ALTERNATIVE CONTRAST AGENTS AND PREVENTION OF CONTRAST NEPHROPATHY

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Carbon Dioxide Digital Subtraction Angiography

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Top 14 Questions Regarding CO2 DSA:

1. Is CO_2 DSA safe?

Yes, with a few caveats. Because CO_2 is a gas, precautions (see text) should be taken to avoid contamination, explosive delivery and gas trapping in vessels. If the unique gaseous properties and a few precautions are understood and implemented, CO_2 can be used quite safely.

2. How can CO_2 be delivered?

Unfortunately there is not a dedicated CO_2 injector available in the US. Currently we suggest a closed fluid management system that has be modified to deliver CO_2 safely.
To prevent excessive volumes and potential death we stress that the delivery catheter should **NEVER** be connected directly to the CO_2 cylinder.

3. Should a three-way stopcock be used with the closed delivery system to permit rapid filling of the plastic bag?

No! Anytime a three-way stopcock is added there is a possibility of aspirating room air and causing air embolus. The new "bag system" uses a special gas O-ring fitting which is incompatible with Luer fittings thereby preventing incorrect assembly.

4. What are the advantages of CO_2?

1. Non allergenic
2. Non-nephrotoxic
3. Unlimited total volumes
4. Low viscosity
5. Inexpensive
6. Minimal or no discomfort

5. What are the indications for CO_2?

1. Iodinated Contrast Allergy
2. Renal insufficiency
3. Arterial bleeding
4. Intervention
5. TIPS
6. Central venous evaluation
7. High volume contrast procedures

1. What are the CO_2 contraindications?

1. Supra-diaphragmatic arterial injections
2. Use with nitrous oxide anesthesia

2. Is the cerebral administration of CO_2 safe?
Uncertain at this time. There are conflicting studies in animals as well as anecdotal human experiences. Whether the problems experienced were due to contamination or explosive delivery is uncertain. Therefore the current policy is to avoid exposure to the cerebral vessels

3. Can I use CO_2 in patients with COPD?
Yes, as long as the patients with severe COPD can compensate with hyperventilation. Also as a precaution, limit the volumes of CO_2 and allow for a longer interval prior to another injection

9. Do I have to purge the catheter before delivering CO_2?
Yes, otherwise the CO_2 may be explosively delivered. To clear the catheter approximately 5 cc. of CO_2 should be forcefully injected.

10. How should the catheter be flushed between injections?
CO_2 can be used if the catheter is flushed every 3-4 minutes. We feel that the elimination of saline may prevent the possibility of producing carbonic acid. (less pain etc.)

11. Can a small syringe (1-3 cc) be used for interventional procedures?
No! If one injects CO_2 between the guide wire and the catheter using a small syringe and a Y-connector the gas will only compress and not exit the catheter. At least a 20cc syringe should be used.

12. Can large volumes of CO_2 be used in situations where the gas may be trapped? (e.g. transplanted kidneys, intestinal ischemia).
No! Only small volumes (20cc or less) with prolonged delay (>3-5 minutes) between injections can be used effectively if the patient is positioned to permit optimal filling e.g. cross table lateral to fill the celiac and SMA.

13. In lower extremity arterial CO2 DSA, should the injection rate be increased if the feet do not fill?
Usually increasing the rate simply results in reflux into unwanted areas. To optimize visualization, the total volume should be increased, a vasodilator injected, and the feet elevated. For example selective injection of CO_2, approximately 10cc/sec for a total of 50 cc, following NTG 150 ug.

14. Should wedge injections be used for portal vein visualization in TIPS.
We would recommend using a central parenchyma injection (needle advanced from hepatic vein into central parenchyma). With this method the portal always fills and extravasation has not occurred. With wedge injections the capsular perforation can occur. Several deaths have been reported.

CO2 DSA:

The use of CO_2 as an imaging agent dates back to 1914 when it was originally used for the visualization of the abdominal viscera (1). It was subsequently utilized in the evaluation of the retroperitoneum, hepatic veins, as well as in the diagnosis of pericardial effusion (2, 3, 4). In the 1970's, the intraarterial use of CO_2 was pioneered by Hawkins (5). With the development of digital subtraction angiography, stacking software, tilting tables and reliable delivery systems, it became viable as an angiographic imaging agent.

Unique Properties of CO_2:

CO_2 is a nontoxic, invisible gas that is highly compressible, non viscous and buoyant. Most importantly, CO_2, as an intravascular imaging agent, lacks both allergic potential and renal toxicity. It is 20 times more soluble than O_2 and is rapidly dissolved in the blood.

Unlike iodinated contrast, CO_2 does not mix with blood but must displace it to render an image. Also the buoyancy of CO_2 causes it to rise to the anterior, nondependent portion of the vessel. Therefore in larger vessels (aorta and iliac arteries), if an insufficient volume is injected, there will be incomplete displacement of blood resulting in incomplete filling and potentially, a spurious image. Normal vessels may appear smaller than their true caliber. To overcome this phenomenon, either a larger amount of CO_2 must be administered or, using the buoyancy principle, the area of interest should be placed in the nondependent position.

Indications:

CO_2 can be injected as a contrast agent in any luminal structure (arterial, venous, biliary tree, urinary tract, abscess cavity, fistula). We previously used CO_2 primarily in patients with iodinated contrast allergy and renal failure. However, its gaseous characteristics can occasionally provide additional information otherwise unattainable. Its very low viscosity permits detection of arterial bleeding; visualization of the portal system by hepatic parenchymal injection for TIPS procedures, visualization of small collaterals in ischemic disease and AV shunting in tumors. The very low viscosity also allows delivery via microcatheters and injections between the guidewire and the needle or catheter, making it ideal for interventional procedures such as angioplasty and stent placement. Furthermore, because of its rapid dissolution and elimination from the lungs there is no maximum dose if less than 100 cc's are injected every 2 minutes. This is of great benefit in complex interventional procedures where CO_2 can be used alone or in combination with iodinated contrast to minimize the risk of renal compromise.

Contraindications:

Recent literature and our studies with rats (6) suggest that the safety of cerebral CO_2 is questionable. We therefore avoid any arterial injections above the diaphragm and never administer CO_2 with the patient's head in an elevated position.

CO_2 DSA has not been a problem in patients with chronic obstructive airway disease (COPD). However, in these patients, we do attempt to reduce the volume and allow more time between each injection. In a recent evaluation performed in our laboratory using swine, CO_2 was administered directly into the IVC at different volumes. This resulted in no significant change in either PO_2 or pulmonary artery, central venous or systemic arterial pressure at an injection of 1.6 ml/kg. This is well below the individual dose required for diagnostic purposes. Use very cautiously in patients with ischemic bowel or in situations where the gas may cause a "vapor lock".

Potential Complications and Precautions:

Because CO_2 is invisible, it is susceptible to contamination without detection. Our initial studies revealed water, rust and particulate matter within reusable sources. Therefore, a pure medical-grade source and disposable cylinder are mandatory. Furthermore, a closed delivery system is imperative to eliminate the additional possibility of room air contamination. Because of its extreme diffusivity, an open syringe containing CO_2 can be replaced with less soluble room air in approximately 72 minutes. In addition, a system employing stopcocks can be easily contaminated if they are inadvertently malpositioned or loose. In a closed system, one-way "check" valves and glued stopcocks can be utilized to reduce this possibility.

Another rare, yet potential, complication is "trapping." This occurs when an excessive volume of CO_2 is delivered or the blood-gas interface is reduced and interferes with normal dissolution. As a result, a bolus of gas can cause a vapor lock that can restrict blood flow and potentially cause ischemia. Abdominal aortic aneurysms, pulmonary outflow tract, celiac, superior and inferior mesenteric arteries are most susceptible because of their nondependent location.

If trapping does occur, it can be reduced by positional maneuvers. For example, if trapping during an inadvertent excessive, large volume injection occurs in the pulmonary artery, bradycardia, hypotension and coronary ischemia can result. By placing the patient in the left lateral decubitus (Durant's) position,

CO_2 migrates to the nondependent portion of both the pulmonary artery and the right atrium. This allows blood flow to be reestablished beneath the residual CO_2. Similarly, trapping in an AAA can be reduced by rolling the patient, first to one decubitus position and then to the other. As a precaution for trapping, fluoroscopy of susceptible sites can be performed between CO_2 injections. If persistent gas is visualized, positional changes can be instituted. For venous injections, fluoroscopy of the pulmonary artery will demonstrate dissolution of the gas within 10-30 sec. If the gas remains longer, the possibility of room air contamination must be considered.

Injection of excessive volumes (> 400 cc) is the most dangerous potential complication. Excessive doses are first and foremost avoided by ensuring that the **CO_2 cylinder is never connected directly to the catheter**. A CO_2 cylinder usually contains 3,000,000 cc of pressurized gas and can flood the low resistance circulatory system if a stopcock is inadvertently malpositioned. Also, because it is compressible, a syringe loaded under pressure will have an indeterminate volume of CO_2 and potentially result in an excessive dose. It is suggested that a non-compressed, known volume (usually 30-50 cc, or less, depending on the site of evaluation) be administered via a dedicated injector or closed plastic bag system. Purging the catheter of saline or blood with a small volume of CO_2 should be performed prior to injection to eliminate compressed CO_2 and explosive delivery. We have also found that the elimination of explosive delivery reduces the subjective discomfort of pain, nausea and the urge to defecate. Moreover, if using CO_2 to evaluate permanent dialysis access, great care should be taken to avoid explosive delivery and reflux into the artery and possibly into the cerebral circulation (7).

CO_2 should be used cautiously with nitrous oxide anesthesia. In theory, nitrous oxide may diffuse from the soft tissue into the CO_2 “gas bubble” and cause a five-to-six fold increase in the occlusive effect (8). An innocuous 100 cc CO_2 injection may have the effect of 500-600 cc of gas and result in a “vapor lock” condition.

Delivery:

During the last 30 years we have tried many different delivery systems including many hand systems with manifolds and more than 5 dedicated mechanical and computer controlled systems. Most were potentially extremely dangerous, however the complications that occurred were fortunately short lived. Others (including many with considerable experience) are using homemade systems with multiple stopcocks etc., which have resulted in severe complications. Most have occurred from air contamination with stopcocks placed incorrectly. Currently, there are two safe delivery mechanisms: dedicated injector and the closed plastic bag hand delivery system (9). Since a dedicated CO_2 injector is not currently available in the United States, the closed bag system can be utilized (Fig. 1). Several operators including us have added additional stopcock etc. to the plastic bag system which when incorrectly used resulted in room air delivery. Also the original plastic system had too many ports which could be incorrectly used. A recent modification has eliminated the purge port and is equipped with O-ring gas fittings to reduce the possibility of aspirating air. It consists of a 1500 cc. plastic bag reservoir, extension tubing, two one-way check valves with glued fittings, and a delivery purge syringe. Using a pure source, the bag is filled with CO_2 and flushed three times to purge any residual air. Following this, the bag should be left flaccid to avoid any CO_2 compression. Next the bag is connected to the delivery fitting. The delivery system is similarly flushed to eliminate room air prior to injection. It is then connected to the angiographic catheter that is subsequently relieved of any residual blood or saline by forcefully injecting three to five cc of CO_2. Always completely empty the syringe to ensure total clearing of the catheter A controlled, non explosive delivery of known volume can then be performed. The check valves prevent reflux of blood into the catheter and permit rapid injections without stopcock manipulation. No additional connecting tubes or stopcocks should be added to the system. All ports should be occupied and syringes attached to prevent any possibility of air contamination. The security of the attachment of the bag to the O-ring fitting should be checked each time the syringe is filled. This is the <u>only point</u> where air contamination can occur.

Previously we flushed the catheter after CO_2 injections with saline. During the last 3 years we have only flushed with CO_2 (2-4cc) every 2-3 minutes. We have noted a definite decrease in discomfort. Elimination of saline prevents formation of carbonic acid, which may cause unexplained pain and ischemia in the rare case.

General Delivery Principles:

1. Use a closed system, i.e., the plastic bag or a dedicated CO_2 injector.
   a. **Never** connect the catheter directly to the CO_2 cylinder. This avoids the potential inadvertent delivery of excessive and possibly lethal volumes.
   b. Don't use additional stopcocks. Malpositioned stopcocks can result in room air contamination and air embolus.
2. Avoid explosive delivery. Purging fluid (blood or saline) from the angiographic catheter prior to CO_2 injection results in a more consistent delivery with less discomfort.
3. Initially, inject small volumes of CO_2. Increase or decrease volume as required for specific anatomy.
4. Wait 2-3 min. between injections to allow any potentially trapped CO_2 to dissolve. Wait 3-5 minutes in patients with possible intestinal ischemia
5. Elevate area of interest in poor flow conditions (feet, 10-15°; renal artery, 30-45° occasionally up to 90°).
6. Vasodilators (nitroglycerin 100-150 ug IA) can be used to improve filling.
7. Delivery catheter
   a. Since CO_2 is not radiopaque a radiopaque-tipped catheter is advisable.
   b. Any flush catheter is acceptable however catheters with only an end hole produce less gas "breakup".
8. DSA imaging
   a. Three-to-four frames/sec. using a 60 ms pulse width with adequate penetration.
   b. Obtain frequent scouts. Correct exposure is difficult, however, extra effort results in good contrast and images comparable to iodinated contrast
   c. When the CO_2 bolus is "broken up" (fragmented), use image stacking, if available.
   d. If imaging is consistently poor, consult an equipment applications specialist to optimize acquisition.

Specific Procedure:

1. Runoff
   a. Initially, obtain pelvic angio with the catheter in the distal aorta. Perform aortogram after the runoff.
   b. Inject 20-40 cc in 1 second for pelvic angio..
   c. If injecting from the lower aorta, elevate the feet 10-15° for optimal filling and obtain images of pelvis, thigh, knee, lower legs and feet.
   d. If IMA is filled and patient experiences pain , urge to defecate or has symptoms of intestinal ischemia, multiple distal aortic injections should be keep to a minimum. Selective iliac, or more distal injection produce better filling and are unlikely to cause intestinal ischemia.
      We prefer selective injections of the lower extremities to avoid exposure to the IMA even if the patient does not have symptoms. 10-20 cc's in 1-2 secs is the usual injection.
   e. If there is no stacking program, a longer injection (~ 20-40 cc over 3-4 sec.) is necessary.
   f. Problem - poor filling of the lower leg and feet.
      - Perform a selective injection of the common femoral or more distal arteries. Most runoff exams are currently examined in this fashion.
      - With stacking, inject 10-20 cc in two sec. If filling remains poor, inject 20-40 cc over 3-4 sec.
      - Without stacking, begin with 20-40 cc over 3-4 sec.
      - Intraarterial nitroglycerine, 100-150 ug prior to injection.
      - When large volumes are required, discomfort may occur, precipitating patient motion and distorting images.

   3. Aortogram
      a. Usually performed after the runoff. We believe this allows the patient to become acclimated to CO_2 and, as a result, less discomfort and nausea are experienced with larger aortic injections.
      b. Attempt to obtain the aortogram without glucagon. Our experience is that CO_2 and glucagon may cause nausea. Others have used glucagon without incident.
      c. Higher flow rates may be necessary (25-50 cc in 1/2 sec.).

d. The left renal is more difficult to image and may be better visualized by elevating that side. If necessary, a selective injection with a shepherd hook catheter (10-20 cc CO_2 in 1 second) can be performed. The ostium is usually apparent secondary to CO_2 reflux. Also x-table DSA with the patient in the decubitus position can be useful to fill the renal arteries. However, use low volumes since the lumbar arteries may also fill better which could potentially cause spinal cord problems. Never inject with patient prone as the spinal arteries may fill with unknown consequences.

f. Selective injections of the visceral arteries commonly require 10-30 cc in 1-2 seconds.

4. Venous - always image the pulmonary artery after the first injection to rule out air contamination (persistent gas). Normally, CO_2 should disappear after 10-30 sec.
   a. SVC and IVC - 20-40 cc in 1-2 sec.
   b. Subclavian - 20-40 cc in 1-2 sec.
   c. Peripheral veins - 15-25 cc, 4-8 sec. Rapid injection precipitates pain.

5. Interventional Procedures
   a. Using a Touhey-Borst fitting, CO_2 can be injected between the guidewire and needle or catheter. Wires without coil wrap are better (glidewire, .018 torque wire).
   b. Use a 20-40 cc Luer-locked syringe. With a smaller syringe, CO_2 will simply compress without injecting.
   c. With initial purge wait 20-30 sec. for CO_2 to exit the catheter. CO_2 will compress, purge fluid from the catheter and inject.
   d. After purging, subsequent injections require less pressure and delay.

6. TIPS
   a. Using any needle, inject 20 cc of CO_2 into the hepatic parenchyma for visualization of the portal vein.

   b. With the guidewire in place, CO_2 can be used to verify the needle entry site and determine stent positioning.

7. Renal PTA and stent placement.
   C02 can be injected between the guidewire and the stent catheter to verify its exact position before the stent is deployed. The extreme buoyancy of the gas always results in reflux into the aorta, which visualizes the exact position of the renal artery ostium.

8. CO2 has been advantageous in Interventional Oncology. It has been used successfully in TACE, UFE and portal vein embolization. It eliminates the contraindication for these procedures of allergy and poor renal function. CO2 is an excellent contrast agent in those responsible for these procedures. Its low viscosity is extremely useful for identifying the portal vein with hepatic parenchymal injections as well as readily flowing through microcatheters yielding excellent images of the more peripheral vasculature.

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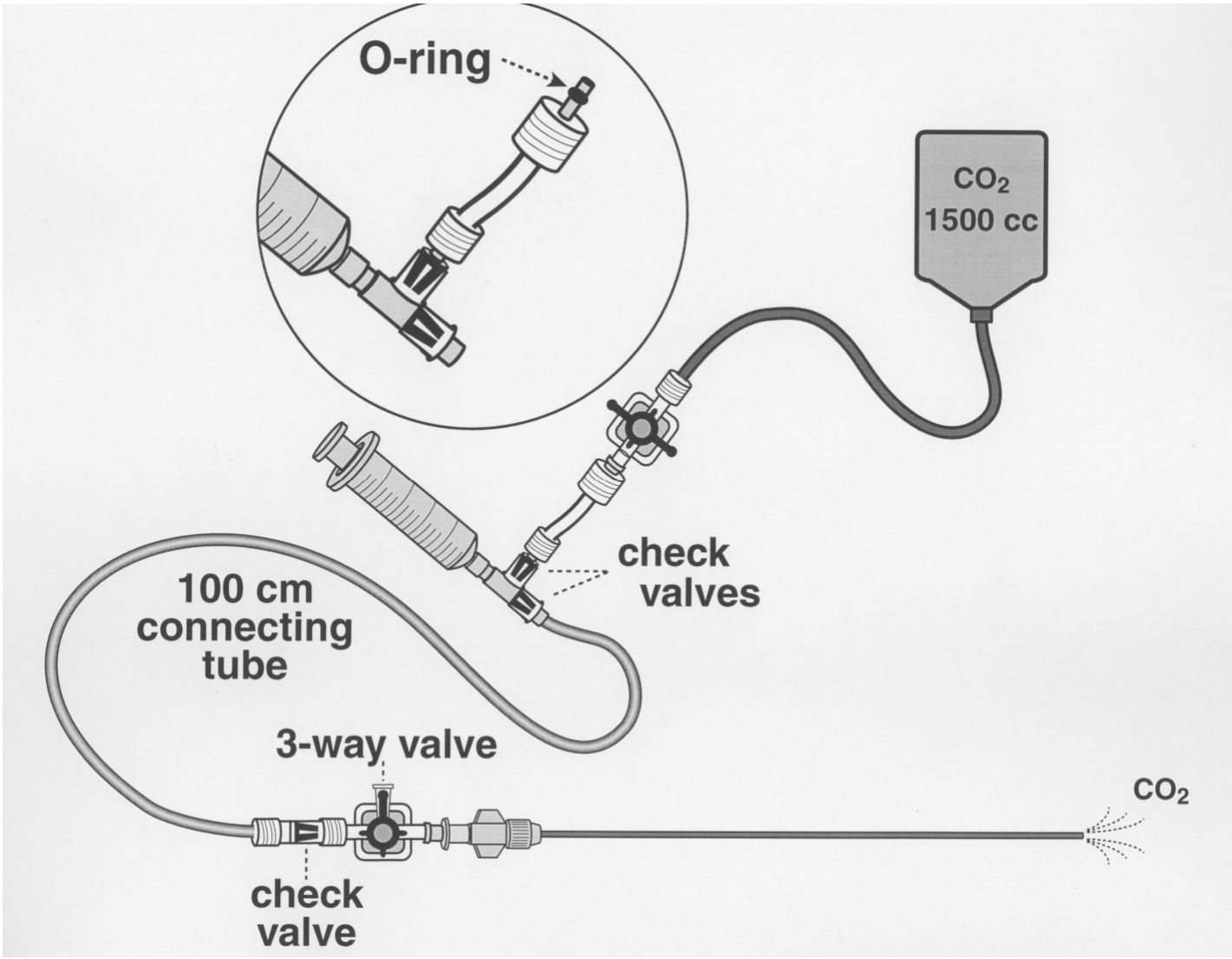
Figure 1: Closed Plastic Bag Delivery System



Prevention of Contrast Nephropathy

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Acute kidney injury (AKI), following, iodinated contrast administration is relatively uncommon, however, the incidence of contrast-induced nephrotoxicity (CIN) increases in patients with elevated serum creatinine, diabetes, dehydration, concurrent nephrotoxic medications, and large volumes of contrast. In most cases of CIN, there is a rise in serum creatinine 1 to 2 days after contrast administration. Because the treatment for CIN is mainly supportive, emphasis is placed on preventing CIN from occurring.

CIN prevention strategies include, using low volumes of contrast media, avoiding iodinated contrast when possible, using low-osmolar and iso-osmolar contrast agents, and hydration. In particular IV hydration with sodium bicarbonate and with sodium chloride has been studied. A recent randomized prospective trial suggested that hydration with sodium chloride is equivalent to hydration with sodium bicarbonate for prevention of contrast-media-induced nephropathy in the patients with moderate-to-severe chronic kidney disease.

Typical fluid infusion protocol for sodium chloride or for sodium bicarbonate involves infusion starting one hour prior to start of contrast administration at a rate of 3 ml/kg for one hour, which is decreased to 1.5 ml/kg per hour during the procedure and for 4 hours following the completion of the procedure. N-acetylcysteine (NAC) has also attracted attention as possibly protecting the kidneys from CIN. In 2000, Tepel et al showed that oral NAC administration 600 mg twice daily on the day before and the day of contrast administration resulted in a 2% incidence of CIN compared to a 21% in placebo treated patients. Follow-up work has conflicted this initial study. Gonzalez et al performed a meta-analysis and found no evidence to support the efficacy of NAC in the prevention of CIN. Despite this conflicting evidence, NAC is often used given its lack of toxicity and inexpensive cost. Gadolinium is currently not used for patients with renal insufficiency because of the association between gadolinium and NSF in patients with poor renal function.

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