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chapter 52

Carbon Dioxide (CO_2) as a Contrast Agent for Angiography and Angioscopy

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Many advances in vascular surgery have resulted from the ability to image the vascular tree. The first arteriogram was done in a cadaveric extremity several months after the discovery of the x-ray by Roentgen in 1895. Unfortunately, the initial use of arteriography in humans was limited by contrast media, which were very toxic, and by methods of delivery, which required large catheters and surgical cutdowns for vessel access. Delivery methods for arterial contrast and imaging equipment have improved significantly, and currently, the vascular tree can be safely and expediently imaged by a variety of techniques. Contrast media have also improved tremendously. However, adverse reactions still occur in more than 1 percent of patients, and mortality secondary to anaphylaxis and renal failure[1] still occurs after arteriography.

Newer nonionic contrast agents have decreased the incidence of allergic reactions associated with arteriography. In addition, use of these agents is definitely associated with less discomfort, especially in studies of the extremities. However, mortality and the incidence of renal failure after arteriography using nonionic contrast media remain unchanged.[1] In the future, the vascular system may be imaged with Doppler ultrasound or magnetic resonance arteriography, so that contrast arteriography can be avoided. Unfortunately, these modalities are not currently available and probably cannot be used routinely during endovascular procedures or immediately after surgical arterial reconstruction. Thus, contrast arteriography will likely remain an important diagnostic technique in the management of patients with peripheral vascular disease.

Since 1971, carbon dioxide (CO_2) gas has been used as an arterial contrast agent at the University of Florida.[2,3] We became interested in CO_2 as a contrast agent because it was routinely used at that time for the detection of pericardial infusion and had been injected intravenously in thousands of patients without reported complications.[4,5] In addition, CO_2 gas had been used in radiology since 1924 for the imaging of retroperitoneal structures and during gas endarterectomy of coronary arteries (in the 1960s). We initially used CO_2 gas for arteriography by injecting it by hand and imaging it with standard cut film subtraction techniques.[2] However, the CO_2 gas was difficult to deliver reliably, the images were frequently suboptimal, and the subtraction process was time consuming.

In 1980, with the advent of digital subtraction arteriography (DSA), imaging of this "low-density" contrast agent became more reliable. Study of the use of CO_2 gas as a contrast agent for arteriography was then expanded. To date, we have used CO_2 gas in over 100 laboratory animals and over 700 patients, with surprisingly good results.[2,3] During the past 2 years, we have also used CO_2 gas as a medium to displace blood for clear angioscopic viewing during endovascular procedures.[6,7] In addition, we have developed a reliable delivery system for CO_2 gas. It is hoped that in the near future, digital equipment will be optimized so that CO_2 arteriography will provide resolution approaching that of cut film arteriography using iodinated contrast agents.

PRINCIPLES OF IMAGING

Liquid contrast mixes with blood and, if delivered properly, will fill the entire vascular tree. To increase the density and thus the quality of the arterial image, either the injection rate or the concentration of the iodinated contrast agent is increased. In contrast, CO_2 gas produces an arterial image by totally displacing blood from the vessel. The minimal difference between the density of the gas and that of the surrounding soft tissue is then distinguished using digital subtraction and electronic enhancement. Because CO_2 tends to float, if the blood is not totally displaced, only the upper portions of the vessel will be filled, resulting in incorrect imaging. In addition, if the blood has been totally displaced from the vessel being examined, addition of more CO_2 will not improve the image. The image can be improved only by electronic enhancement. In general, using present DSA equipment, image quality is usually adequate for the diagnosis of even small vessel disease, although density differences between the CO_2 and the surrounding soft tissue are much less than when iodinated contrast is used.

BUOYANCY OF CO_2 GAS

CO_2 gas is extremely buoyant, which can both impede and facilitate vascular filling. Arteries that are dependent (posterior when the patient is in the supine position), such as the lumbar arteries, are not well filled with CO_2. On the other hand, anterior arteries (celiac, superior mesenteric, and inferior mesenteric arteries) are always well filled, even when inadequate amounts of CO_2 are delivered. It is therefore imperative to position the area of interest higher than the injection site. The analogy of injecting helium into a hollow tree can be used. If the tree is inverted, the distal branches would be very difficult to fill with helium. If this tree is lying on its side, the upper branches would fill, and if the tree is in its normal upright position, all the branches would readily fill.

During lower extremity angiography, the horizontal iliac and proximal superficial femoral arteries fill quite well with CO_2 when the patient is supine. However, the more distal vessels that are lower than the injection site are difficult to fill, especially in patients with poor arterial flow. The superficial femoral artery (SFA) slopes downward from its location anterior to the proximal femur to a position posterior to the distal femur, and injected CO_2 gas tends to float to the higher portion of the SFA when the patient is supine. A Trendelenburg position of approximately 20 to 30 degrees improves filling of the more distal vessels. A tilting table provides the elevation and stability required for a good DSA image. Elevating the legs with wedges may also suffice, but when the legs are elevated without a tilting table, motion frequently occurs, degrading the image.

LOW VISCOSITY OF CO_2 GAS

The very low viscosity of CO_2 (1/400 of iodinated contrast) greatly facilitates filling of collaterals and stenotic vessels. In addition, this low viscosity expedites identification of arteriovenous shunting within malignant tumors and arteriovenous malformations.[3] The low viscosity of CO_2 gas permits its delivery through very small catheters and through the narrow space between instruments such as guidewires, lasers, atherectomy devices, or angioscopes and the inner wall of guiding catheters.

DOES CO_2 GAS BLOCK CAPILLARIES?

Injection of CO_2 gas into the arterial system potentially could lead to ischemia caused by capillary occlusion from trapped gas bubbles. However, CO_2 gas is extremely soluble in blood (20 times more so than oxygen), so that gas bubbles should be quickly dissolved. In addition, when large volumes of CO_2 are injected into the aorta of dogs, the renal veins are always seen. This observation suggests that CO_2 either floats through capillaries or passes into the renal vein through precapillary shunts. CO_2 gas in the renal veins returns to the inferior vena cava and is eliminated very quickly by the pulmonary circulation. Because CO_2 gas does return to the right side of the heart, it is important to limit the volume of CO_2 per injection to 200 ml. In two animals, delivery of massive amounts of CO_2 directly from a CO_2 gas cylinder totally displaced the blood in the right side of the heart, causing the animals' demise.

Although it appears that CO_2 does not block capillaries, it is trapped in any inverted U–shaped structure. If there is good blood flow in the area, CO_2 should be pushed from the inverted U and into the distal circulation. Thus, trapping of CO_2 within a portion of the arterial tree should not result in ischemia if time is allowed for reabsorption between injections. However, if any structure (e.g., a lower extremity, transplanted kidney, liver) is markedly higher than the injection site or blood flow to that area is limited, CO_2 could be trapped within the entire structure and remain for a significant period. This trapping will occur if the buoyant force of the gas is greater than the force of the returning blood flow. This problem can be prevented if the position of the structure is changed after the injection (i.e., the organ is inverted or the patient's feet are lowered) so that the CO_2 is released to return to the inferior vena cava and be eliminated by the pulmonary circulation.

INJECTION TECHNIQUE

CO_2 gas is very difficult to deliver for angiography because it is compressible, invisible, and heavier than air. Initially, for aortography and extremity angiography, we filled a 50-ml syringe with CO_2 using a standard oxygen regulator connected to a medical-grade CO_2 gas cylinder. With use of a three-way stopcock, air was purged from the syringe by filling and emptying it multiple times. The syringe was then connected to the angiographic catheter, and the CO_2 gas was pushed rapidly into the catheter. DSA imaging was initiated prior to injecting the CO_2. We attempted to deliver 50 ml of CO_2 gas in 2 to 3 seconds, as would be done with standard iodinated contrast. Unfortunately, because of the compressibility of the gas, initially the syringe plunger moves forward quite easily but little CO_2 is delivered. Movement of the plunger then becomes increasingly difficult, and the entire 50 ml of gas is delivered in the last half-second of the injection.

Delivery of CO_2 gas using a standard mechanical liquid injector is somewhat more reliable. The injector can be programmed to advance the plunger at a constant rate, such as the equivalent of 25 ml of liquid per second for 4 seconds (total of 100 ml). However, even with this system, CO_2 is not injected instantaneously but is simply compressed for 3.5 seconds, and the entire 100 ml is delivered during the last half-second of injection. This method results in a flow rate of between 100 and 200 ml/sec, which creates an "explosive-type" delivery.

If saline is completely cleared from the angiographic catheter prior to CO_2 delivery, the gas is compressed to a lesser degree during injection, resulting in a much less explosive type of delivery. Unfortunately, clearing the angiographic catheter of saline is difficult without injecting a large amount of CO_2, which will interfere with the DSA image. We have attempted to clear the catheter using tandem syringes (a 3-ml syringe and a 50-ml syringe). CO_2 from the 3-ml syringe is rapidly delivered through the catheter to displace the saline, and then the 50 ml of CO_2 in the larger syringe is quickly injected. Unfortunately, this technique is awkward because several stopcocks have to be opened and closed during the procedure and frequently blood will refill the angiographic catheter before the major bolus of CO_2 can be delivered. Alternatively, a standard mechanical injector set at a delivery rate of 10 ml/sec, for a total of 50 to 100 ml, can be used. At this setting, the plunger moves forward at a slow rate, and within the first 1 to 2 seconds, saline is cleared from the angiographic catheter. The remainder of the CO_2 is then delivered without being compressed.

To fill the syringe of the mechanical injector, the regulator of the CO_2 tank should be set at approximately 5 psi. In addition, the stopcock on the syringe should be open to room air so that the gas being drawn into the syringe is at atmospheric pressure. In this manner, the amount of CO_2 gas within the syringe is equal to the amount indicated by the syringe plunger position. Otherwise, if the stopcock on the syringe is not open, more than the measured amount of CO_2 will be loaded into the syringe owing to the compressibility of the gas. When the stopcock on the syringe is vented, the syringe should be pointed upward because if it is pointed downward, the heavier CO_2 gas will be displaced by room air. Finally, care must be taken to ensure that the cylinder from which the CO_2 is loaded does not contain water. Water will combine with CO_2 to produce carbonic acid, which could then be injected into the patient. One cannot assume that medical-grade CO_2 is pure, as we have found water and a large amount of rust in several CO_2 cylinders. Because of this, we have recently begun to use gas from disposable CO_2 cylinders (Medipure carbon dioxide, Union Carbide Gases, Linde Division, Danbury, CT).

DEDICATED INJECTOR*

With hand delivery of CO_2 or delivery using a standard mechanical injector, the quality of angiographic images may be variable. This finding appears to be due to the marked variability in CO_2 delivery using these techniques. Occasionally, delivery is excellent. However, often the gas is delivered in a pulsatile fashion, resulting in the vessel's being filled with CO_2 one second and with blood the next. This situation obviously results in poor image quality and limits the diagnostic utility of CO_2 angiography. Other significant disadvantages also occur when CO_2 is delivered using hand injection or standard mechanical angiographic injectors, including the possibility of air contamination and the potential for delivering CO_2 gas in an explosive manner.

*E-Z-EM Company, Westbury, NY.

A new, dedicated CO_2 injector for use with CO_2 angiography is being developed at the University of Florida. This injector is gaited to the electrocardiogram and delivers CO_2 so that blood is totally displaced during the injection. No more than 200 ml per injection can be delivered, and the injector includes many other fail-safe systems. Multiple 0.24-μ filters ensure sterility of the injected gas, and a very sensitive oxygen detector will prevent air contamination. The injection rates and volumes of injection can be programmed, and indicators will show the rates and volumes of CO_2 gas actually delivered. A system that automatically flushes the angiographic catheter with saline between injections will also be included. The injector is currently undergoing clinical trials.

X-RAY EQUIPMENT

The low density of CO_2 requires subtraction and electronic enhancement, available in DSA equipment, to produce adequate images for arteriography. Unfortunately, the present DSA equipment has been designed for use with iodine contrast. However, adequate images are usually produced when CO_2 is used. The resolution of the new 1024 × 1024 pixel DSA systems approximates that of standard cut film arteriography, and several companies are modifying DSA equipment to increase contrast and thus improve CO_2 arteriography. Finally, a tilting table is essential for CO_2 angiography, and most angiography suites are not equipped with tilting tables. An operating room type of table that tilts in both longitudinal and transverse axes (approximately 20 degrees) is available from AMSCO (Erie, PA).

DIAGNOSTIC ACCURACY

Imaging of the aorta and its first- and second-order branches is excellent approximately 90 percent of the time using CO_2 angiography (Fig. 52–1). Failure of CO_2 aortograms to provide diagnostic information is usually due to respiratory and bowel motion. In the pelvis and lower extremities, the success rate is even higher (Figs. 52–2 and 52–3). However, the vessels below the knee are definitely more difficult to fill, especially in patients with poor blood flow. If the extremity is not elevated and only a small amount of CO_2 is delivered, the CO_2 may become absorbed before it reaches the trifurcation. In contrast, if the leg is elevated, the CO_2 will readily flow to the trifurcation and even to the level of the digital arteries (Fig. 52–4). Filling of distal vessels can also be improved by advancing the angiographic catheter closer to the area of interest. With such techniques, at times collaterals and distal vessels will fill better with CO_2 than with liquid contrast. Even structures with little or no flow will readily fill because of the buoyancy of CO_2. For example, we have seen many tumors that appeared totally avascular when an iodinated contrast medium was used but were seen to be very vascular when CO_2 was used.

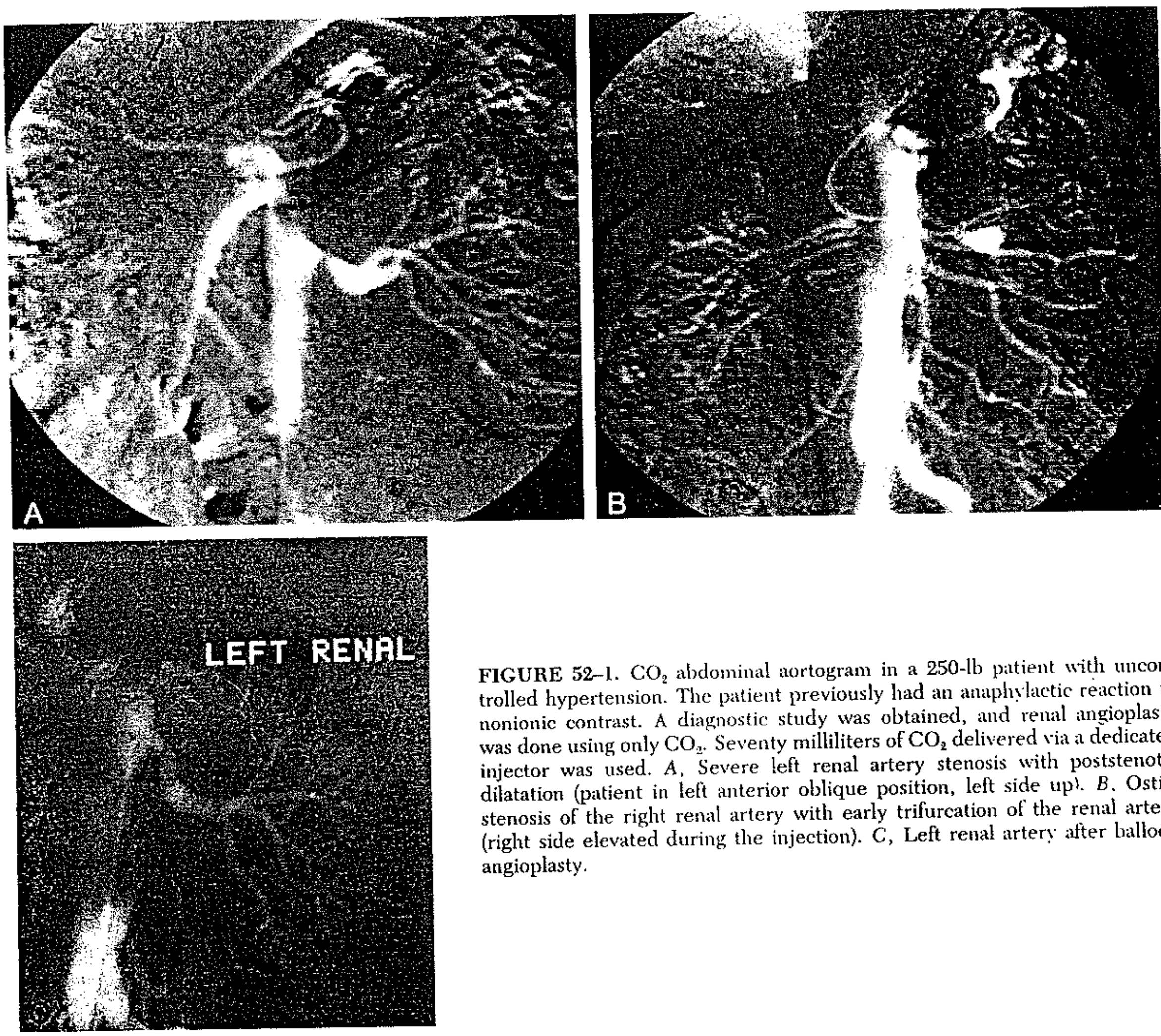

FIGURE 52–1. CO_2 abdominal aortogram in a 250-lb patient with uncontrolled hypertension. The patient previously had an anaphylactic reaction to nonionic contrast. A diagnostic study was obtained, and renal angioplasty was done using only CO_2. Seventy milliliters of CO_2 delivered via a dedicated injector was used. *A*, Severe left renal artery stenosis with poststenotic dilatation (patient in left anterior oblique position, left side up). *B*, Ostial stenosis of the right renal artery with early trifurcation of the renal artery (right side elevated during the injection). *C*, Left renal artery after balloon angioplasty.

FIGURE 52–2. *A*, The distal abdominal aortogram with the injection of 15 ml of iodinated contrast (Omnipaque), demonstrating apparent right common iliac artery stenosis. *B*, Ninety milliliters of CO_2 injected at the bifurcation, demonstrating a normal common iliac artery. No pressure gradient in the iliac artery was found. Aneurysmal dilatation of the proximal external iliac artery is seen.

Interpretation of the images from CO_2 angiography is considerably more difficult than when iodinated contrast is used. For accurate interpretation, one must be assured that the CO_2 has totally displaced the blood from within the vessel. If small amounts of CO_2 are delivered, only the anterior portion of the vessel will be filled, and the vessel may appear smaller than it actually is. Because of this problem, any area of apparent arterial pathology should be imaged in at least two different positions to demonstrate that a narrowed area within a vessel is due to arterial disease and not to filling artifacts. In addition, multiple images are necessary to document that a defect within a vessel is not secondary to trapped CO_2 from a previous injection. When CO_2 has not cleared from the artery prior to a DSA imaging series, the trapped CO_2 gas will cancel out the current CO_2 and will appear as a void, which will be interpreted as a stenosis or an occlusion.

COMPLICATIONS AND CONTRAINDICATIONS

The only documented complication directly related to CO_2 injection in our series has been severe diarrhea after CO_2 aortography in one patient. Two thousand milliliters of CO_2 was injected into the abdominal aorta during this study, and the inferior mesenteric artery circulation was exposed to very high volumes of CO_2 because it originated from an aneurysmal infrarenal aorta. The CO_2 apparently was trapped in the aneurysm and created a "vapor lock" in the inferior mesenteric artery, resulting in ischemia. Although this is the only complication from CO_2 injection that has been observed in patients undergoing CO_2 angiography at the University of Florida, other potential toxic effects of CO_2 gas used as a contrast agent have been carefully investigated.

Neurotoxicity

We do not use CO_2 gas above the diaphragm because a preliminary study in rats suggested that it may be

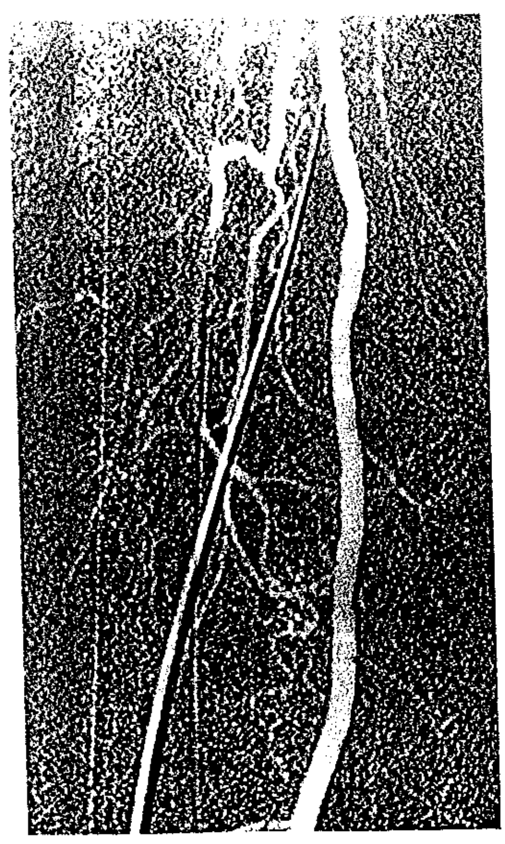

FIGURE 52–3. CO_2 arteriogram of the superficial femoral artery with second-generation digital subtraction angiography (DSA). Note good visualization of the small arteries.

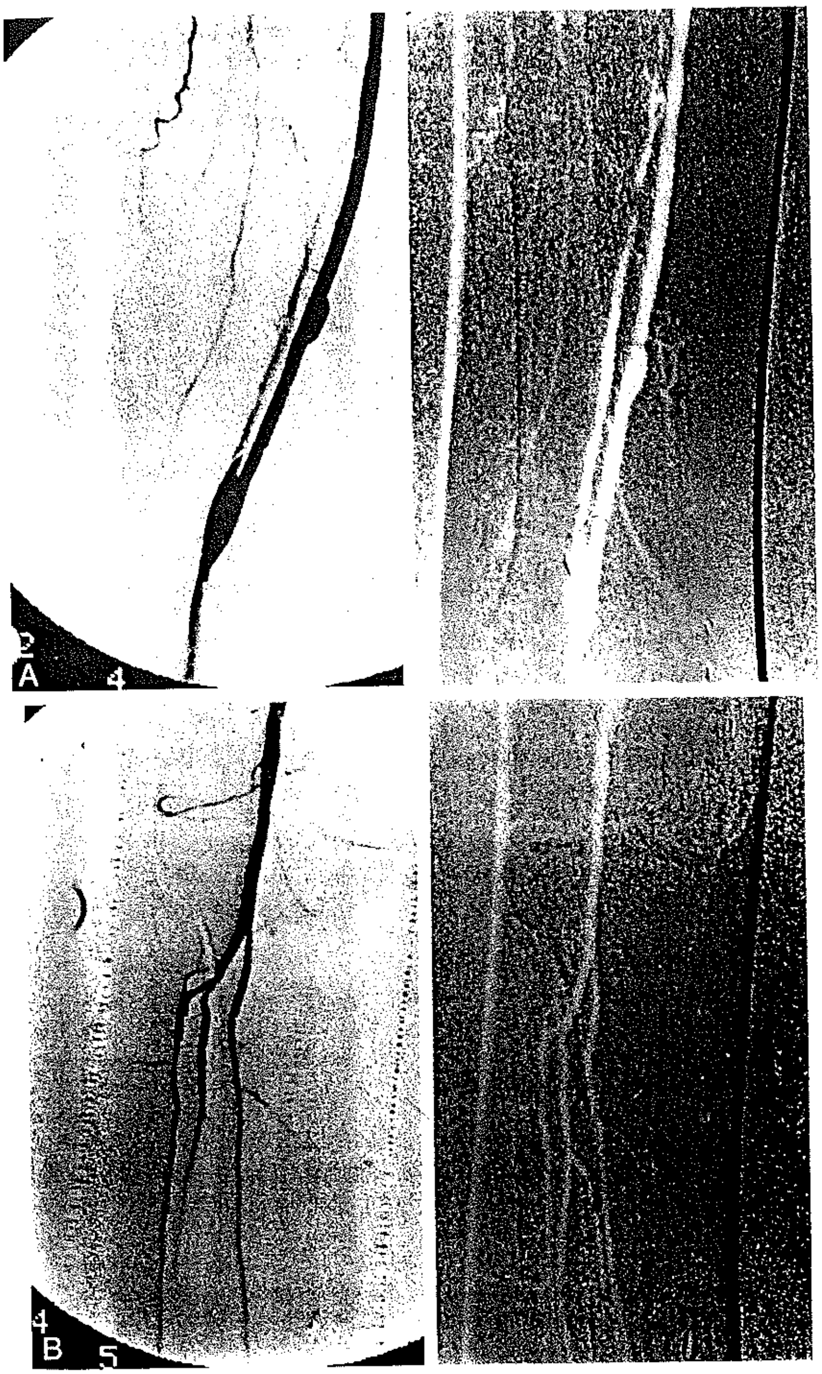

FIGURE 52–4. *A*, Comparison studies of a patent femoropopliteal vein graft done with 5 ml of iodinated contrast *(left)* and 90 ml of CO_2 *(right)*. *B*, Comparison views of the trifurcation area showing comparable imaging with contrast *(left)* and CO_2 *(right)*.

neurotoxic.[8] We also do not inject CO_2 into the aorta when patients are in the prone position because the buoyancy of the gas may fill vessels that feed the spinal cord. In contrast to findings in rats, injection of CO_2 into the canine cerebral circulation produces no neurological deficits. However, until the question of the neurotoxicity of CO_2 gas is resolved, *CO_2 is definitely contraindicated* in any situation in which the cerebral circulation could be exposed to the gas.

Renal Toxicity

In using CO_2 for aortography and for selected renal artery injections in patients with renal failure, we have noted no decrease in renal function. However, the majority of these procedures are done with patients in the supine position, and the distal renal arteries do not fill well. Positioning the patients so that the kidney to be studied is above the injecting catheter improves visualization but also increases the exposure of the kidney to CO_2 gas. To investigate the risks of this exposure, a renal toxicity study in dogs has recently been completed. Overall, no decrease in renal blood flow or renal function (as measured by ^{99m}Tc dimercaptosuccinic acid and ^{131}I sodium iodohippurate [Hippuran] scans) was seen within 24 hours after the injection of large volumes of CO_2 into the kidney. In addition, no microscopic changes in the endothelium of major renal arteries or in the glomeruli were seen by scanning or transmission electron microscopy. However, when the kidney was positioned vertically above the injection site in three animals, minimal acute tubular necrosis and minimal transmissional electron microscopic changes were seen. A preliminary ultrasound study demonstrated that if the kidney is vertically oriented, a period of approximately 2 minutes is required for the CO_2 to clear from the cortex of the kidney after injection. In contrast, when the kidney is positioned horizontally, the CO_2 completely clears from the kidney at approximately 30 seconds.

Injection into Large Aneurysms

If CO_2 is trapped in a large aneurysm, there is a possibility that nitrogen will exchange with the trapped CO_2 because of the high solubility of CO_2 and the high partial pressure of nitrogen in soft tissue. If nitrogen is later released into the circulation, ischemia could occur, as nitrogen is relatively insoluble in blood and bubbles can form. Ischemia secondary to nitrogen bubbles has not been observed in our clinical series of CO_2 angiography, despite occurrences of CO_2 being trapped in large aneurysms for several hours. However, because of this potential problem, nitrous oxide anesthesia should not be used with CO_2 angiography, and repeated injection of CO_2 should not be done when trapping of CO_2 within an aneurysm is seen.

Use in Respiratory Failure

Because CO_2 is eliminated through the lungs, CO_2 angiography should not be done in patients with severe respiratory compromise unless blood gases are obtained at frequent intervals during the procedure. We have done CO_2 angiography in several patients with respiratory failure, without untoward effects. However, patients with high arterial P_{CO_2} values (suggesting difficulty in eliminating CO_2) may not be able to eliminate the excess CO_2 that accumulates during CO_2 angiography and thus may be at risk from this procedure.

Discomfort

In more than 90 percent of patients, minimal or no discomfort occurs during CO_2 injection. Only if large volumes of CO_2 are injected very rapidly does discomfort, which approaches that experienced with iodinated contrast agents, occur.

CO_2 ANGIOSCOPY

Clearing the intraluminal field of blood is essential for angioscopy. Balloon occlusion, arterial clamping, and clearing blood from the artery to be inspected with saline have been used, with variable results.[9] High injection rates of saline, which can be provided with dedicated irrigation pumps, will readily displace the blood in most vessels. However, in larger arteries, such as the iliac arteries or the aorta, particularly when percutaneous angioscopy is attempted, it is difficult to maintain with reliability a field of view that is clear of blood.

CO_2 can displace blood and hence serve as a viewing medium for angioscopy. In addition, because CO_2 is eliminated by the lungs, unlimited quantities of CO_2 can be used without significant risk if sufficient time is allowed for the CO_2 to be expired. Finally, the low viscosity of CO_2 means that large volumes of the gas can be delivered through the small channels found in angioscopes. Thus, CO_2 gas would appear to be an ideal agent to use to improve arterial visualization during angioscopy.

In an initial animal study of the use of CO_2 to clear the visual field of blood during angioscopy, Silverman et al.[10] demonstrated that the use of CO_2 gas was associated with a shorter interval from onset of infusion to total visual field clearance, a longer duration of a clear visual field once blood was displaced, and a greater percentage of viewing fields totally cleared of blood than were achieved when heparinized saline was used (80 percent versus 14 percent). In a separate animal study, we also showed that in large vessels CO_2, when compared with saline, definitely improved angioscopic images and increased the clarity of the image.[11] Finally, we have used CO_2 with angioscopy in several patients, with excellent results (Fig. 52–5). Injection of 200 ml of

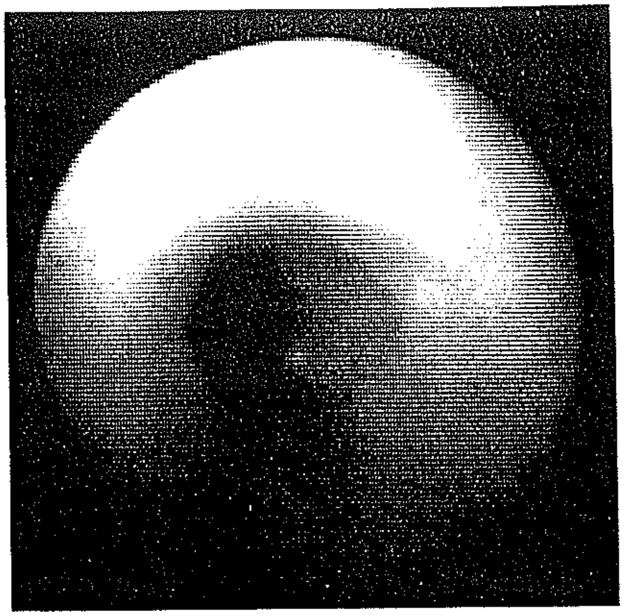

FIGURE 52–5. CO_2 angioscopy of the superficial femoral artery, demonstrating a clear view of a normal artery.

CO_2 over approximately 20 seconds provided clear visual fields for 20 to 60 seconds. Comparison with heparinized saline injected with a mechanical contrast injector demonstrated a significantly longer interval of clear viewing with CO_2. These results are obviously preliminary but suggest that the injection of CO_2 to clear the field of blood may be an important adjunct to angioscopy and potentially may allow percutaneous angioscopy to be done.

The same principles are important in CO_2 angioscopy as in CO_2 angiography. Elevation of the extremity improves CO_2 delivery to distal vessels. If the artery is occluded and the extremity is properly positioned, only a small amount of CO_2 is required to clear and maintain an unobstructed visual field. Regardless, time should be allowed between injections for the CO_2 to return to the venous system and to be eliminated by the lungs. Finally, a tilting table should be used to elevate the extremities and trap the CO_2 and then to release it periodically.

CONCLUSION

CO_2 has many significant advantages for both angiography and angioscopy. With CO_2 as a contrast agent, there is no chance whatsoever of allergic reaction, no renal toxicity, and minimal discomfort during injection. In addition, the low viscosity of CO_2 permits delivery by very small catheters. Finally, CO_2 is very inexpensive compared with nonionic contrast agents. Although CO_2 can be delivered by hand injection or with a standard liquid contrast injector, we would not recommend its general use until a dedicated delivery system is available that will prevent air contamination, explosive delivery, or inadvertent injections of large volumes of CO_2. In addition, CO_2 is not currently approved by the Food and Drug Administration.

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