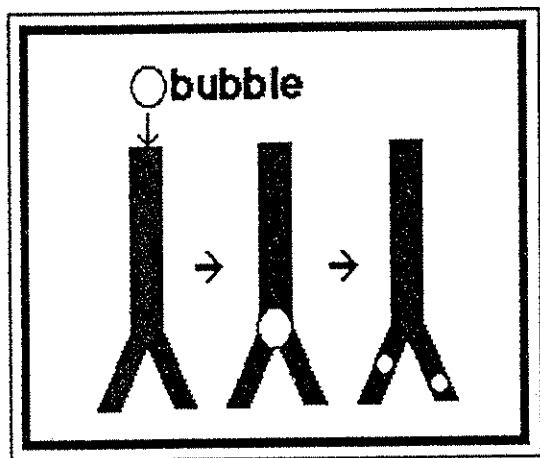


CARBON DIOXIDE ANGIOGRAPHY

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HISTORY

The use of carbon dioxide as a contrast agent was well established in the 1920's. While the value of contrast material in arteries was already shown in cadavers shortly after Roentgen's discovery in 1896, widespread and safe clinical use of contrast was not prevalent until the 1940's. The first practical use of gas as a contrast agent was for radiographic studies of the peritoneal cavity and retroperitoneal space. By injecting various gases, tumors could be outlined. Most of these studies were done with air, and later oxygen. These procedures were not totally safe, indeed an early survey of 11,000 air retroperitoneal studies showed that 58 of these patients had died of air embolus following the injection!



embolus following the injection!

Numerous studies on air embolism were performed in the 1940's as intravenous fluid use became more widespread. In animals one could give high doses of air into the systemic veins without problems. However, even small doses (15-20 cc) of air given into pulmonary veins would consistently cause death from occlusion of the coronary circulation and ventricular fibrillation. It would seem that the lungs trap the bubbles of air when it's given intravenously, and since there's such an

abundance of small vessels, no problem occurs and the air eventually breaks up. If given into the left heart, the bubbles occlude the coronary circulation, with terrible effects

The bubble of gas has a certain surface tension which prevents it moving on past a bifurcation for awhile. Carbon dioxide (CO_2) on the other hand rapidly dissolves so that the bubble doesn't occlude the circulation.

Two important facts came out of early research on air embolus. First, air in systemic veins is safe unless large volumes are used. Second, the treatment of air embolus is to turn the patient on their left side. This has two effects:

a) The bubble of gas is "trapped" (rises) in the "up" chamber, namely the right atrium, SVC and IVC. b) The pulmonary arteries are dependent ("down"), so blood continues to flow past the gas bubble.

It was observed that air is churned to a froth in the right heart and trapped by the lungs. In 1800, Magendie observed that "I have thrown, with all the force and celerity of which I am capable, forty or fifty pints of air into the veins of a very old horse, without his dying immediately".

In 1919, Rubin introduced CO₂ for peritoneography. Early deaths from CO₂ were likely due to the contamination of commercial CO₂ with air. In 1921, Alvarez and Carelli, respectively, emphasized the safety of CO₂ for peritoneography and retroperitoneography.

Following research in animals demonstrating the safety of CO₂ given intravenously, this agent was considered for angiocardiology. It was not very effective and didn't produce good quality angiograms, but was adopted as an agent to fill the right atrium and demonstrate pericardial thickening. The patient is turned on their left side, 100-200 cc of CO₂ is rapidly injected and accumulates in the right atrium on the "up" side. Cross table views show thickening between the CO₂ bubble (outlining the lateral right atrial wall) and the heart border if pericardial fluid is present. The bubble of CO₂ rapidly disappears. In the 60's and 70's, many thousand such examinations were performed with a very low complication rate. A few scattered reports of fatalities were nevertheless described.

To finish the history of the use of CO₂, Dr Irvin Hawkins, in Gainesville, Florida, began the use of CO₂ in 1971, as an intrarterial contrast. Because of low inherent contrast the method didn't catch on until the 80's, when subtraction angiography came along.

Other uses of CO₂, all more recent, include the following:

- * - microbubble solutions used as an intravascular and intracardiac contrast agent for ultrasound imaging.
- intrarterial injection to clear an artery for angioscopy. CO₂ has proven more effective than saline for this purpose.
- * - a recent report from Baylor notes high quality portal venography when 60 cc of CO₂ is injected with a balloon occlusion catheter in the hepatic vein. The CO₂, being less viscous than contrast, provides excellent fill of the portal vein, which provides guidance for the TIPS portal vein puncture.
- * - CO₂ has such low viscosity that it can be used with DSA to produce an angiogram even through a 2-3 F catheter or a 25G needle, or even the small side port on the Walstent introducing catheter.
- * - injections of CO₂ into the right atrium, upper IVC, or even peripheral veins, will usually demonstrate the right hepatic veins, if the patient is positioned in left decubitus position.
- * - Dr Hawkins has recently shown that CO₂ arteriography of transplant renal arteries is safe and effective. The transplant is "up" relative to the injection site, so the vessel fills well.

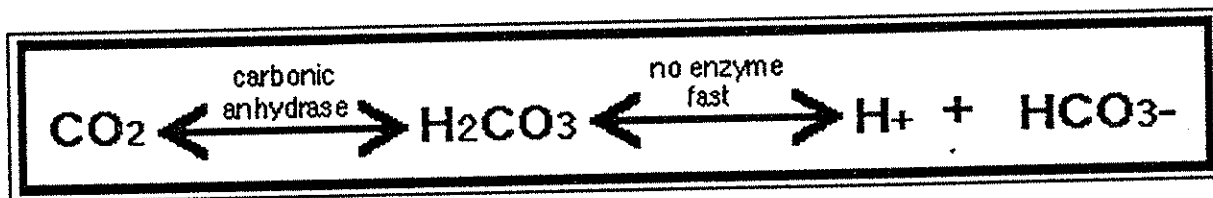
PHYSICS OF CARBON DIOXIDE

CO₂ is safe because it dissolves rapidly in blood and is quickly excreted from the lungs. It simply doesn't hang around long enough to block the small arteries, like air, which is much less soluble.

The solubility of CO₂ in a liquid such as plasma, is 20 times greater than that of air or oxygen. CO₂ is nearly completely exhaled in one passage through the lungs. The speed with which a gas passes out through the lungs is related to the absorption coefficient (*ac*), and the density (*d*) of the gas, in a liquid at 40° C. A comparison of the physical characteristics of oxygen, nitrous oxide, and carbon dioxide follows. Although nitrous oxide has a little better physical absorption than carbon dioxide, the latter is more quickly absorbed in the body because of certain chemical reactions.

gas	<i>ac</i>	<i>d</i>	<i>ac</i> / \sqrt{d}	Time to dissolve 600 ml from a dog's pleural space
O ₂	0.023	1.1	0.022	10 hours
N ₂ O	0.544	1.5	0.440	30 minutes
CO ₂	0.530	1.5	0.430	2-3 minutes

In addition to being very soluble and passing quickly out of the lungs, CO₂ undergoes a chemical reaction with the water of plasma, cells, and interstitial fluid as follows:



This reaction is relatively slow in plasma, but much faster within cells, particularly red blood cells with their high concentration of the enzyme carbonic anhydrase. Furthermore, HCO₃⁻ reacts with protein amino groups to form carbamino compounds, especially with hemoglobin. The net result is rapid absorption of CO₂, and equally rapid release in the lungs. Most of the gas which remains undissolved escapes directly from the lungs.

Several authors have described testing the right atrial gas bubble after it's been present 30-40 seconds, and finding that oxygen rapidly diffuses into the CO₂ bubble and may make up 20% of the gas remaining! Thus it has been recommended to keep the patient in the left decubitus position until the bubble has totally dissolved (30 seconds to 4 minutes). This is a potential cause of fatal CO₂ embolus in a patient who might have a right to left intracardiac shunt. A dose of as little as 20 cc of a non-soluble gas like oxygen, given into the left heart may be fatal!

When given into extremity arteries, there's rapid dissolution and movement of CO₂ into the interstitial space of muscle, a further site for rapid absorption.

EXPERIENCE IN ANIMALS

Intravascular CO₂ in rats is nearly always fatal, they are very susceptible to this gas and not good experimental animals. Work with medium or large dogs allows injection rates to be extrapolated to humans. Rather extraordinary volumes of CO₂ can be given into the peripheral veins of dogs without any effect as long as the injection rate is not too high. For instance, at rates of 100 cc/minute, over 10 liters of CO₂ has been given without any side effects. On the other hand with higher rates of infusion death results with smaller volumes. It's apparent that there's a balance between the CO₂ dissolving in blood, how fast it's given, the total volume, and the site of injection. If injected into the abdominal aorta of dogs at high injection rates (50-100 cc/sec), it may reflux back up to the arch and embolize to the brain, especially if the head is positioned higher than the aorta.

Large volumes of CO₂ given into the left heart or aortic arch may be fatal in dogs, but smaller volumes in the range of clinical usage (10-20 cc) are well tolerated. The CO₂ appears in the coronary arteries, but disappears within 15 seconds. With larger volumes, brain histology after 24 hours shows areas of edema and neuronal ischemia, even though the animals act normally. Carotid injections of 8cc produce good quality arterial and venous DSA images in dogs.

After large intravenous doses of CO₂, dogs frequently hyperventilate, which further improves the elimination of the gas. In cats, intravenous CO₂ produces dilation of pulmonary vessels with an initial drop in pulmonary pressure, which rapidly returns to normal.

In dogs who received repeated doses of 15 cc CO₂ into the renal arteries, there is an immediate reduction in renal blood flow, which rapidly returns to normal. Histology at 24 hours does show some focal areas of tubular necrosis, but renal function remains normal.

EXPERIENCE IN HUMANS

Credit for selective arteriography using CO₂ is fairly given to Dr Irvin Hawkins, Jr. of Gainesborough, Florida. He describes an inadvertent celiac injection of 60 cc of air in 1971, and observed two good things about the misadventure. First there was a decent arteriogram and second nothing bad happened to the patient. Based on prior clinical experience with CO₂ in humans, he proceeded to use it in patients with a prior severe reaction to iodinated contrast. By 1982, with digital subtraction, he began to do more cases, and published his important articles. At this time he has performed over 800 angiograms using CO₂ as the contrast agent.

In 1978, Dr Lantz wrote of his experience in treating ischemic rest pain with infusions of CO₂. He made downstream injections of 100 cc of CO₂ into the femoral artery, and repeated it again 10 minutes later. He described hyperemia and immediate relief of pain in all patients. He frequently did a second infusion a few days or weeks later. Surprisingly he described prolonged relief of pain and healing of ulcers in many of the patients! To the best of my knowledge, this work has not been duplicated.

In the 1970's and 80's, Dr Bendib of France, and Dr Plich of Moscow and later Israel described their work on CO₂ angiocardiology. They used intravenous or right-sided cardiac injections and filmed or cined the results.

Bendib performed many hundreds of examinations. He advised that CO₂ not be used in severe COPD because of the already high pCO₂ levels and risk of CO₂ narcosis. This risk has not been validated, but it's still probably a good idea not to use CO₂ in this group. Carbon dioxide narcosis occurs when the pCO₂ reaches 90 mm, and is said to be like anesthesia, the patient is highly sedated, somnolent, even comatose. Bendib also advised that CO₂ not be injected into the aorta in the prone position because the spinal cord would then be "up" and might be injured.

Plich performed 147 angiocardigrams in children and had "no complications", even though he saw gas in the left heart and aorta in a number of patients with septal defects. He was able to visualize coarctation of the aorta with vigorous right heart injections, so apparently if you use enough CO₂ and inject it vigorously, some will pass through the lungs into the systemic circulation.

Neither of these authors really spell out their methods of evaluating clinical safety (neurologic exam?, blood gases?, etc.). Bendib did describe arrhythmias and hypotensive episodes after the injections.

An excellent recent review by Dr Hawkins is in the AJR, pgs 735-741, vol. 164, March, 1995.

PERFORMING THE EXAMINATION

Important factors to be discussed are:

- | | | | |
|------------|------------------|-------------|----------|
| - volume | - injection rate | - site | - safety |
| - position | - filming | - reactions | |

Remember, CO₂ floats, like a beach ball.

Drs Krasny and Gunther from Germany studied vessel opacification and introduced the concept of the "fill ratio". Iodinated contrast mixes well with blood. If mixing isn't complete, the size of the artery could be falsely underestimated. Therefore they take the measured diameter of the artery following iodinated contrast, and measure the same diameter after CO₂ to calculate the fill ratio. The goal is to displace all the blood with the bolus of CO₂ so as to get a true picture of the artery in question. If one injects at too slow a rate, the CO₂ will enter the vessel as a dribble of frothy bubbles. Rates below 5 cc/sec are not advisable. If one uses too high an injection rate, you can reflux the CO₂ back up the aorta, perhaps even up to the arch and great vessels. This occurs with rates higher than 100-150 cc/sec. Clearly the position of the injecting catheter is critical, and one would have to be much more careful injecting into the thoracic aorta than the femoral artery. Indeed, one should probably not inject the thoracic aorta. The patient's head should never be elevated, lest the CO₂ "float" up to the brain.

A good (> 90%) fill ratio can be obtained in dogs:

- arteries > 10mm. Volumes of 10-60 cc at rates of 10-50 cc/second.

Increasing the injection rate above 15 cc/sec does not improve the fill ratio.

- arteries < 10 mm. 5-10 cc at 5-10 cc/sec.

- **in general, volumes and injection rates of CO₂ 2-3 times greater than used for iodinated contrast media are appropriate.**

Since humans are bigger than dogs, these volumes and injection rates need to be higher. The optimal injection volume and rate are likely a range of "best" values, just like iodinated contrast agents.

PURCHASING CO₂

Find out from your hospital purchasing department where they buy their oxygen. Oxygen suppliers always sell other gases, such as nitrogen and carbon dioxide. The gas is made by liquefying air and allowing each gas to boil off at carefully controlled temperatures. The pure gas is then reliquefied and shipped to the supplier. Available grades of CO₂ are:

- **Medical Grade USP.** The FDA carefully spells out the procedures to be used in loading the tanks. Purity is 99.8%.

- **Coleman Grade.** This is used in labs for chromatography and is 99.99% pure, and considerably more costly.

- **Industrial (Welding) Grade.** This is used for some welding processes but is still 99% pure.

The supplier actually uses the same source of liquid CO₂ for all grades, but handles the filling of the tanks with much more care in the case of Medical and Coleman Grades. Medical Grades would be used for angiography.

Ask for disposable or small cannisters, since water vapor can form carbonic acid inside the cannister and cause corrosion. Replace the cannister periodically, it's not very expensive. Small disposable syringes of CO₂ can be ordered from AngioDynamics, Glens Falls, NY, but are more expensive than from your local gas man.

Even pinhole leaks in connecting tubing may suck in air by Venturi effect, and one cannot use too much care in loading and purging the air from your injection system, be it a syringe or injector!

This table is from Dr Hawkin's recent review, (AJR, March 1995)

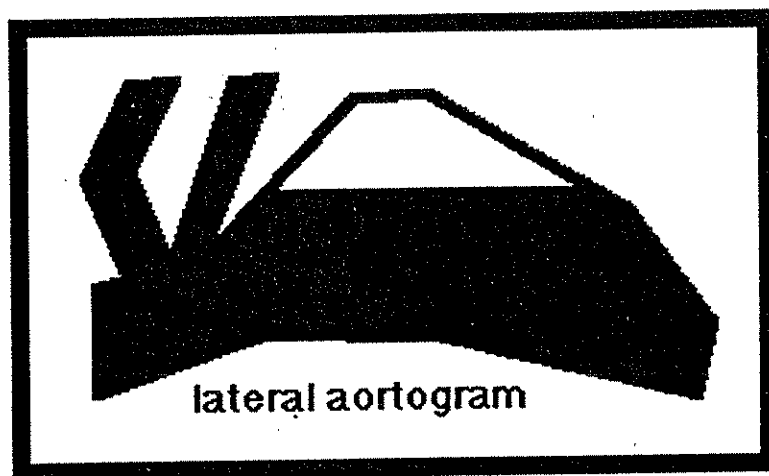
Type of study	Rate (ml/sec)	Volume (ml)
Abdominal aortogram	100-150	75-100
Pelvic arteriogram	40-60	40-60
Leg arteriogram	10-20	20-40
Dialysis fistula	10-20	20-40
Arm venogram	10-20	25-50
Inferior vena cavogram	50-100	40-50
Renal transplant	10-20	10-20
Mesenteric arteriogram	10-20	20-30
Wedge hepatic portogram	50-100	40-50

TOTAL DOSE OF CO₂ SHOULDN'T EXCEED 1000 cc.

As with all contrast, you may need more. The longer you wait, the safer it is to use more CO₂. In our safety studies, we used 1500 cc in one patient without any reaction or complication. Always wait 2 minutes between injections, so that the last bolus of CO₂ has time to dissolve and be excreted.

- very slow injections of small volumes may result in such rapid dissolution that the gas doesn't even reach the peripheral vessels.
- a very gassy abdomen may result in non-visualization overlying the gas. Glucagon should be used in the abdomen.
- CO₂ injected into an external iliac artery in a supine patient, at rates above 30-50 cc/sec will reflux back up and fill the opposite iliac artery. If you plan to visualize both sides, use 60-100 cc.
- Position of the patient is very important. It is always difficult to fill peripheral branches of a vessel, even in the legs. We can reliably study the pelvic and thigh arteries, but usually switch to iodinated contrast below the knee. Turning the patient into each oblique position places one of the pelvic arteries in the "up" position and improves the image quality. Hypogastric arteries are "down" and don't fill well.
- If the object you want to see is dependent ("down"), it doesn't show well. For example, an abdominal aortic injection will fill the first 3 cm of the renal arteries, but more distally, as the renal arteries run posteriorly ("down"), the fill is poor. The leg(s) need to be elevated 18-20", which in many digital systems puts the feet above the image intensifier, or else use a tilt table to 20-25°. Reactive hyperemia or pharmacologic angiography should be used to optimize fill of the distal legs. Turning the patient on their side will more optimally fill the "up" vessel, as the CO₂ floats.

- CO₂ does not have the inherent contrast of iodinated agents, and so



digital subtraction angiography is critical. Because the artery may fill in short segments as the CO₂ moves along, a "stacking" technique where multiple sequential frames are added together before subtracting from the mask.

PATIENT REACTION.

Most authors list lack of pain as an advantage of CO₂. In our safety

evaluation of 10 patients studied with CO₂ and compared to 10 control patients using Optiray® at a 2:1 dilution (107 mosm/L), the CO₂ injections were slightly more painful than the Optiray®. However, if using full strength Optiray® I would expect more pain and heat than with CO₂. The point is, though, some patients have heat and pain with CO₂. Other authors have described nausea and vomiting after CO₂ injections, and we have seen this in our patients also. Hawkins describes a 25% incidence of nausea in his retrospective chart review of 208 patients having CO₂ angiograms. Coughing after intravenous injections has been described.

Avoid Nitrous Oxide anesthesia which interferes with the excretion of CO₂.

In our safety studies, we obtained arterial blood gases, pH, extensive blood chemistries, and careful histories, and found no significant difference between the patients receiving 500-1500 cc CO₂ as compared to the control group receiving 30-150 cc dilute Optiray®.

INJECTION OF CO₂

Dr Hawkins early recognized the difficulty of using ordinary angiographic injectors, or hand injections from a syringe. Reproducible volumes and flow rates are difficult to obtain because the gas is so compressible. As you start a hand injection, there may be no delivery, and the pressure builds up until the whole of the syringe is explosively delivered in the last 10% of the injection time. Trying to inject a partial syringeful of CO₂ is even harder. Purging the syringe in any system is important as you want to flush out all the air. Complete purging of a liquid power injector is difficult.

Dr Gunther in Germany devised a system which is computer controlled and varies the injection with system pressures and flow rates to keep it constant.

We have been working with and evaluating the Angio Dynamics, (Glen Falls, NY) Model C Carbon Dioxide injector, designed in conjunction with Dr Hawkins.

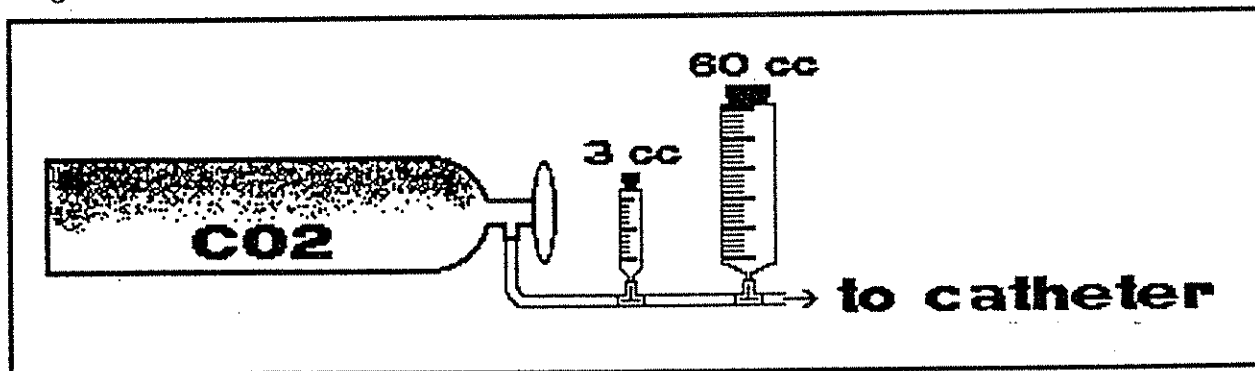
Design advantages are:

- self-purging
- continuous heparin flush of catheter
- will not inject if blood pressure is <40 or >300 mm
- varies injector speed by monitoring pressure in injection line
- is EKG gated and injects during diastole
- closed system, protected by sterile 0.2 micron filters
- automatically flushes catheter with CO₂ just before injection
- injection syringe pre-pressurized to 10 psi
- the CO₂ source is an integral part of the injector

WHAT TO ACTUALLY DO, PRACTICAL TIPS

Automatic CO₂ injectors are not widely available, so it comes down to hand injections. If you use your regular power injector, remember to load and flush it with the tip up, as CO₂ is heavier than air and sinks down.

60 cc syringes are widely available. Check the tubing and 3-way stopcocks system with pressurized saline to be sure there's no pinhole leak. Flush the two syringes with CO₂ several times to get all the air out. Then flush the catheter with CO₂ from the 3 cc syringe. Clearing the catheter of blood and saline is critical. Put a little pressure on the 60 cc syringe before opening the stopcock and with a little practice you get a smooth, non-explosive injection. You have to be vigorous for aortograms, to deliver the whole syringe full in 1.5-2.5 seconds.



CO₂ PORTOGRAPHY

This powerful technique allows consistent visualization of the portal vein from a wedged hepatic vein position, and is invaluable during TIPS procedures. One can use the needle puncture sheath, wedged in the right hepatic vein, and using the above technique do a hand injection. Use 60 ml of CO₂. Film in AP and lateral if needed. Avoid explosive injections. It really works!

FILM QUALITY

There is a problem in filling small peripheral vessels, especially if they are dependent (such as the distal renal arteries). Partial fill of a vessel may be misleading as the artery will appear smaller than it is, producing a pseudo-stenosis. The contrast level is reduced as compared with iodinated media. Nevertheless the films are diagnostic, if careful attention is paid to the details of the procedure as listed above. Digital subtraction is critical. Patient or extremity position and reactive hyperemia add to film quality.

ADVANTAGES OF CO₂**CHEAP****SAFE IN PATIENTS WITH PRIOR REACTIONS****CAN BE USED IN PATIENTS WITH RENAL FAILURE****VERY LOW VISCOSITY****SAFE**