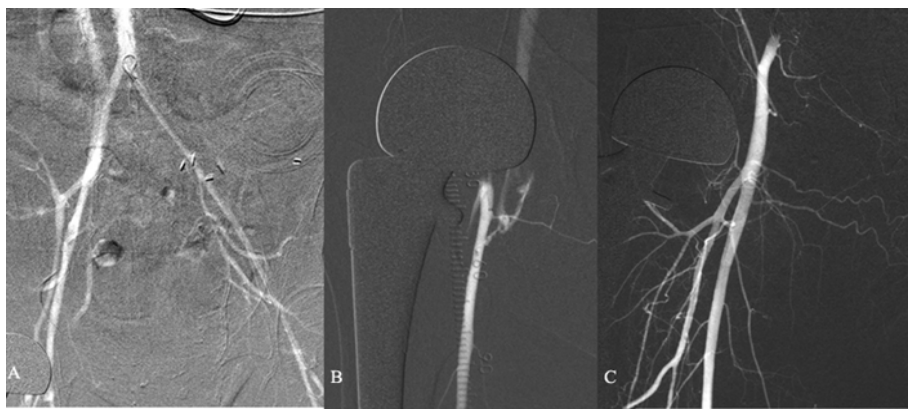


Figure 18. CO_2 pelvic arteriogram from left femoral approach in a patient with right femoral artery puncture-site hematoma shows simultaneous filling of the right iliac artery and vein (A). Magnified femoral DSA with CO_2 shows arteriovenous just caudal to the prosthetic femoral head (B). After placement of a covered stent, the arteriovenous fistula is no longer seen with CO_2 injection.

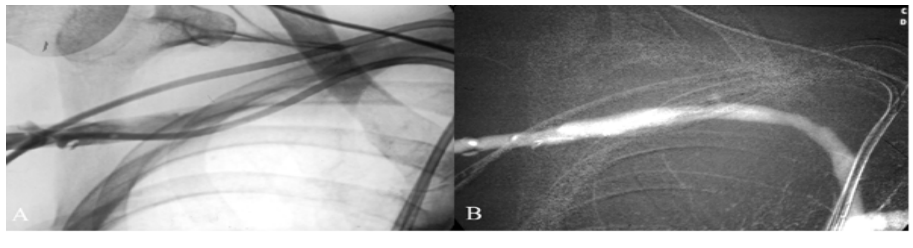


Figure 19. Subclavian venogram with CO_2 in a patient with dialysis access from right internal jugular vein (A). CO_2 digital subtraction angiography after injection into a small hand vein shows a patent subclavian vein (B).

INDICATIONS

- Iodinated contrast allergy
- Intravascular contrast procedures in high-risk patients for contrast-induced neuropathy
- High-volume contrast procedures
- Renal transplant evaluation
- Detection of hemorrhage
- Peripheral artery occlusive disease
- Endovascular aneurysm repair
- Interventional oncology
- Venous diagnosis and intervention (central veins, hepatic/portal, IVC) TIPS
- Splenoportography

Contrast-Induced Nephropathy

There are many clinical scenarios that predispose a patient to CIN. These include myeloma, diabetes, acute cardiac abnormalities, hypotension, nephrotoxic drugs and underlying renal disease. Unfortunately, one or more of these conditions is commonly present in patients requiring invasive vascular procedures. In these patients, the incidence of CIN is increased, but can be lessened with the use of CO_2 DSA. Although rare, CIN can also occur in patients without comorbidities. Most commonly, the incidence of CIN is related to the volume of iodinated contrast, the route of administration (intra-arterial carries higher risk than intravenous) and pre-existing renal insufficiency.[17,50-52] Of these 3 variables, only volume of contrast is controllable. Therefore, when performing procedures requiring significant volumes of contrast, CO_2 can be used alone or as an adjunct to decrease this possibility. More importantly, CO_2 should be the preferred contrast in evaluation and intervention of the renal artery in renal transplants and renal arterial reimplantation cases. CO_2 not only avoids CIN in these highly susceptible patients, but the position of the renal artery anatomy is ideal for visualization. These arteries typically arise anteriorly where CO_2 is best at imaging **(Figure 20)**.

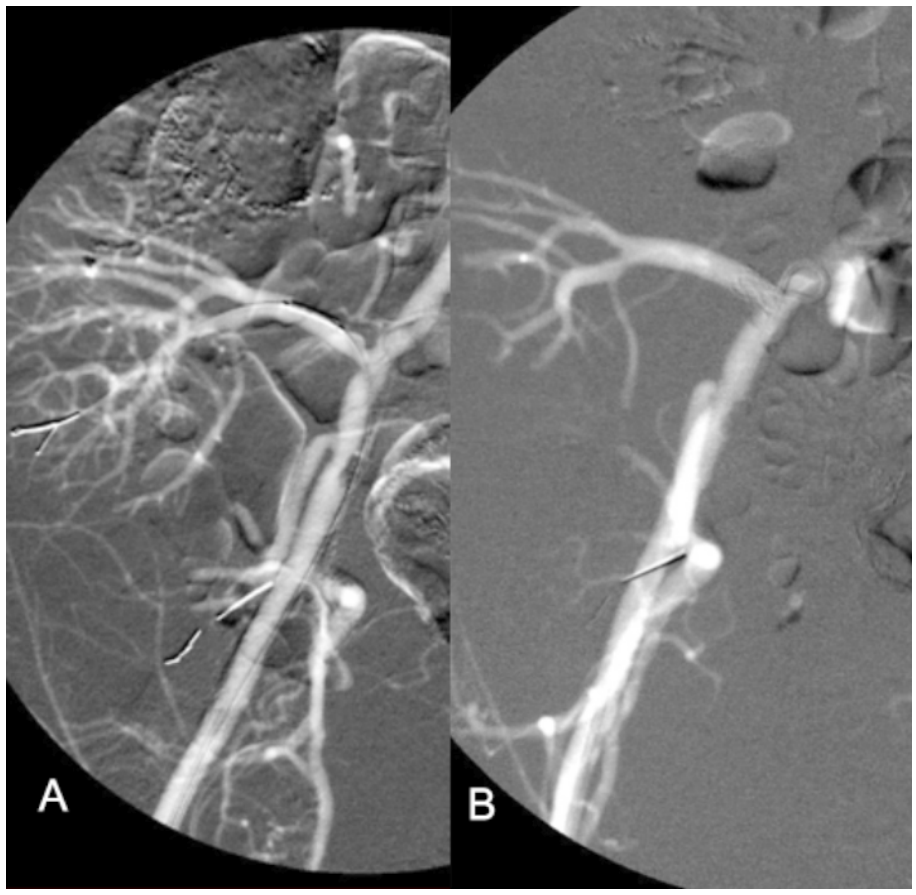


Figure 20. CO_2 renal digital subtraction angiography (DSA) in a patient with renal transplant and hypertension shows ostial stenosis (A). After stent placement, CO_2 DSA shows the patent stent with patent intrarenal arteries (B).

Hemorrhage

One area in which CO_2 DSA has been extremely beneficial is in the diagnosis of acute arterial hemorrhage **(Figure 21)**. Regardless of the etiology, whether iatrogenic, traumatic, or GI bleed, delineating the origin of bleeding and treating it precipitously can lead to significantly less morbidity and mortality. Iodinated contrast has typically been ineffective at demonstrating the offending vessel and as a result large volumes are often utilized with no diagnosis. Hawkins reported that the use of CO_2 DSA has approximately 2.5 times the sensitivity for defining the acute hemorrhage when compared to iodinated contrast.[47] There are several

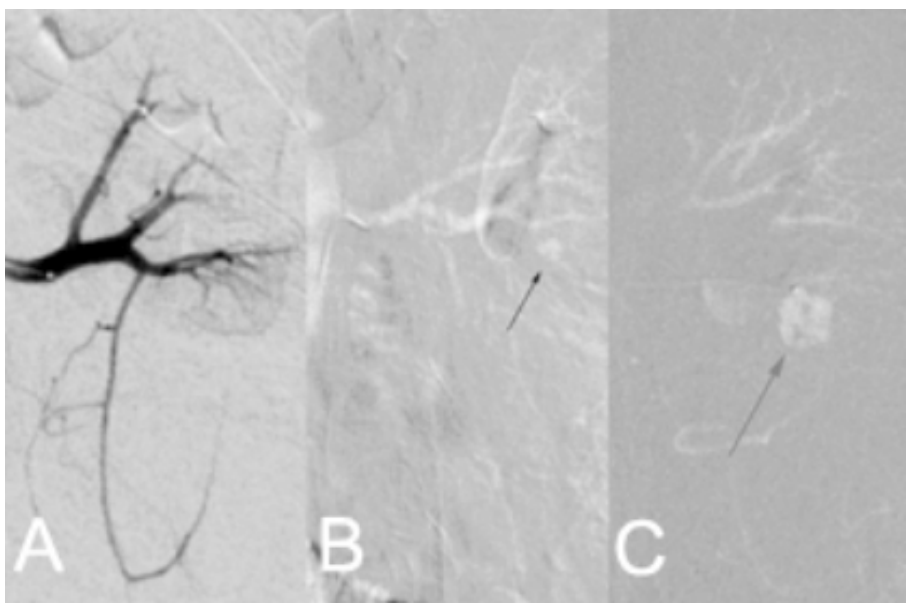


Figure 21. Massive bleeding complicating robotic surgery for renal cell carcinoma. Left renal digital subtraction angiography with iodinated contrast medium shows no active contrast medium extravasation (A). Repeat arteriogram with CO_2 shows a pseudoaneurysm in the lower pole of the kidney (arrows) (B, C).

reasons for this, the primary one being its low viscosity. It is much easier for a gas to pass through a pinhole as opposed to the more molasses-like iodinated contrast. In addition, CO_2 tends to be under pressure in the vasculature so it expands and appears cloud-like when it exits. Once out of the vessel it does not mix with the pool of blood and dilute away like liquid contrast. Finally, there is no capillary phase with CO_2 to obscure a small potential bleed. In combination, these factors lead to the improved sensitivity.

Again, CO_2 is not the ultimate contrast agent, and there are shortcomings when it involves acute GI hemorrhage. Bowel motion can significantly degrade a CO_2 DSA image and preclude diagnosis. Some operators have addressed this by administering glucagon 1 mg/mL intravenously prior to the injection of CO_2. Compression of the abdomen by the image intensifier or paddle may also help. Occasionally, the offending vessel is small or posterior and the CO_2 refluxes centrally and does not define the entire vessel. In this instance, there are two options. One can place the catheter in a superselective position and allow reflux, or it is sometimes better to administer the bolus in the larger central vessel, such as the aorta, so that all vessels fill. Once identified, the offending vessel can be embolized appropriately. It is critical to realize that when performing post embolization follow-up with CO_2 DSA, it should be done extremely gently. If CO_2 is forced into the embolized vessel, the explosive delivery can cause the embolic thrombus to migrate and result in rebleeding. To prevent this, a small amount of dilute contrast can be utilized, instead of CO_2.

Peripheral Arterial Occlusive Disease

The incidence of peripheral arterial occlusive disease (PAOD) and endovascular repair is increasing. CO_2DSA is vital and extremely useful in this clinical scenario but it is currently underutilized. Successful correlation of CO_2 and iodinated contrast in PAOD was demonstrated by Seeger's group in the mid 1990s.[52] They demonstrated a 92% correlation with an increase to 100% when a small amount of iodinated contrast was administered. It is well known that PAOD exists as part of a systemic process. Patients with intermittent claudication and rest pain undergoing angiography and intervention commonly have concomitant renal artery disease and insufficiency. In a review of 127 patients presenting with intermittent claudication or lower-limb ischemia, approximately 45% had coexistent renal artery stenosis. Seventeen percent had mild, 16% had severe, and 12% had bilateral renal artery disease.[53] In another review of

100 patients, greater than 50% had renal artery occlusion and unilateral or bilateral stenosis.[54] More importantly than the actual stenosis is the occult renal impairment that accompanies PAOD even with a normal serum creatinine. In one series of 76 PAOD patients requiring angiography with normal serum creatinine, 86% had subnormal creatinine clearance with 65% below 60 mL/min.[55] Another author reported that serum creatinine is inaccurate in 33% of patients 40 years to 49 years of age and 90% of patients older than 70.[56] This latter group is where most of the PAOD occurs. Considering these facts and the susceptibility of this group to CIN it would seem intuitive to use CO_2 as a contrast agent whenever possible. Again it can either eliminate or lower the total volume of iodinated contrast thereby lessening the potential for CIN.

Most operators begin by performing a common injection at the aortic bifurcation. If evaluation of the aorta is also warranted, this can be performed before or after the aortic bifurcation. Typically, a somewhat forceful injection of 30 cc to 60 cc CO_2 at the level of the renal arteries is sufficient. The left renal artery lies slightly posterior and if not visualized can be reexamined with a mild right lateral decubitus position, placing the left renal artery in a nondependent position **(Figure 22)**. Some operators administer glucagon 1 mg/mL intravenously to reduce bowel gas motion. Using an end-hole catheter will provide the best CO_2 bolus. For better visualization it is also recommended to employ a catheter with a radiopaque tip if contrast is to be avoided. As described above, with aortic injections it is imperative to monitor for AAA and potential trapping of gas. CO_2 can be visualized fluoroscopically

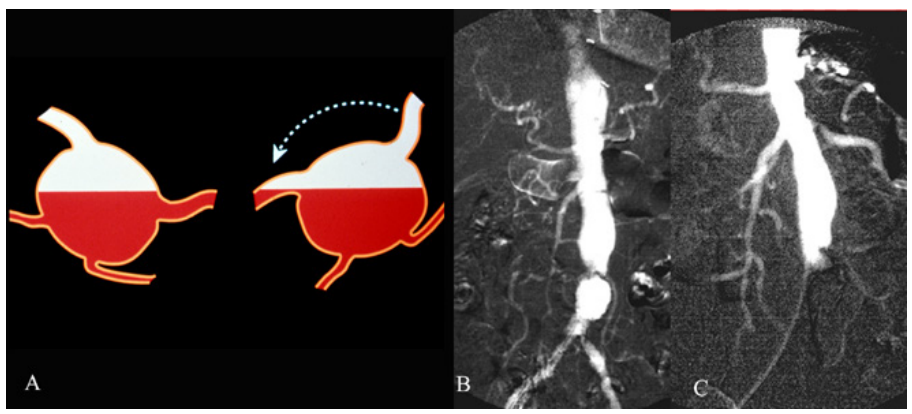


Figure 22. Cartoon showing axial view of aorta and renal arteries with CO_2 (white). Rotating the patient so the left side is up will opacify the more posteriorly positioned left renal artery (A). Frontal CO_2 angiogram without visualization of the left renal artery (B). CO_2 DSA with the patient rotated to left side up demonstrates the left renal artery (C).

and if a stagnant bolus is seen the patient should be rotated from side to side to dissipate the gas.

After evaluating the abdominal aorta, the central axial and nonaxial arteries of the pelvis and lower extremities can usually be evaluated with nonselective injections at the bifurcation. Volumes of 15 cc to 30 cc are usually adequate. Elevation of the lower extremities by 15 degrees to 30 degrees assists in peripheral delivery and visualization.[57] When performing this maneuver with the presence of advanced PVD, it may be prudent to wait longer and lower the patient's legs between injections to avoid trapping. Furthermore, selective injections can be made to improve imaging. It is not unusual to perform selective injections for visualization below the knee. Microcatheters are ideal for this purpose. Initially the catheter should be placed at the common femoral artery to include the profunda and collateral vessels. The catheter can then be advanced more peripherally towards the trifurcation as necessary. Gentle, nonexplosive doses of 5 cc to 10 cc are commonly sufficient **(Figures 23-26)**. Regarding the dose, if it does not appear appropriate,

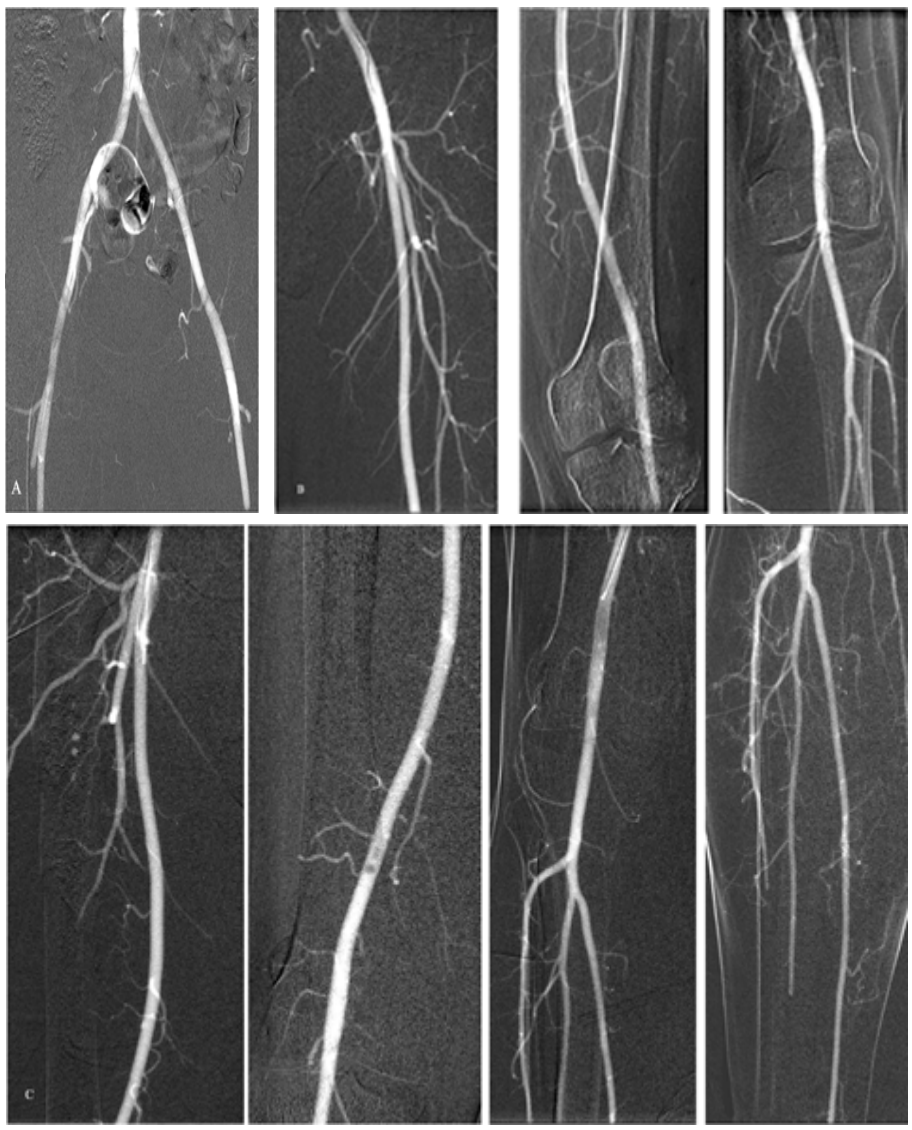


Figure 23. Pelvic angiogram with CO_2 digital subtraction angiogram using a 3 Fr pigtail (A). Run-off in the left and right legs using central 3 Fr pigtail at bifurcation (B, C).

it can be tailored to more or less without concern, as none of these injections will jeopardize renal function. If there is poor filling of the vessels, 1 mL of nitroglycerin (100-200mcg/mL) can be administered intra-arterially just prior to CO_2 injection.

Stacking software can also be employed with post processing. This program allows the superimposition of multiple frames to generate one composite image **(Figure 27)**. It takes the "bubble" effect out of CO_2 DSA and creates a solid vascular image. Finally, once the infrapopliteal vasculature is evaluated with CO_2 many authors in the literature advise administering one-quarter to one-half strength iodinated contrast

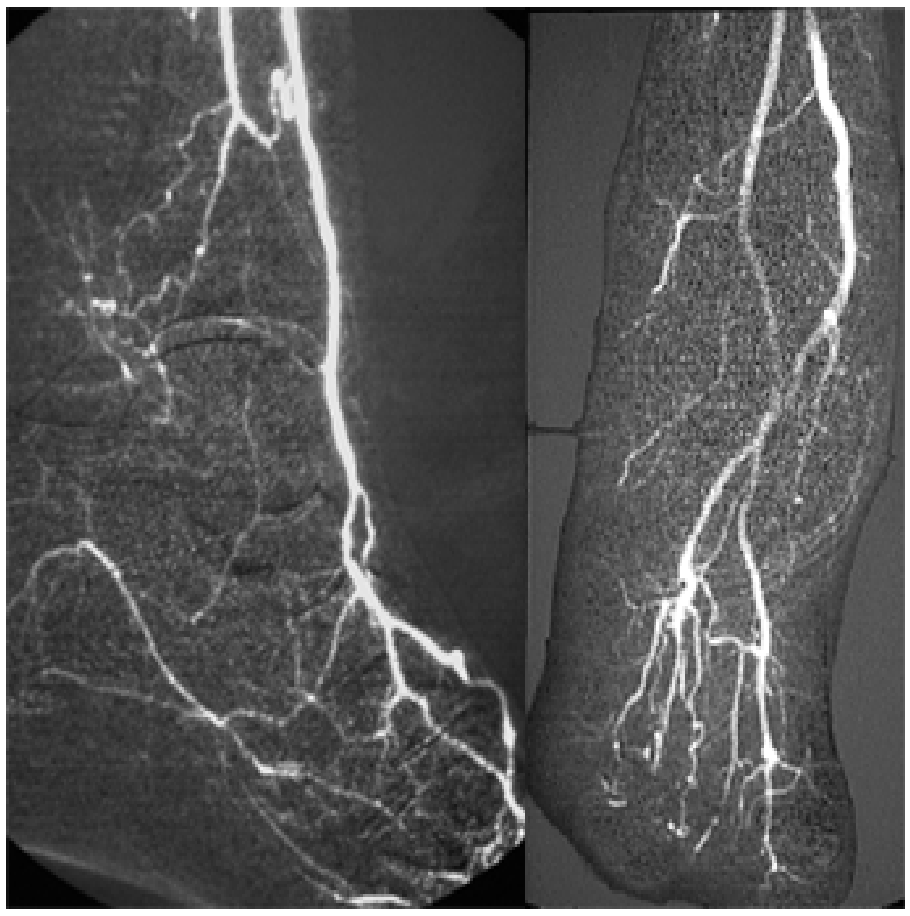


Figure 24. Advanced arterial disease can be demonstrated using refined imaging techniques enumerated below.

Table 3. Hints for Improving Peripheral Vascular Evaluation
1. Elevate the feet 30 degrees (Trendelenburg)
2. Decrease patient motion
3. Selective injections
4. End-hole catheter
5. 1 mL (100-200 mcg/mL) nitroglycerin intra-arterially prior to injection of CO_2
6. MA of 60 ms
7. Frame rate of 6 or more/sec
8. Stacking software to superimpose multiple frames for 1 composite image

in small volumes to confirm their diagnosis. Table 3 is a list of hints at obtaining better images during a peripheral run-off study. It is important to note that, very rarely, when peripheral vascular disease is so severe there can be pre capillary shunting of CO_2 from artery to vein. This mimics, but does not represent,

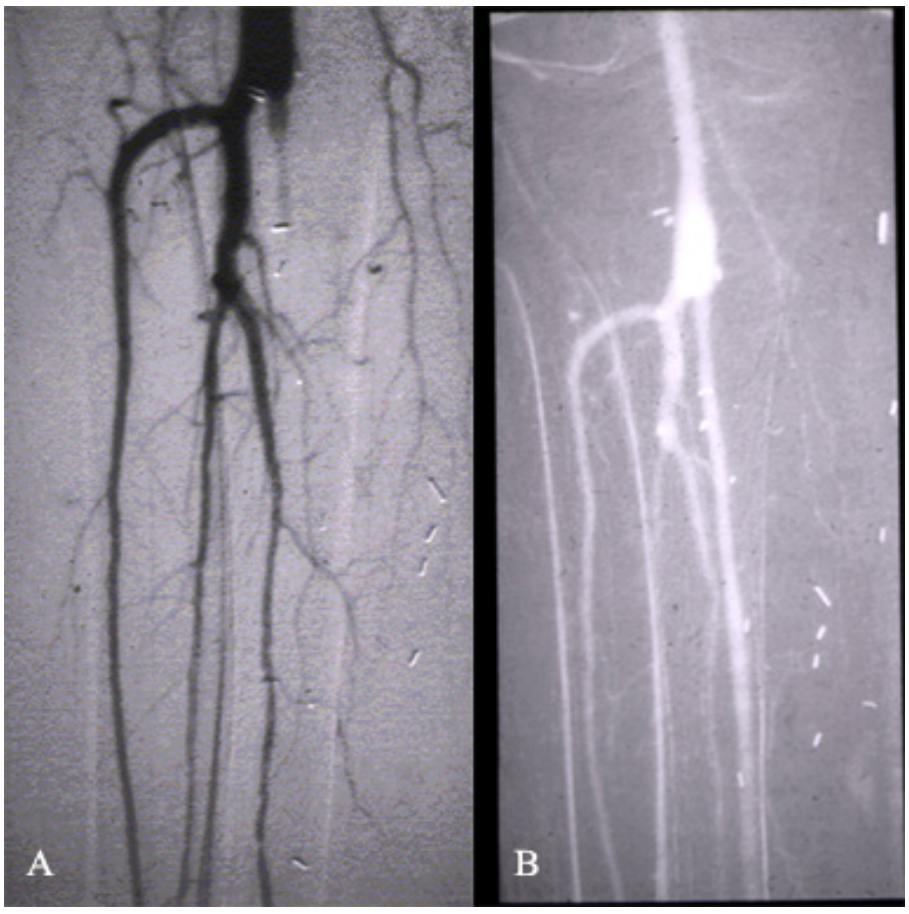


Figure 25. Higher viscosity iodinated contrast fails to demonstrate patency of distal graft (A). Carbon dioxide digital subtraction angiography correctly shows patency and the disparity may be due to slow flow (B).

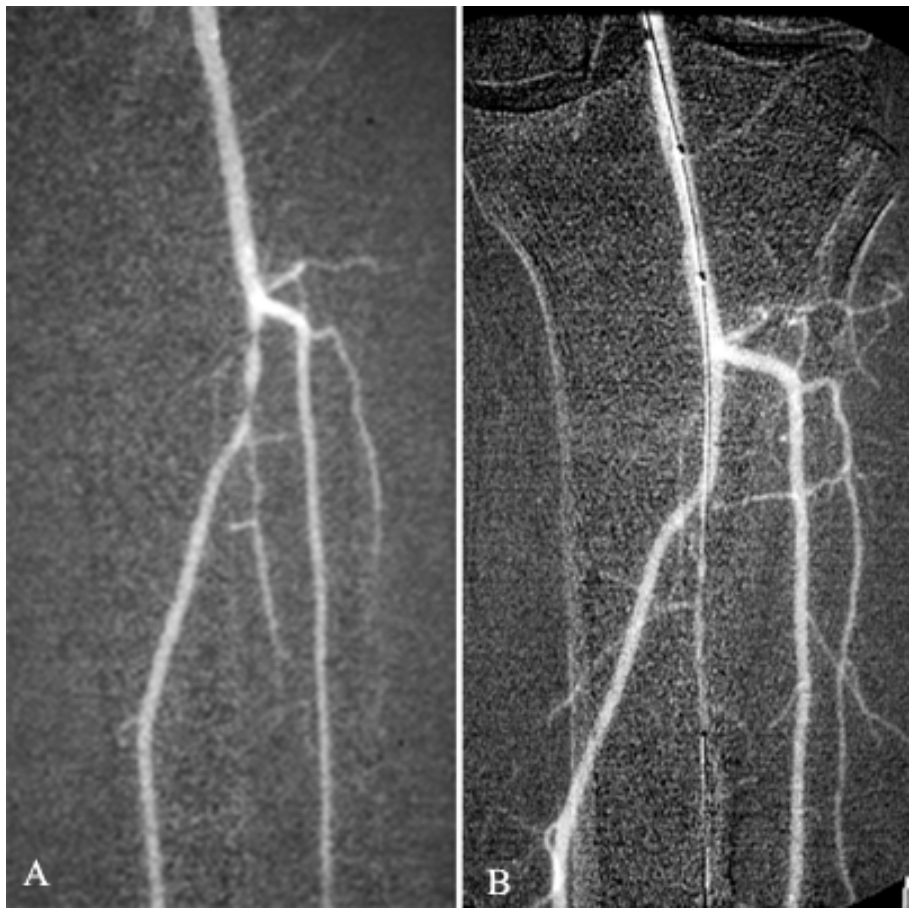


Figure 26. Infrapopliteal CO_2 digital subtraction angiography showing stenoses in tibial trunk (A). Post percutaneous transluminal angioplasty CO_2 delivered between balloon and wire to assess results without losing purchase (B).

an AV fistula. Close examination in multiple views and the appearance of peripheral vasculature will determine the true nature of the shunting.

Endovascular Abdominal Aneurysm Repair

One currently employed use of CO_2 DSA has been in the placement and evaluation of abdominal aortic endografts. This use has been proliferating among numerous operators for a variety of reasons, including decrease of iodinated contrast load, more sensitive evaluation of endoleaks, safety, and cost.[28-31]

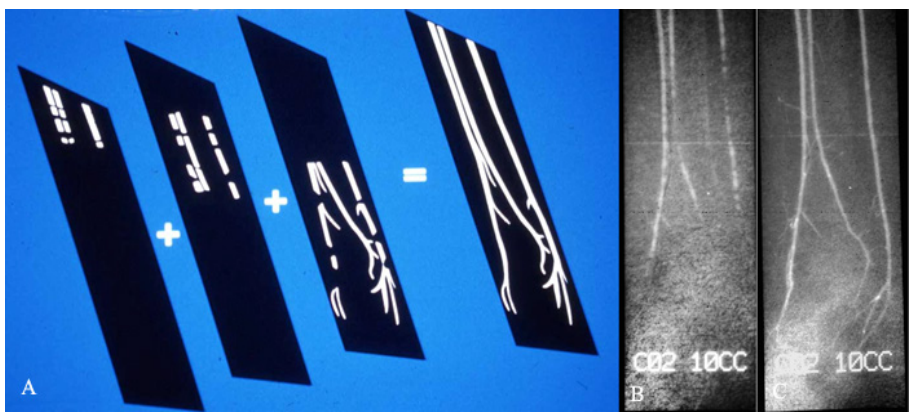


Figure 27. Cartoon showing stacking program, which superimposes multiple images to generate a composite image (A). Pre stacking image shows disparate contrast (B). Stacking combines the images to show more linear representation (C).

With the maturation of endovascular abdominal aneurysm repair (EVAR), it has become clear that there is a propensity for developing renal failure that is permanent and cumulative.[58-61] The number affected exceeds those having open repair and is not limited to patients with underlying renal insufficiency. The typical EVAR patient is usually greater than 70 years of age. This group of individuals has approximately a 30% incidence of abnormally low glomerular

filtration rate that may not be reflected by serum creatinine levels alone. They also tend to have comorbid conditions that predispose them to renal insult. The incidence of renal insufficiency in patients undergoing EVAR approximates 7% to 25% with acute renal failure occurring in 2% to 16%, resulting in an associated mortality of 30% to 50%. Even when there is no pre-existing renal dysfunction, there is a 2.5% incidence of renal impairment. Associated with this renal compromise is an immediate and delayed increase in mortality. Although these changes may be multifactorial, iodinated contrast has been implicated as the major precipitating factor. CO_2 can be used as the exclusive contrast agent or in addition to smaller volumes of iodinated contrast, allowing accurate and complete endovascular repair without inducing renal compromise. In addition, because of its low viscosity, it has also been noted by several of the above authors that CO_2 is more sensitive for detecting endoleaks. These benefits, plus safety, make it the ideal agent for the placement and evaluation of abdominal aortic endografts.

Typical doses of 20 cc to 50 cc per injection are utilized when evaluating endografts. One author described performing the entire exam without a catheter by simply injecting CO_2 through the groin access sheath side ports **(Figure 28)**.[31]

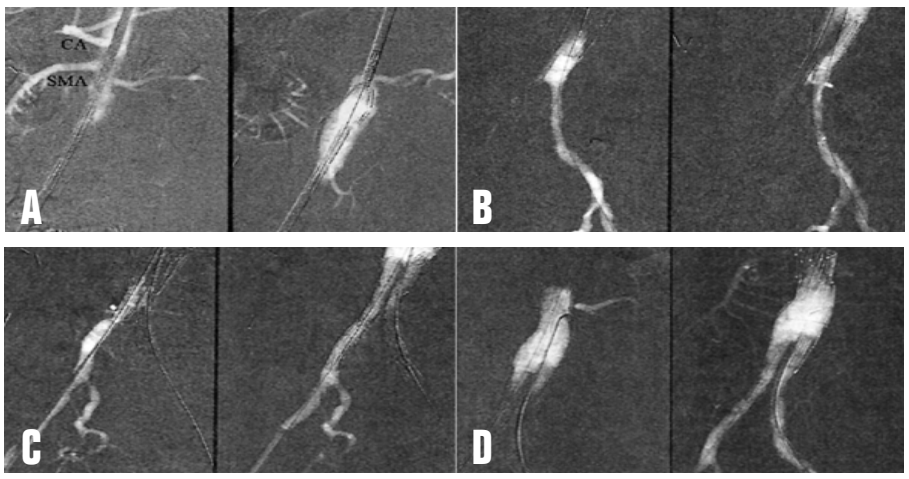


Figure 28. Two DSA images obtained with the injection of 30 cc CO_2 through the connecting tube of the hemostatic valve show excellent filling of the celiac, superior mesenteric, and left renal arteries (A). Right renal artery is surgically absent. Using the left renal artery landmark, the system is retracted until the graft markers are 2 mm below the renal artery. Two CO_2 images obtained with the injection of 20-cc CO_2 show excellent filling of the common iliac, hypogastric and external iliac arteries allowing deployment of the left leg graft (B). Two CO_2 images obtained with the injection of CO2 through the sheath visualizing the common, hypogastric and external iliac artery guiding right iliac leg graft (C). Final images confirm patent left renal artery (D). There is no endoleak.
Reprinted with permission from Criado et al. Catheter-less angiography for endovascular aortic aneurysm repair: A new application of carbon dioxide as a contrast agent. *J Vasc Surg*. 2008;48:527-534.

INTERVENTIONAL ONCOLOGY

Interventional oncology is a recent catch-all phrase for a specialty that includes a multitude of minimally invasive procedures in the treatment of a variety of tumors. One aspect of this specialty is catheter-directed and requires angiography/venography and embolization. The contrast load for these patients is often high. This, combined with a host of other compromising factors, places these patients at risk for CIN.

Transarterial Chemoembolization, Drug-Eluting Beads, and Yttrium-90

There are procedures that use angiographically directed therapy predominantly for liver tumors. Transarterial chemoembolization (TACE), drug-eluting beads, and yttrium-90 therapy are utilized with liver tumor patients, who tend to be older and usually have

other comorbidities such as renal insufficiency, diabetes, and hypertension. Patients with primary hepatic tumors also have significant underlying liver disease and are at risk for hepatorenal compromise. Approximately 75% of patients with cirrhosis will have renal insufficiency at some time during the course of their disease. At the same time, these individuals are often on renal-compromising medications and tend to be more hypovolemic. Cirrhosis, plus nonsteroidal anti-inflammatory drugs (NSAIDS) plus hypovolemia are a conduit to acute renal failure (ARF). Commonly, a large volume of contrast is required for interrogation of the vasculature, treatment, and follow-up exam. These risks can be exacerbated by post-embolization syndrome followed by decreased oral intake or very rarely non-target embolization and tumor lysis syndrome. All of these factors, especially the high volume of contrast, place the patient at risk for CIN. Alternatively, and perhaps more significantly, some of these patients may be denied life-prolonging therapy because of their elevated creatinine and risk for CIN **(Figure 29)**.

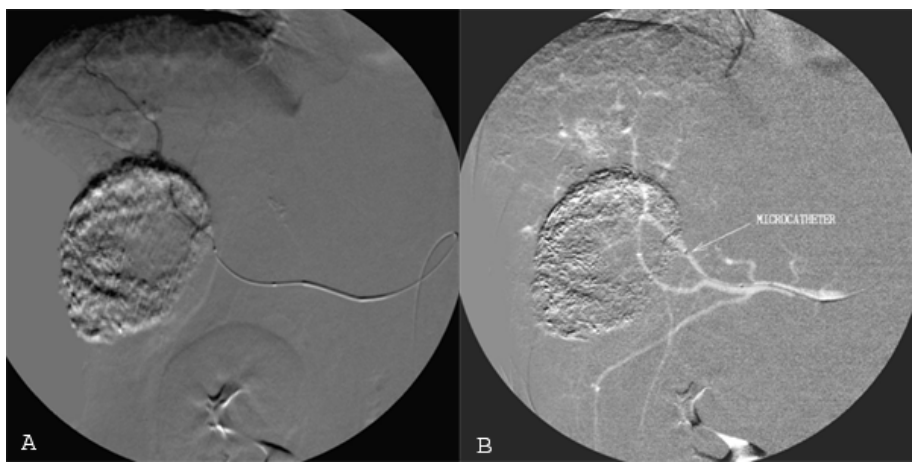


Figure 29. A patient had previous transarterial chemoembolization and needs repeat delivery in a right hepatic artery branch. Iodinated contrast injected travels peripherally and the tumor is not seen (A). CO_2 digital subtraction angiography demonstrates central reflux and filling of the culprit vessel, so inadvertent embolization is avoided and the catheter can be redirected for appropriate treatment (B).

The problem appears to be under diagnosed; however, there are several reports that describe the incidence of CIN in this group of patients.[62-64] Huo, in a group of 140 TACE patients with a creatinine 1.1±0.2 of had an incidence of ARF of 8.6% and irreversible renal failure in 2.8%. All of those in the latter category had diabetes. Acute renal failure correlated with the number of TACE procedures, severity of liver disease, and presence of post-embolization syndrome. Jang prospectively evaluated 319 patients who had 463 TACE procedures and resultant ARF in 3.2%. Fifty-eight patients were denied TACE due to a creatinine of greater than 2 mg/dL. Acute renal failure correlated with a creatinine of greater than 1.5 mg/dL and the presence of ascites. Similarly, Yamazaki prospectively looked at 120 patients with 180 TACE procedures and a normal creatinine. There was ARF in 6% of patients.

Another procedure, uterine fibroid embolization (UFE), is usually performed in young, healthy individuals. Less invasive transarterial therapy can be precluded if there is an elevation of the serum creatinine. In fact, renal insufficiency is listed as one of the relative contraindications[65] and has been described.[66] Because of chronic bleeding these patients may have a decreased effective arterial blood volume and may also be subjected to NSAIDS for periprocedural therapy. As with TACE procedures, they may also be subjected to high volumes of iodinated contrast and develop post embolization syndrome **(Figure 30)**.

Similarly, some patients with renal cell carcinoma require embolization of the primary tumor or the

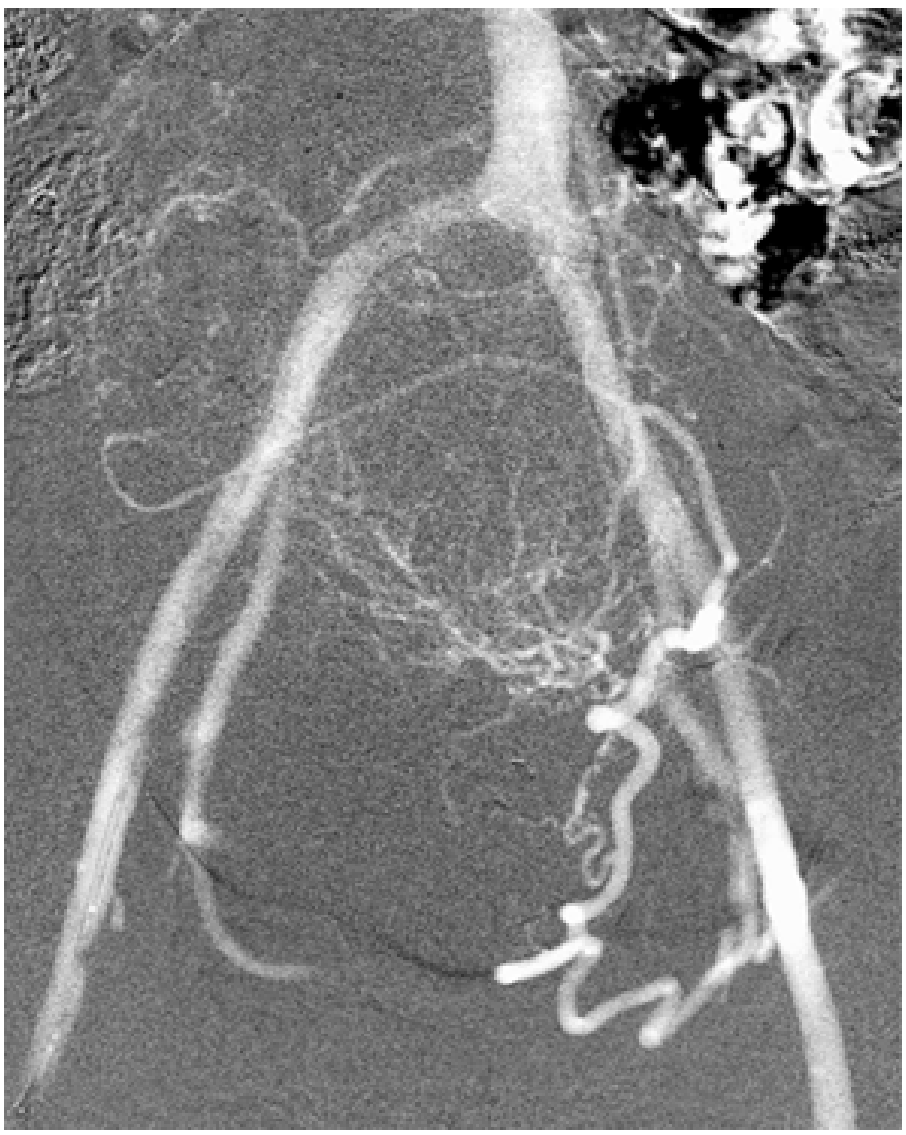


Figure 30. CO_2 digital subtraction angiography of pelvis demonstrating hypertrophied uterine arteries as well as tumor vascularity in the uterine fibroid.

hypervascular metastasis. Obviously, many of these patients are susceptible to CIN.

In each of the clinical scenarios delineated above, CO_2 can usually be used as the predominant contrast agent with the addition of a small or limited amount of dilute iodinated contrast. The vessels necessary for evaluation and treatment are less than 10 mm in diameter and have a strong correlation with liquid contrast. Doses ranging from 5 cc to 20 cc are more than sufficient. Occasionally the low viscosity of CO_2 will make tumor vessels more apparent. Carbon dioxide, because of reflux, can evaluate the celiac artery and its branches at the same time as the SMA. To visualize the patency of the portal vein, the microcatheter can be wedged peripherally in the artery and 10 cc to 20 cc of CO_2 administered. In the case of UFE, the uterine arteries are anterior and therefore easily demonstrated. Carbon dioxide can also be more readily injected through the commonly utilized microcatheters and give a better demonstration of the feeding vasculature. The reflux attribute of CO_2 will also permit visualization of the entire system of vessels to determine if the catheter is in the appropriate position and all culprit vessels are embolized. Most significantly, the use of CO_2 DSA not only permits inclusion of a group of patients that may be denied treatment but also reduces the incidence of CIN in all individuals undergoing the procedure.

VENOUS EVALUATION AND TREATMENT

As noted, CO_2 was used safely in the venous system early in the 1960s. Since the discovery and refinement of DSA, the myriad uses for CO_2 as a venous vascular contrast agent have proliferated. The gaseous properties noted above make it an ideal venous contrast agent.

In the extremities, the low viscosity of CO_2 permits delivery of sufficient volumes through smaller 25 ga needles. This is less invasive and less painful to the patient. Because CO_2 doesn't mix with blood, it is not diluted and a peripheral hand injection will yield good opacification centrally. This is unlike contrast. In the presence of venous occlusion, the properties of low viscosity and reflux will often demonstrate collateral cervical and thoracic veins bilaterally **(Figure 31)**. This is critical in patients with renal insufficiency and chronic venous occlusive disease. Because of CIN and nephrogenic systemic fibrosis respectively, venous CT

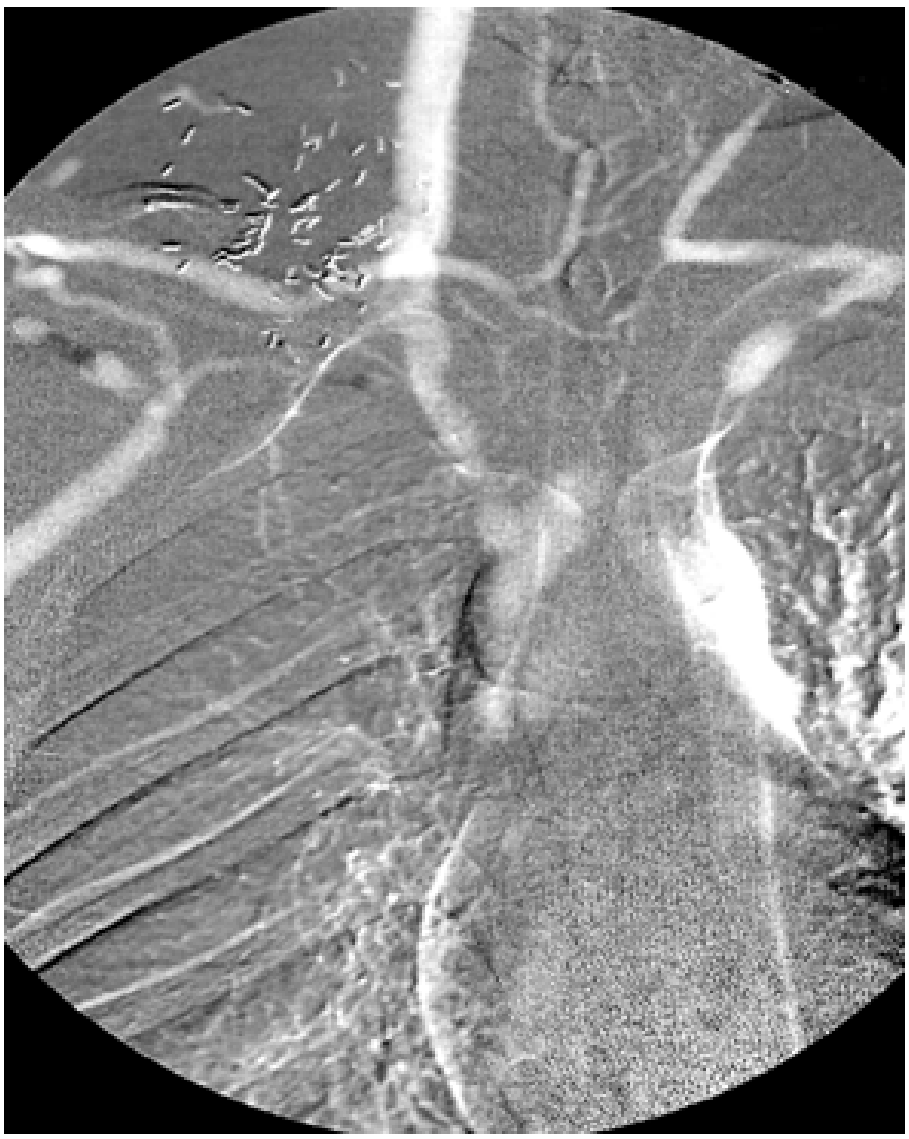


Figure 31. Right upper extremity venogram demonstrates an occlusion of right subclavian vein and collateral veins reconstituting the right internal jugular and innominate veins.

and venous MR cannot be utilized for a roadmap prior to venous access procedures. This can be circumvented nicely with CO_2 extremity venography. It can help determine venous patency as well as potential access sites. CO_2 venography can also be employed in patients with iodinated contrast allergy. It is unnecessary to prep and wait and the procedure can be performed immediately. Slow, controlled, nonexplosive doses of 5 cc to 20 cc usually produce excellent DSA images. It is important to remember that the thinner media in veins cause more sensitivity and pain to more forceful injections. The efficacy of venous CO_2 DSA has been documented by numerous authors.[67-69]

Carbon dioxide DSA can be extremely useful in the examination of dialysis fistulas or interposition grafts **(Figure 32)**. It helps preserve what little renal function reserve some of these patients have. It is excellent at demonstrating the veins and central circulation. One caveat is the evaluation of the arterial anastomosis. It should not be evaluated via compression of central veins with forceful injection. Reflux to the cervical arterial supply can occur.[16] When examining the arterial anastomosis it is helpful to place the patient in the Trendelenburg position and maneuver a microcatheter into the feeding artery. A slow gentle injection of 5 cc to 10 cc will usually show the anastomosis and

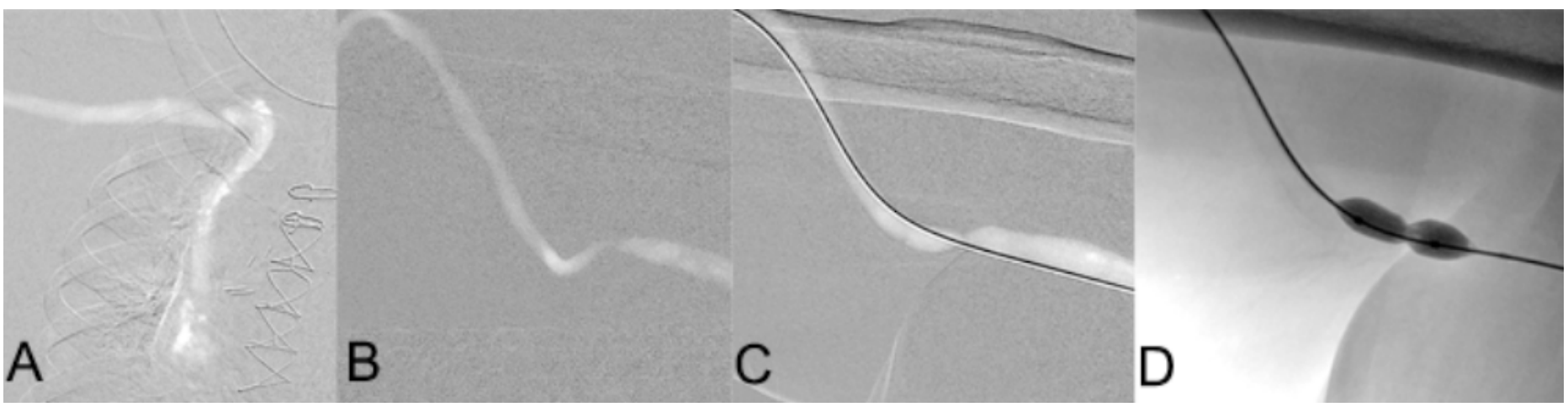


Figure 32. Carbon dioxide fistulagram. Patent central veins (A). Stenosis at the site of anastomosis (B, C). Upon balloon inflation a tight waist is seen at the stenosis (D).

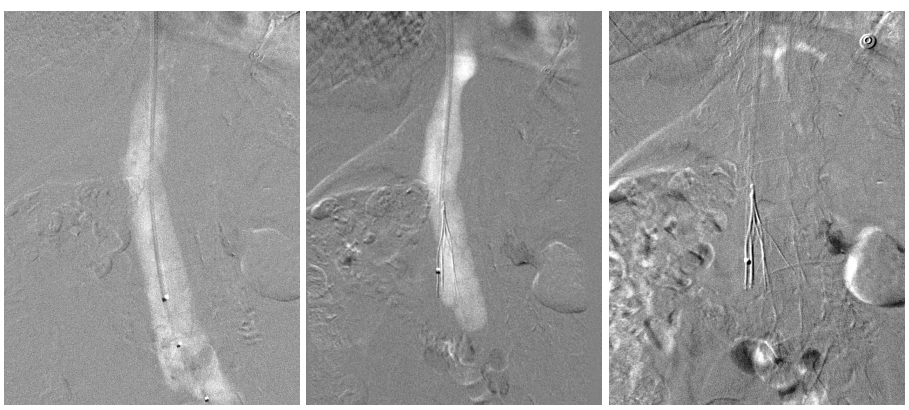


Figure 33. Carbon dioxide inferior vena cavogram from the internal jugular vein showing patent inferior vena cava, followed by post-deployment inferior vena cavagram and finally filter post deployment.

pathology if present. With extremity and/or dialysis venous evaluation, if pathology is present, percutaneous transluminal angioplasty and stenting can also be performed using CO_2 DSA as the primary imaging agent.

Venous CO_2 DSA is advantageous in IVC evaluation, especially for filter placement. Many times these are emergent and patients may have allergy, have elevated creatinine, or do not need the additional volume of iodinated contrast boluses. Carbon dioxide has been shown to be a very effective imaging agent for the evaluation of the IVC, even at the bedside **(Figure 33)**.[70-73] There is close correlation regarding size when compared to liquid contrast. Because of occasional undersizing with CO_2, borderline diameters should be confirmed with dilute contrast, if computed tomography (CT) is not available.

As with contrast, the renal veins may not be readily apparent. Occasionally, the right renal vein lies slightly posterior and may not be visualized. If there is no prior imaging to locate the origin of the renal veins, the patient can be rotated so the ipsilateral side is up. Another simple method the authors have used rarely is to place a wire in the renal veins to determine the level of origin.

When a CT is not available to review anatomy beforehand, we usually inject 20 cc to 30 cc into an endhole catheter placed in the left common iliac vein to exclude left-side IVC. Some operators use 50 cc to 60 cc. If the renal veins are not evident, it helps to move the catheter more centrally, closer to their origins. If the anatomy is still uncertain, and the renal veins have not been identified, a selective catheter is advanced into the renal veins and CO_2 venography performed.

Carbon dioxide renal venography can also be performed in this and in other procedures (adrenal vein sampling, balloon occluded retrograde transvenous obliteration of varices) where evaluation of these veins is essential. The one caveat, as addressed above, is caution in the patient with pulmonary hypertension.

The next venous use of CO_2 involves a variety of clinical scenarios in the liver and spleen. It has been shown by Culp and Hawkins that, as opposed to iodinated contrast, CO_2 does not have any negative effect on the splenocytes or hepatocytes when injected directly into the respective parenchyma.[74] Hawkins showed that an injection of as little as 12 cc per second had a negative effect as compared to CO_2 at 200 cc/second.

One of the more unusual but effective uses of CO_2 is in patients with abnormalities of the splenoportal system **(Figure 34)**.[12,75-77] Occasionally, three-dimensional imaging is not sufficient in defining the presence or absence of an abnormality. This is more common in children. In these cases, the splenic parenchyma can be accessed with a 25 or 27 gauge spinal needle using ultrasound guidance. Carbon dioxide of 10 cc to 20 cc can be administered. The low viscosity of CO_2 will cause opacification the splenoportal system, identifying the normality, pathol-

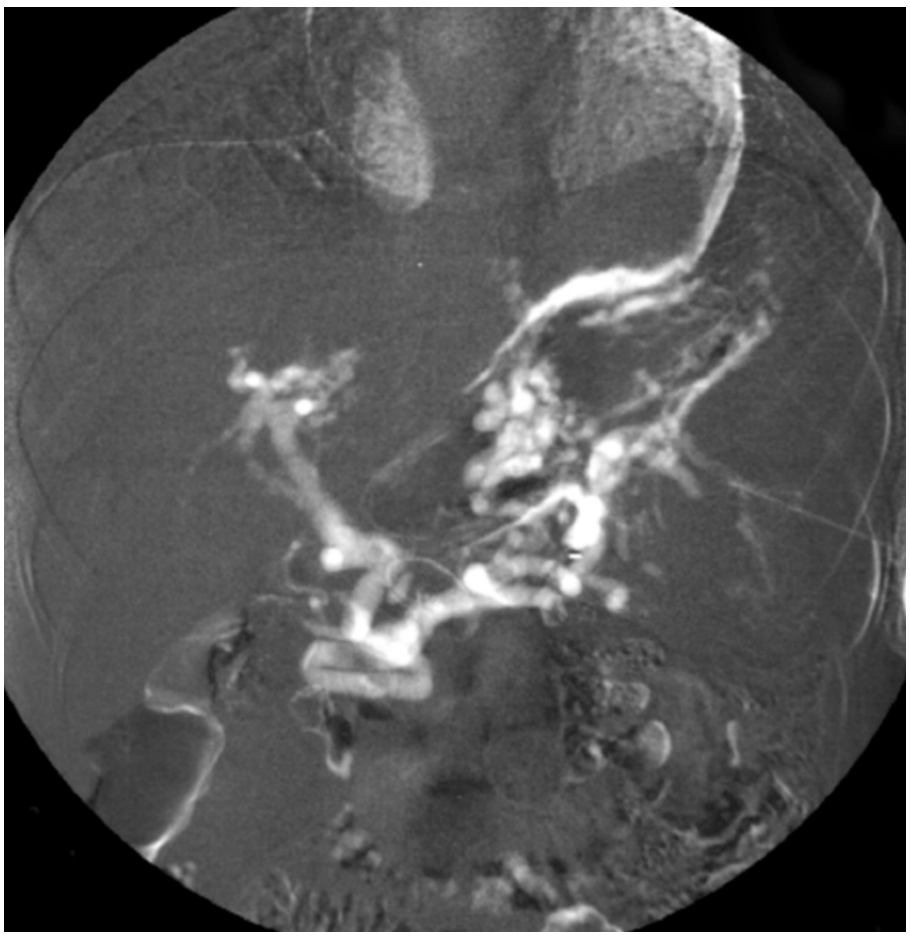


Figure 34. Carbon dioxide splenoportography with a 25-gauge needle placed in the spleen of a 9-year-old female who had undergone prior spleno-renal shunt demonstrates the evidence for splenic and portal vein occlusion with collaterals.

ogy, or collaterals. Due to the small caliber of the access needles plus the use of CO_2, this has been shown to be safe without significant bleeding.[12,75-77]

More commonly, it has become routine for many operators to use CO_2 in TIPS procedures **(Figure 35)**. The incidence of renal compromise post TIPS approximates 2% to 3%. The entire procedure, including hepatic and portal venography as well as tract measurement, portal localization, and post-TIPS placement, can be performed with CO_2, reducing the possibility of CIN.[10] Occasionally, in about 75% of patients, a tractogram can be performed with CO_2 with a measuring catheter in place. The low viscosity of CO_2 will sometimes simultaneously visualize the portal vein, tract, and IVC for stent measurement. As in many other clinical scenarios, a dose of 5 cc to 20 cc is sufficient for each step in TIPS.

Where CO_2 is most helpful in TIPS is in the localization of the portal vein. Since the inception of TIPS, localizing the portal vein has been the most difficult and invasive step. Many different methods, including ultrasound, CT, and angiography were attempted. Subsequently, it appeared that hepatic vein

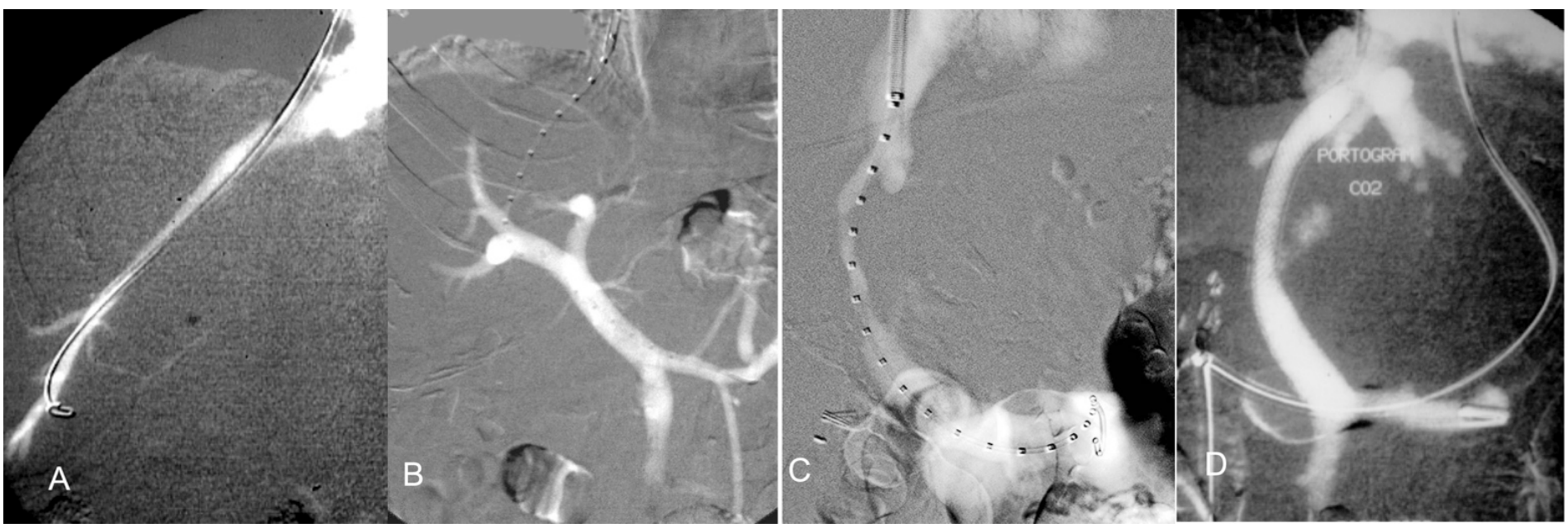


Figure 35. Right hepatic venography (A), splenoportography (B), CO_2 tractogram and measuring the length of stent (C), and completion CO_2 portogram after stent placement within the parenchyma from the portal vein to the hepatic vein (D).

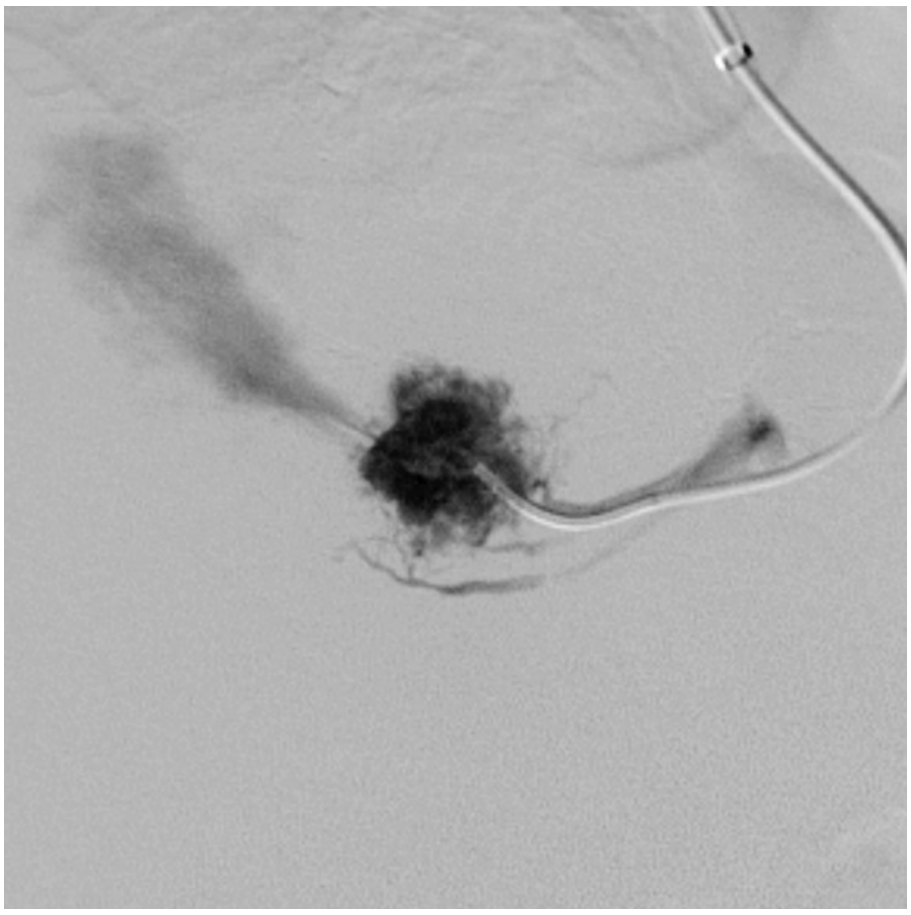


Figure 36. Capsular rupture with extracapsular extravasation after wedged hepatic venography using iodinated contrast.

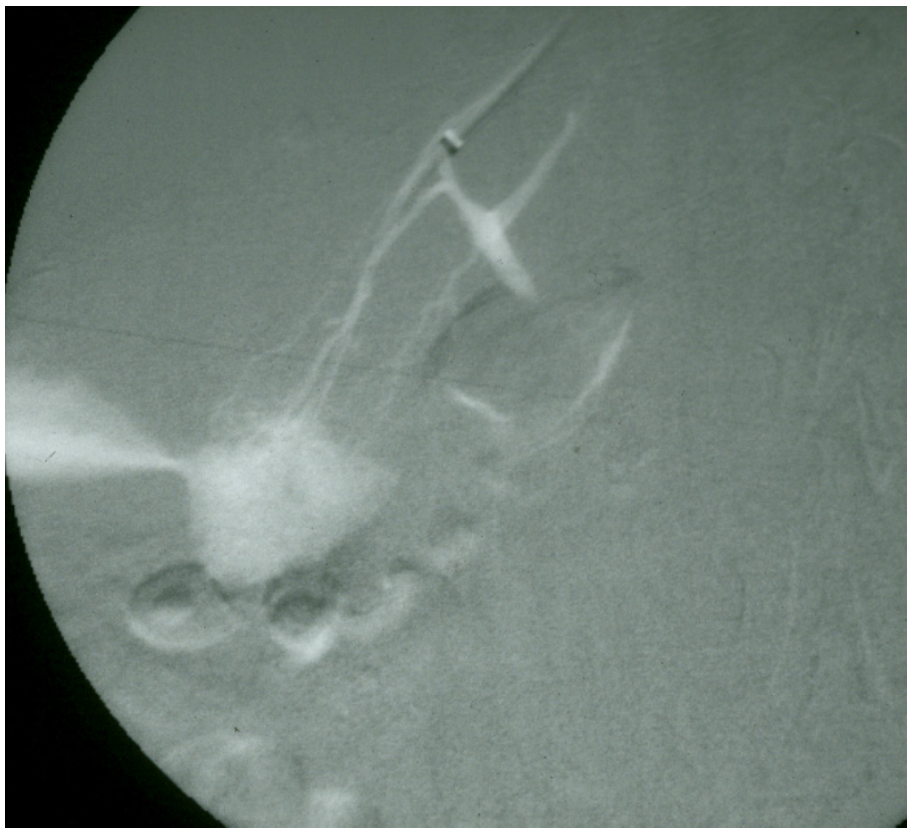


Figure 37. Capsular rupture with extracapsular extravasation during wedged hepatic venography with CO_2.

wedged catheter or later balloon occlusion injections of iodinated contrast were the most efficient method.

Unfortunately, these injections caused hepatocyte congestion and infarction as well as elevation of transaminases, obscuring parenchymal staining and even rupture of the capsule and its consequences **(Figure 36)**. Additionally, these injections unreliably visualized only a small portion of the portal vein.[78] Reese described using CO_2 in the same fashion.[79] The low viscosity permits excellent visualization of the portal vein in greater than 80% of cases and visualizes more of the system than iodinated contrast without most of the consequences. Carbon dioxide passes very easily through the sinusoids into the portal system against the direction of blood flow. An occasional benefit is that CO_2 remains in the portal vein as a target. However, because of a few complications of capsular rupture with catheter-wedged CO_2 injections, balloon occlusion of the hepatic vein with venous CO_2 injections became the preferred method of choice **(Figure 37)**.[79-82] Complications are fewer with the advantage of better portal visualization.

To simplify the process, Hawkins later demonstrated and described the parenchymal injection of CO_2 through the same needle used in localizing the portal vein **(Figure 38)**.[10] Typically, the hepatic vein is accessed and the needle angled in the direction of the portal vein. The needle is advanced to access the portal vein. Once in the parenchyma, 10 cc to 20 cc of CO_2 can be injected and the portal vein will be visualized almost 100% of the time without the adverse effects of other methods, especially capsular rupture. If anterior or posterior location of the portal vein is not clear, repeat injections can be made with and without rota-

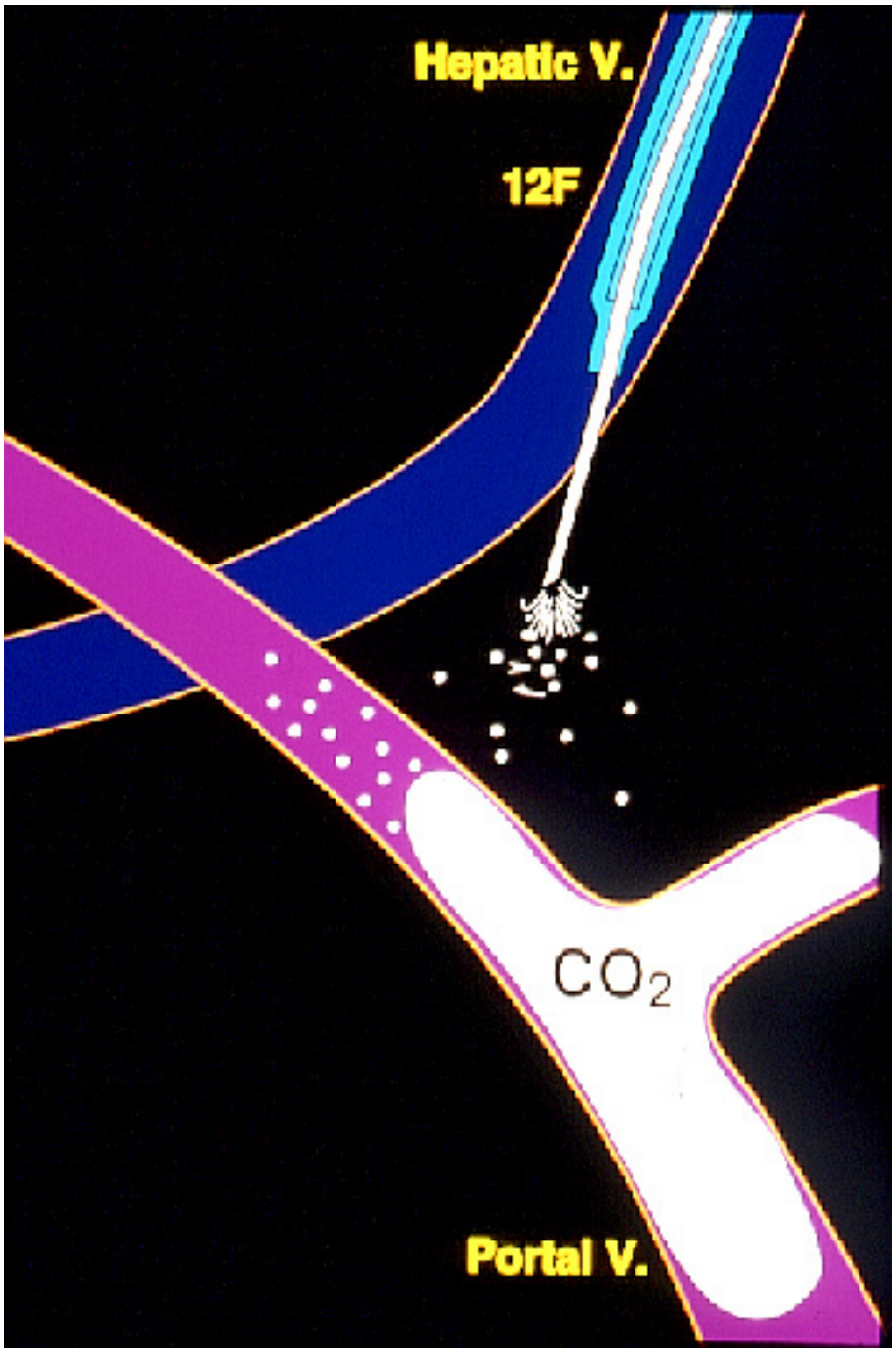


Figure 38. Rendition of hepatic intraparenchymal injection of CO_2 for portal vein visualization.

tion of the image intensifier **(Figure 39)**. Adopting this method eliminates the extra step and expense of the occlusion balloon, yields accurate and consistent visualization of the portal vein, and can be used with any TIPS needle.

Visualizing the portal vein has also become more important with the rise in interventional oncology. Transhepatic portal vein access is necessary for certain procedures. More specifically, it is critical in performing selective portal vein embolization (PVE) to generate hepatic parenchymal hypertrophy of the remaining future liver remnant when extended hepatectomy is necessary. Portal vein access can often times be difficult and can extend the duration of the procedure. Quick, safe, peripheral portal vein access without transgressing the hepatic artery or neoplasm is essential. Appropriate access also permits easier catheter manipulation and can reduce non-target embolization. Once again, to expedite this a 22-gauge needle can be placed peripherally in the hepatic parenchyma followed by injection of 10 cc to 20 cc CO_2 to demonstrate the portal vein anatomy **(Figure 40)**. This can be used as a guide for advancement of the needle into the most appropriate portal vein radical and follow-up PVE procedure. Once accessed, CO_2 administration to the portal vein will reflux and demonstrate the entire vein as opposed to contrast, which only travels peripherally **(Figure 41)**. This same approach can be utilized in any portal vein intervention, for example lysing portal vein thrombus,

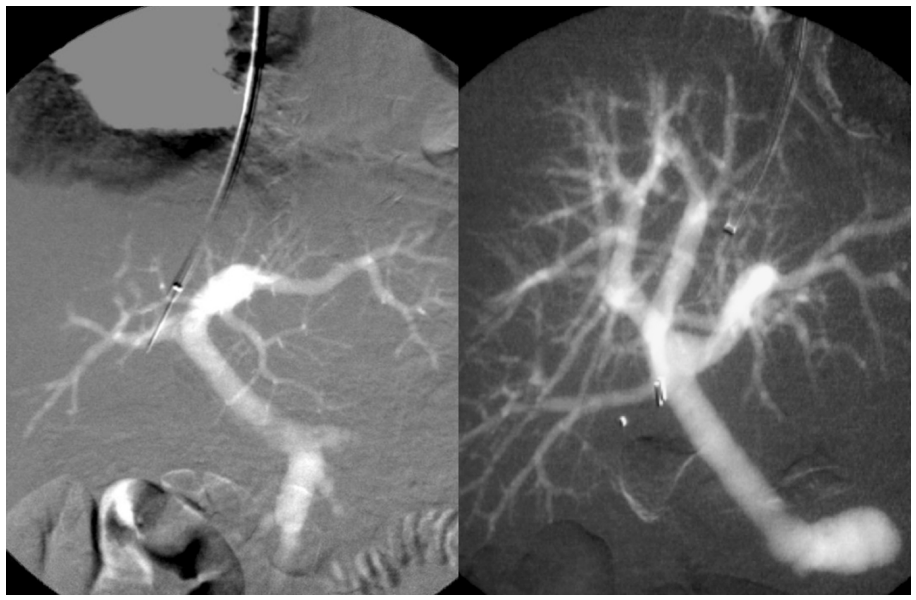


Figure 39. Hepatic parenchymal injection of CO_2 through a 21-gauge fine TIPS needle before and after rotating the image intensifier to assess the relationship of the needle to the portal vein. Both extra- and intrahepatic portal veins are nicely demonstrated following CO_2 injection.

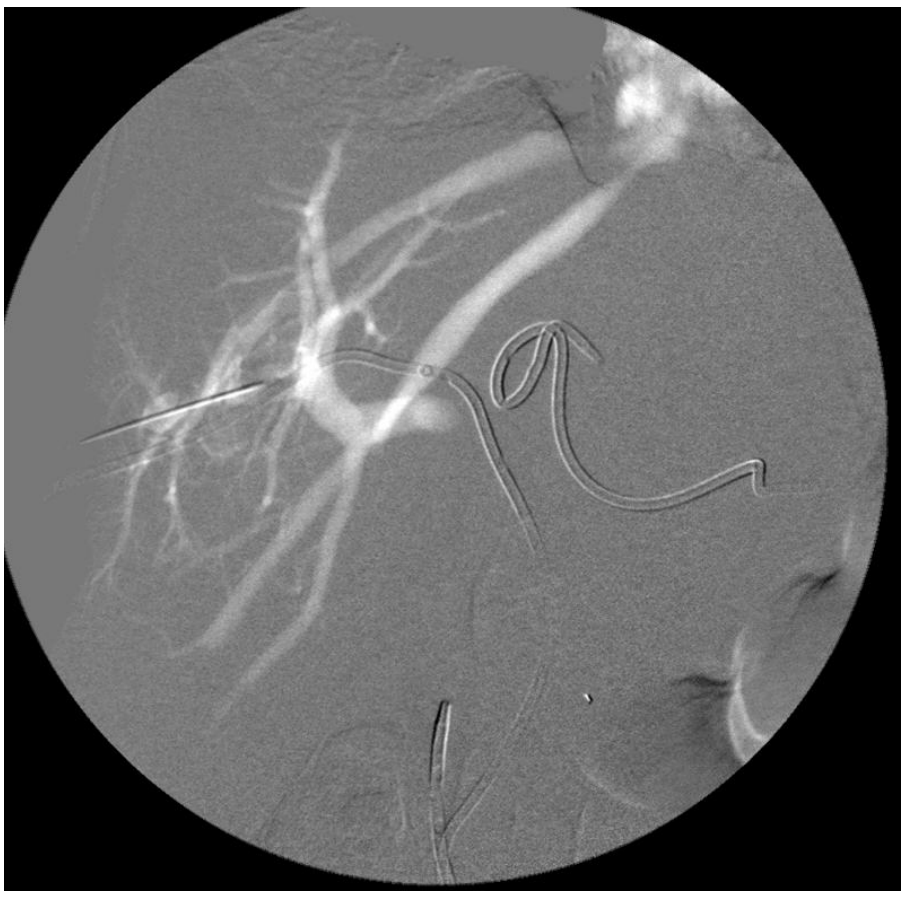


Figure 40. Percutaneous transhepatic CO_2 parenchymal injection and digital subtraction angiography imaging using a 22-gauge needle. Both right portal and hepatic veins are filled.

venous sampling, or treatment of portal vein strictures.

Rarely, three-dimensional imaging has failed to diagnose certain patency of the portal vein prior to liver transplant. Many of these patients also have concurrent ascites and coagulopathy. In this scenario, a 25-gauge needle can be placed with impunity into the liver without correcting ascites or the coagulopathy. Injection of 10 cc to 20 cc CO_2 can determine the critical presence or absence of patency of the portal vein **(Figure 42)**.

Finally, there have been additional reports of limited numbers of patients using CO_2 for atypical procedures. One of these is in pain management. Carbon dioxide has been used instead of iodinated contrast prior to neurolysis when the patient is highly allergic.[83] Another newer area of use requiring additional investigation is for intraosseous venography in per-

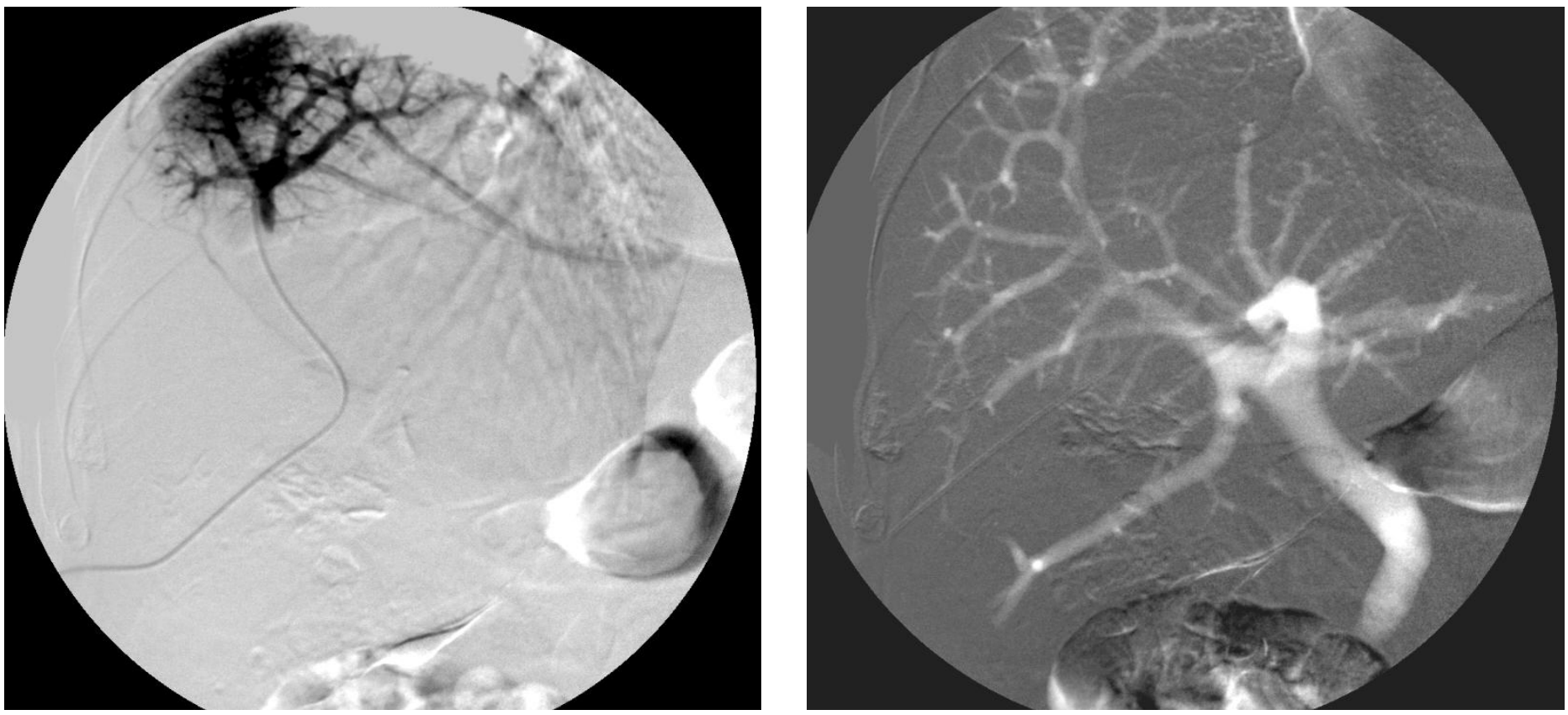


Figure 41. Percutaneous transhepatic portogram with the injection of contrast medium and CO_2 into a peripheral portal vein branch. During injection of contrast medium, peripheral portal vein branches distal to the injection site are filled (A). With CO_2 injection the entire intrahepatic and main portal veins are filled yielding a more accurate image for treatment planning (B).

cutaneous vertebroplasty.[84] Reportedly the CO_2 does not obscure the procedure like iodinated contrast. Carbon dioxide can also be used in angioscopy.[85] It persists longer than saline, giving a clearer view of the vessel. Similarly it can be used percutaneously to separate organs prior to and during ablative procedures. The CO_2mmander/AngiAssist (AngioAdvancements) is ideal for this. It can be connected to the displacement needle and CO_2 is puffed in as needed. Another area of interest is using CO_2 with CT, especially in the angio suite.[86-88] Basically, there are a variety of interventional applications for CO_2 and the repertoire of procedures is increasing as operators become increasingly familiar with its capabilities and safety.

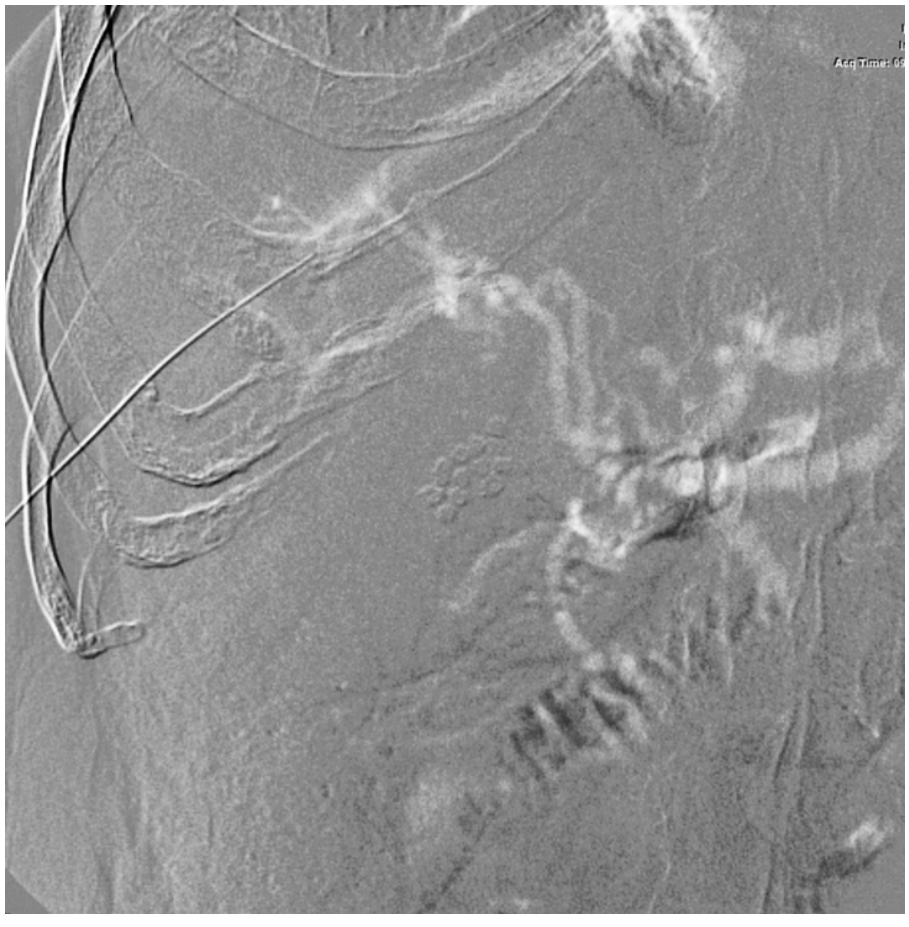


Figure 42. Percutaneous transhepatic CO_2 injection of 20 cc through a 25-gauge needle in a patient with massive ascites and elevated international normalized ratio. The CO_2 fills periportal collaterals indicating portal vein occlusion. The splenic and inferior mesenteric veins are also filled.

CARBON DIOXIDE DELIVERY

Since the advent of intravascular CO_2 delivery there have been a number of innovative methods of delivery developed.[89-93] CO_2 delivery begins with a source. As stated above, a research-grade CO_2 should be used and because of potential impurities over time, the source should also be disposable. Next there must be a mechanism to deliver the CO_2 from the source. One must be aware that many of the commercial canisters contain 3 million cc of pressurized gas. Initial applications simply took a syringe of CO_2 from the source and then delivered it into the catheter. The downside of this approach is that a compressed volume of CO_2 is commonly within the syringe, which can result in the problems delineated above. Additionally, if the syringe is inadvertently left patent, over time, CO_2 can be replaced with more occlusive room air.

To circumvent this, CO_2 delivery was initially performed with a typical liquid contrast injector. This set up had a number of weak links and to address the problems the Angioject dedicated CO_2 injector was designed by Angiodynamics **(Figure 43)**. The cost was

DELIVERY TECHNIQUES

- **Research grade or better CO_2 source**
- **Ensure gas cannot go from source directly to the patient**
- **Closed, nonpressurized delivery system**
- **Purge system 3 times to eliminate stagnant room air**
- **Purge the delivery catheter prior to administering CO_2**
- **Gentle, controlled, nonexplosive delivery**
- **Wait 30 to 60 seconds between injections**
- **If CO_2 persists in a lumen for more than 30 second consider trapping or room air contamination**

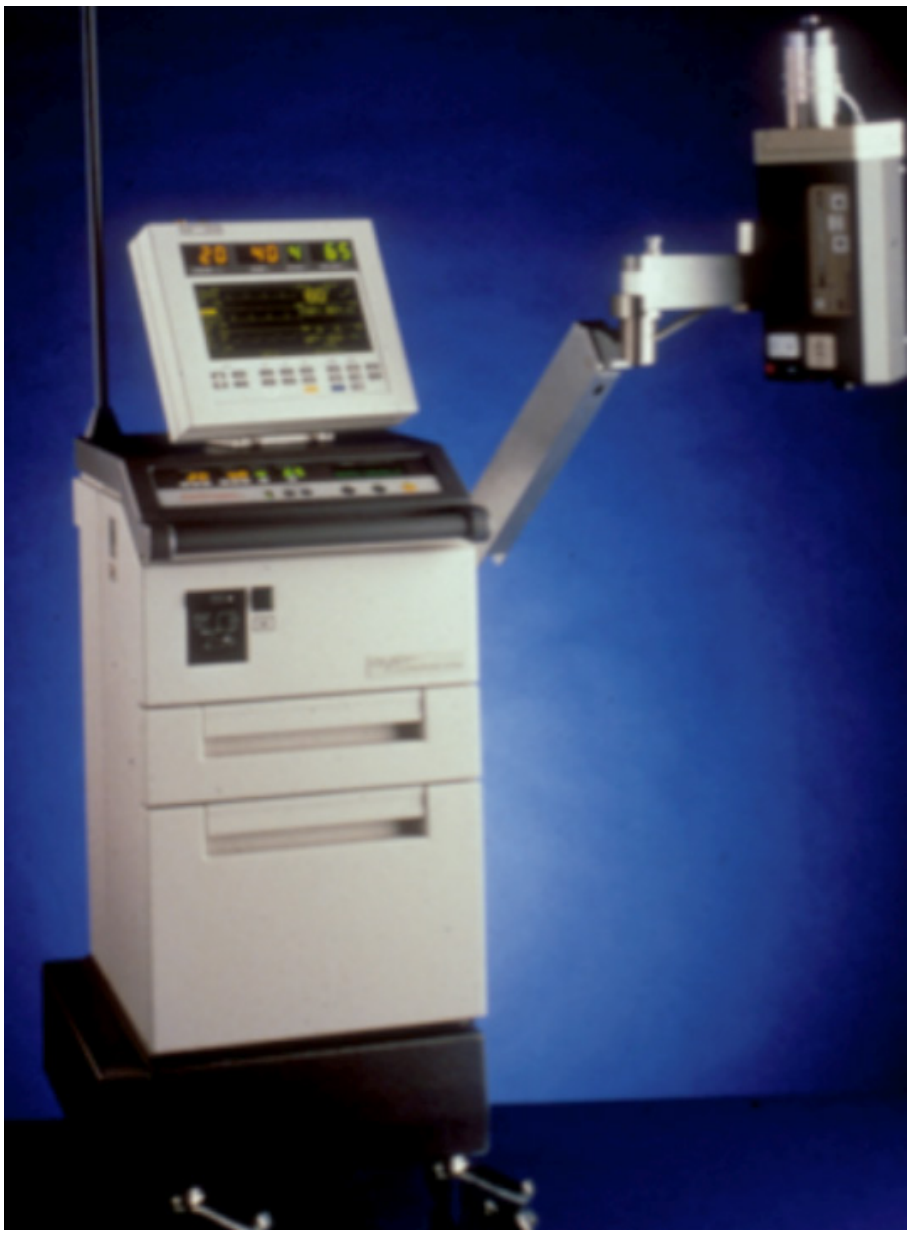


Figure 43. Angioject dedicated CO_2 injector (Angiodynamics). Manufacture of the injector has been discontinued.

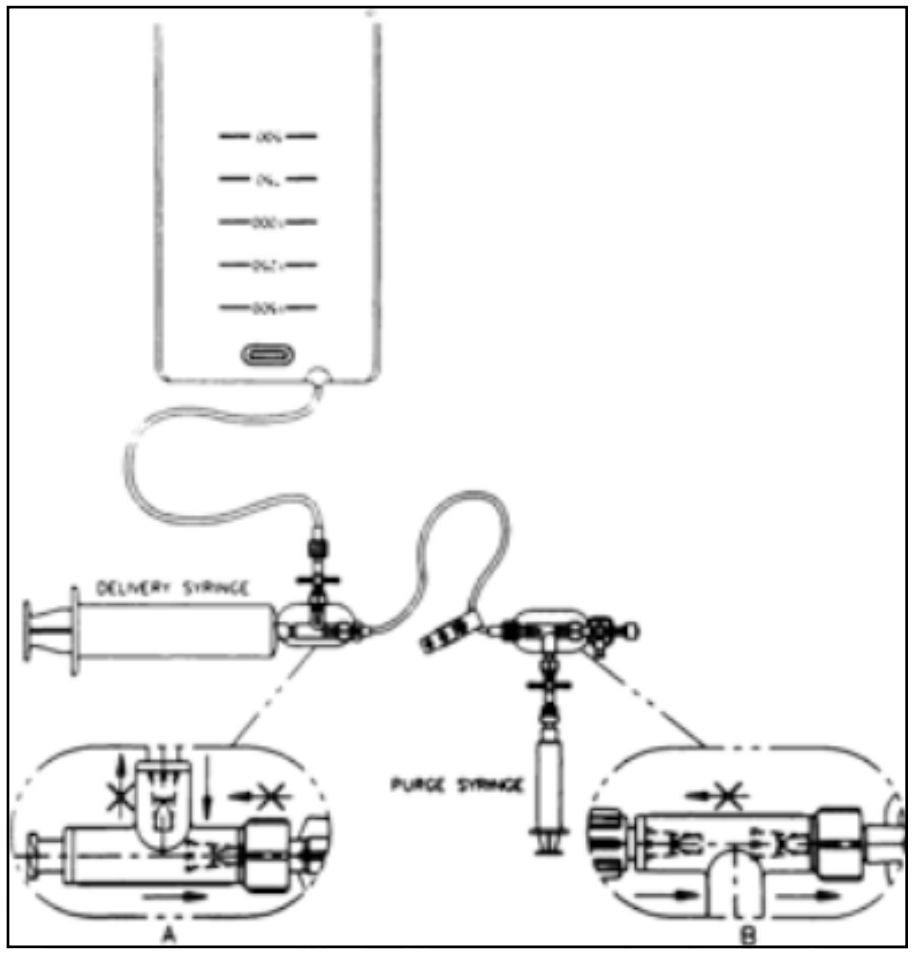
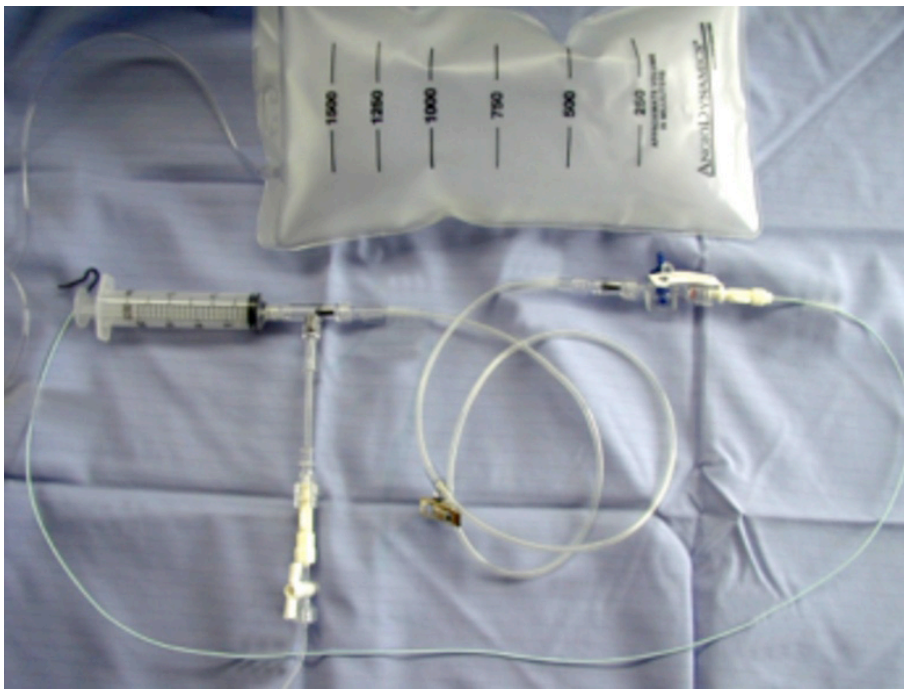


Figure 44. Cartoon representation of the Angioflush III Fluid Collection Bag and Angioflush III Fluid Management System (Angiodynamics). A 1,500-cc nondistended plastic bag is attached to a 3-port fitting with 2 one-way check valves. The 3-port fitting connects to a 100-cm tubing then to a second fitting with 2 in-line check valves and a 3-way stopcock. This system is no longer available.

exorbitant and the efficacy and safety did not exceed homemade systems. The next tactic was to connect tubing from the source to the patient with a series of stopcocks. Again the problem with this is human error. If the stopcocks are positioned inappropriately, the highly pressurized gas in the cylinder can take the path of least resistance and overload the vascular system.

To avoid the inadvertent overload of pressurized gas and the cumbersome presence of a large canister we introduced the use of a flaccid reservoir (bag) with a series of one-way valves **(Figures 44, 45)**. This method used a converted fluid management system by Angiodynamics called the Angioflush III system. A similar system by Merit Medical is also used successfully **(Figure 46)**. The theory behind these systems was that they would be a nonpressurized flaccid reservoir of CO_2 that would avoid explosive delivery and excessive volumes. There is a sufficient reservoir volume and the gas can be easily aspirated and delivered. The one-way glued valves are intended to eliminate stopcocks, prevent room air contamination, and eliminate the necessity to remove the delivery syringe. These systems also are smaller, more mobile, and user friendly as opposed to classical large pressurized CO_2 canisters. The inherent problem in each apparatus is



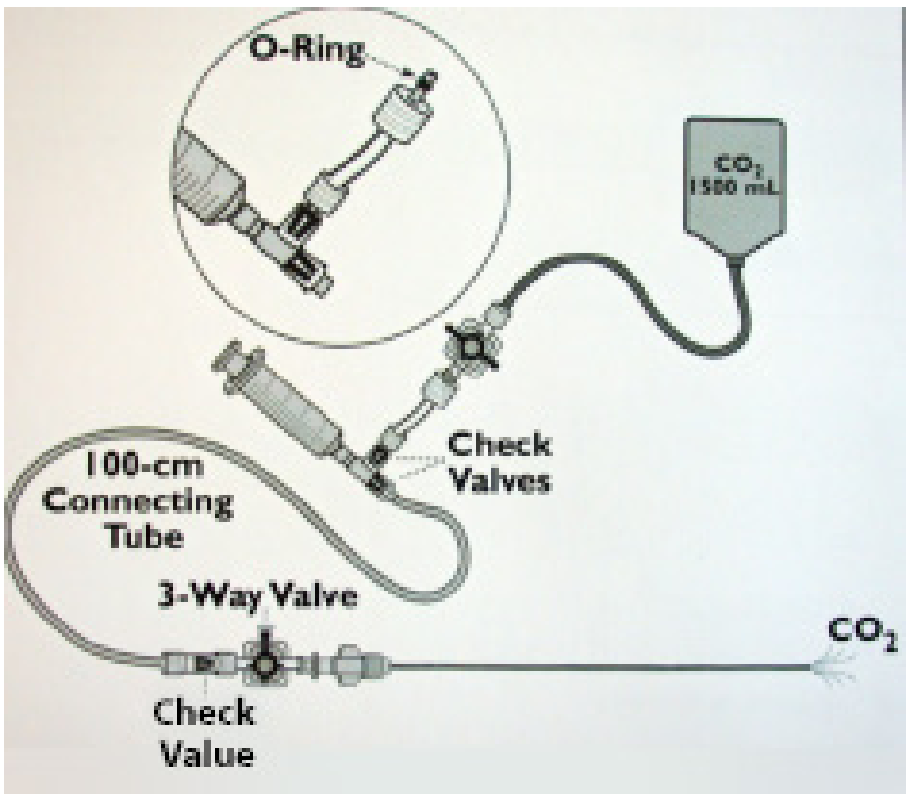


Figure 45. The Angioflush III Fluid Collection Bag and Angioflush III Fluid Management System (Angiodynamics). A 1,500-cc nondistended plastic bag is attached to a 3-port fitting with 2 one-way check valves. The 3-port fitting is connects to a 100-cm tubing then to a second fitting with 2 in-line check valves and a 3-way stopcock. This system is no longer available.

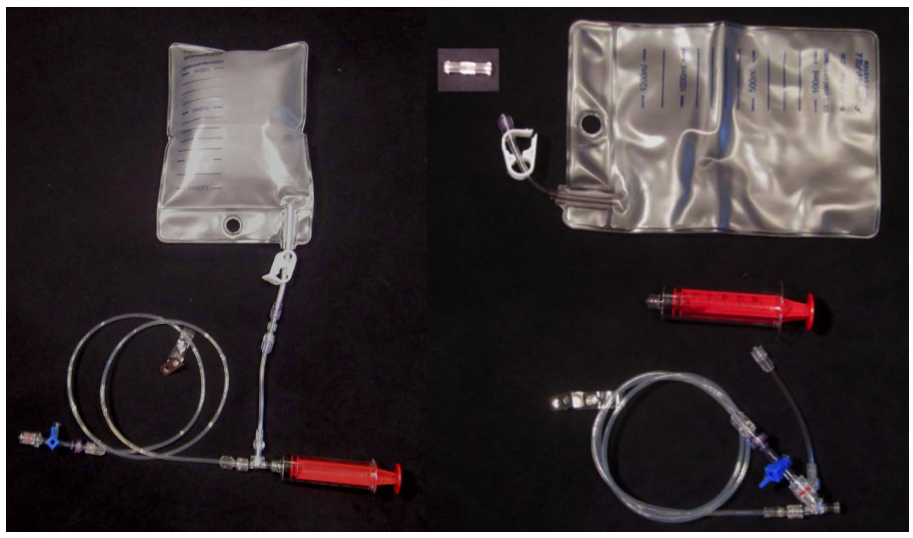


Figure 46. Merit Medical Custom Waste Bag and Contrast Delivery Set. Tubing K12-04967, contrast delivery set/bag K10-04843 Custom Waste Bag kit. This system is not FDA approved. Similar to the Angioflush, it uses a flaccid plastic bag, one-way valves, and tubing.

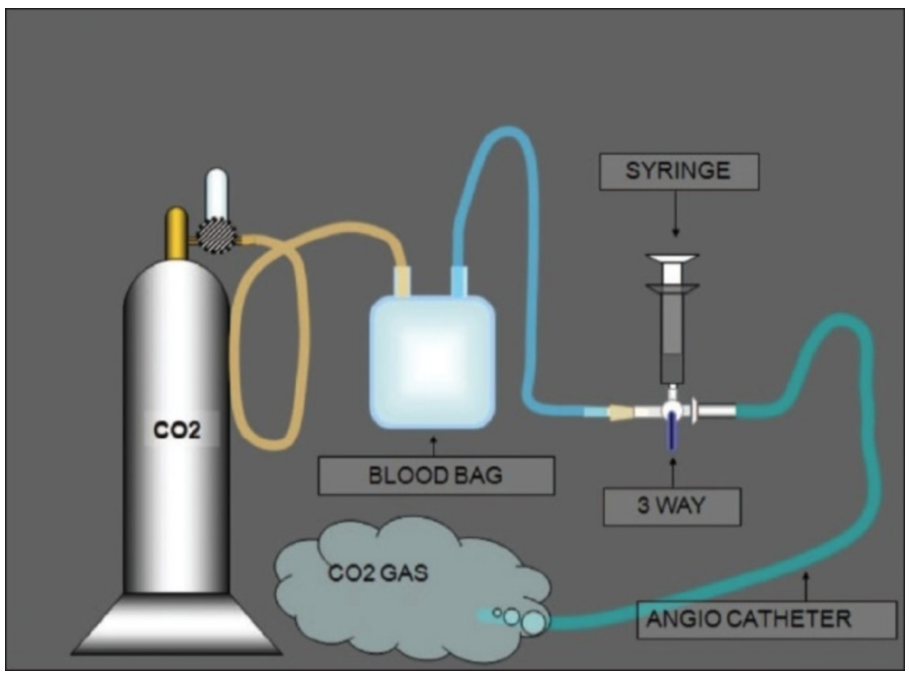


Figure 47. Carbon dioxide delivery system using a blood bag.[90] This system is not FDA approved.

that the systems required assembly. Regardless of the training and simplicity incorrect assembly can result in air embolus. Additionally, the bag must be filled and purged three times to remove residual room air. This step is somewhat cumbersome and time consuming, especially when the decision to use CO_2 occurs spontaneously during the procedure. Other similar systems do exist **(Figure 47)**.

For years, we have reported that the patient should never be connected directly to the cylinder. This has been modified recently due to the development of a K-valve stopcock that precludes the possibility of CO_2 passing

directly from the canister to the patient **(Figures 48, 49)**.

The next generation of delivery systems employs a compact regulator that uses a small 10,000-cc canister of pharmaceutical-grade CO_2 **(Figure 50)**. The smaller system can be placed in a sterile sleeve or left beneath the sterile drape. It is connected to a series of 2 tubes with one-way valves, as well as a K-valve and a reservoir and delivery syringe. The K-valve prevents direct communication with the patient. Carbon dioxide is introduced into the reservoir syringe. From the

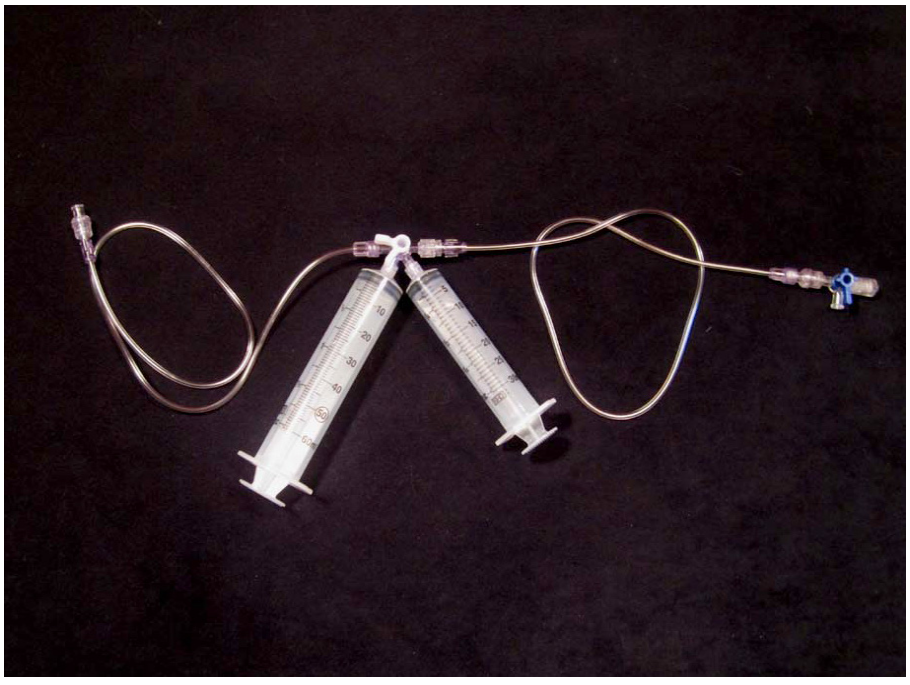


Figure 48. AngiAssist (AngioAdvancements) utilizes a reservoir and delivery syringe with a one-way valve on the receiving and delivery end of the tubing. Carbon dioxide goes to the reservoir syringe and the one-way valve prevents backflow. Carbon dioxide can then be advanced into the delivery syringe after turning the K-valve. The K-valve can be turned again and product delivered. The one-way valve prevents backflow. This system is approved for gaseous delivery but not for intravascular therapy.

IMAGING TECHNIQUES

Volume:

Visceral arteries	5-20 cc
Peripheral extremity arteries	5-20 cc
Iliofemoral arteries	10-20 cc
Aorta	20-50 cc
Inferior vena cava	20-50 cc
Peripheral and central veins	5-20 cc
Portal vein	10-20 cc
Splenoportal venogram	10-20 cc

5-7 frames/second

Pulse width of 60 milliseconds

Decrease patient motion with sedation and decreased discomfort

Decrease bowel gas motion with glucagon 1 mg/mL intravenously

Elevate the area of interest

Vasodilate peripheral vasculature in the extremities with nitroglycerin 100 mcg prior to CO_2

Use an end-hole catheter with radiopaque tip. Microcatheters are ideal.

Post processing including stacking (superimposition of images) to enhance images

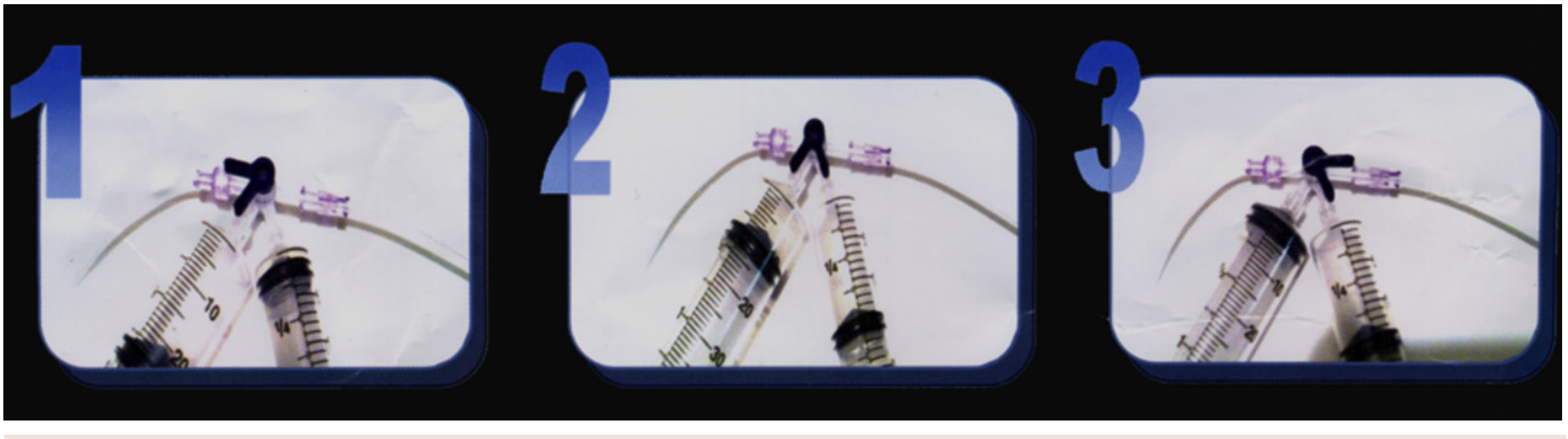


Figure 49. Proprietary K-valve (AngioAdvancements). Product can only be transferred along the lines of the valve stem. Product cannot go from the original source to the patient directly. It must traverse both the reservoir and delivery syringe.

Figure 50. CO2MANDER II and AngiAssist delivery system (AngioAdvancements). This uses a dedicated pharmaceutical-grade CO^2 10,000-cc cylinder containing a compact user-friendly compressor. The AngiAssist is one piece, preassembled and contains one-way valves and a proprietary K-valve, which prevents direct delivery from source to patient.

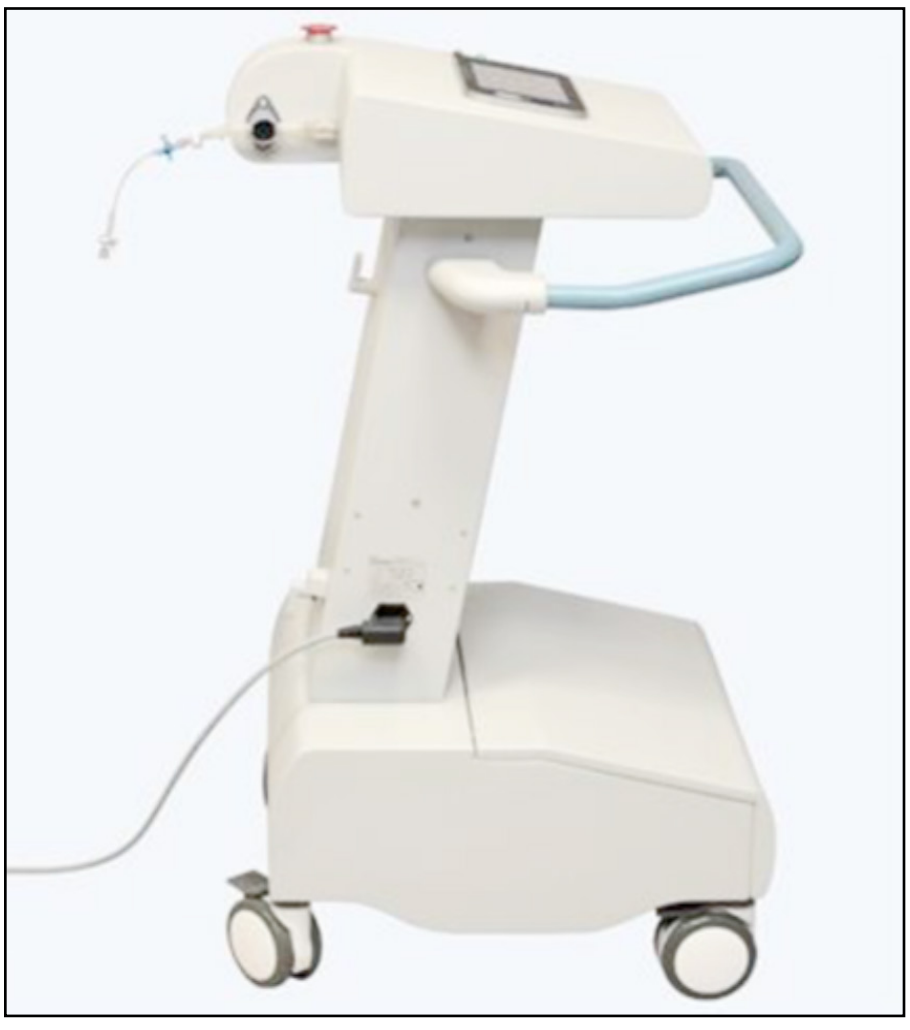


Figure 51. Angiodroid CO_2 injector. Digital vs hand injection.

reservoir, the gas should be pushed, not aspirated, to the delivery syringe to avoid the unlikely possibility of air contamination through the K-valve. Equilibrium with the atmosphere can be achieved with a 3-way stopcock on the delivery catheter. The system does not require assembly and is extremely user friendly. Set-up for use takes approximately 1 minute. Another recently developed type of delivery is the Angiodroid CO_2 injector (Angiodroid) which utilizes digital vs hand injection **(Figure 51)**.

Finally, some operators filter the CO_2 before it enters the vasculature. Carbon dioxide can be delivered and has been delivered without filtration for arteriography and venography, as the gas is not injected as an arterial contrast agent above the diaphragm. However, the use of a filter (0.2 micrometer pore size) can effectively remove particulate contamination and bacteria (0.5 to 5.0 micrometer). At the University of Michigan, infrared gas filtration (FDA approved filter, Syringe Pharmassure .2 micron with HT Tuffryn Membrane Pall Corporation #HP1002) is used for CO_2 delivery, with a new filter used for each procedure as part of the quality and safety program.

CONCLUSION

CO_2 is not the quintessential imaging agent but it offers unique properties when used alone or in combination with iodinated contrast that can expand diagnostic and therapeutic options in a variety of clinical scenarios. Used appropriately it is safe and can not only prevent CIN but also also offer life-extending procedures to patients who would otherwise have been precluded because of their underlying renal status. It can also be used less invasively or when traditional contrast fails to

make diagnoses and avoids more significant intervention. Current technology permits simple, safe administration with images comparable to liquid contrast. It is an inexpensive, versatile tool that should be added to every interventionalist's toolbox. ■

Editor's Note: *Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Caridi reports consultancy to and reimbursements for educational programming from AngioAdvancements. All remaining authors report no related disclosures.*

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