Alternatives to Iodinated Contrast

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CARBON DIOXIDE AS A CONTRAST AGENT

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GENERAL INFORMATION

Carbon dioxide (CO2) may be utilized as a contrast agent for digital imaging by displacing the blood in a vessel with this invisible gas (as opposed to iodinated contrast which mixes with the blood). This agent is very inexpensive, and there is no risk of allergy or renal toxicity. CO2 is rapidly dissolved in blood (20 times faster than oxygen) and eliminated by the lungs in a single pass. Large quantities may be injected in boluses up to 60 cc each. [Radiol Clin North Am 1995; 33:15-29, Am J Kidney Dis 1994; 24:685-694, Ann Surg 1993; 217:688-698]

We use instrument grade CO2 which costs $32/tank, and is 99.99% pure CO2. Each tank contains sufficient CO2 for 150-175 upper extremity venograms and peripheral venous injections during fluoroscopic guidance for venous access. In all likelihood, the operating rooms at your hospital have USP grade CO2 for laparoscopy. USP grade CO2 is 99.5% pure. We have no evidence that the difference in purity between USP and instrument grades is clinically important. There is a research grade of CO2 (99.998% pure) which is slightly more pure than instrument grade, but considerably more expensive. Whichever grade you decide to purchase, it is best to order from the same company which supplies bottled gases to other areas of your hospital, because you should receive a volume discount.

It is now possible to obtain CO2 in aluminum cylinders rather than the traditional steel. Proponents of aluminum claim that the steel cylinders are often old, and contain rust and moisture, unlike the aluminum version. We have no experience with aluminum cylinders.

PREPARATION

The CO2 cylinder should be securely attached to the wall, or placed in a specially designed cart with wheels if a single cylinder is moved between rooms. A regulator is necessary to control the flow rate. This regulator will have a threaded connection, which is attached to a threaded Christmas tree adapter. The latter, in turn, is attached to Tygon tubing. The other end of the Tygon tubing is fitted with another Christmas tree adapter which has a Luer lock. To this Luer lock is attached the type of connecting tube used for power injection of contrast.

A stopcock is placed on this connecting tube from the regulator. We use a 60 cc syringe with a second stopcock attached. The syringe is filled directly from this connecting tubing through both stopcocks. The stopcock attached to the syringe is then opened to air, and the syringe emptied into free air. This purging procedure is repeated three times to clear the syringe of air. Since CO2 is heavier than air, the syringe is held with the plunger handle positioned inferiorly and stopcocks superiorly when emptying the syringe to purge the air from the system. After filling the syringe, one of the stopcocks remains with the syringe, closed to air, and the other remains on the connecting tube. The syringe should be used shortly after filling, as even with a closed stopcock, the syringe can slowly equilibrate with room air, i.e., CO2 will gradually escape, and nitrogen and oxygen will slowly enter the syringe. This, of course, is undesirable as nitrogen and oxygen are much less soluble in water than CO2.

Under no circumstances should the CO2 cylinder be connected directly to a catheter in the patient, even if several stopcocks are in the system. A massive, rapid injection of compressed CO2 could enter the patient if the stopcocks are not turned off, and this could be fatal.
UPPER EXTREMITY VENOGRAPHY

Our primary use of CO2 is for diagnostic upper extremity venography and guidance for peripheral venous access. [JVIR 1994; 5:32, Cardiovasc Intervent Radiol 1995; 18:146-149]

The CO2 is hand injected through a peripheral intravenous line for digital venography. Before entering the vein, the gas will compress in the syringe in order to generate sufficient pressure to clear the IV connecting tube of saline. This may result in an "explosive" delivery of gas as it decompresses into the vein. This will be mildly to moderately painful in 10-20% of patients due to rapid distention of the vein. Subsequent injections will be accomplished more readily without the explosive experience if the tubing remains filled with CO2. Good to excellent quality venograms are generally obtained with rapid digital imaging. Because of the buoyancy and rapid flow of CO2, opacification of the central veins tends to be better with CO2 than with peripheral injections of iodinated contrast. [Cardiovasc Intervent Radiol 1995; 18: 141-145]

VENOUS ACCESS

CO2 may be visualized adequately in the arm and central veins using fluoroscopy. The gas may be slowly injected, providing a column of bubbles in the veins which provides a target for access. This "dribbling" of CO2 is rarely painful, though patients may experience the sensation of bubbles flowing up their arm. If the vein is punctured but access is not achieved, there is no extravasation of radiopaque contrast (as with iodine) which obscures subsequent attempts to visualize the vein. We need to switch to iodinated contrast to improve visualization of arm veins in less than 1% of our patients undergoing peripheral venous access. Over 3000 cases have been performed at our institution with this technique.

ARTERIOGRAPHY

CO2 provides an alternate contrast medium for patients with severe contrast allergies or impaired renal function. In our experience, the quality of arterial images is usually diagnostic though not as good as with iodinated contrast. Since a power injector is not currently available, hand injections of CO2 must be performed. Abdominal aortograms may be performed by injecting 50-60 cc with imaging of at least 4 frames/sec. Image quality in the lower extremities may be improved with selective injections of 10-30 cc in the iliac or more peripheral arteries. The CO2 is injected as rapidly as possible. Maximum opacification or stacking features may improve digital image quality by allowing demonstration of an entire arterial segment. High quality digital imaging systems and absence of motion are critical.

The gas is buoyant, and this property may be used to improve imaging of non-dependent vessels. For example, the leg can be raised so that the gas rises into the distal arteries. However, despite these maneuvers, opacification distal to occlusions is often suboptimal. Likewise, the patient may be turned during abdominal aortography for renal artery visualization. The side of interest is elevated so that the gas rises towards that kidney. When evaluating patients with azotemia for renal artery stenosis, following a positive noninvasive study, our routine is to try CO2 first. If this is inconclusive, we move to Gadolinium. Only if there is still a question do we switch to iodinated contrast. Lateral abdominal aortography will often demonstrate the origins of the visceral vessels quite well since the gas will layer on the anterior surface of the aortic lumen and rise into the visceral vessels.

CO2 should not be used in studies of the cerebral arteries or for injections in which the gas may rise into cerebral vessels (e.g., dialysis grafts). Seizures have been reported. Also, CO2 injection into an abdominal aortic aneurysm with a patent inferior mesenteric artery could prevent blood flow into the inferior mesenteric artery and result in mesenteric ischemia in a
supine patient. Finally, some patients have experienced pain during CO2 injections in the lower extremity when the gas flows through numerous collaterals.

VENA CAVOGRAPHY

In patients with contrast allergy or azotemia, CO2 can be used to image the IVC prior to filter placement. CO2 is injected via a 5 French vessel sizing pigtail catheter with the pigtail at the iliac vein confluence. Sixty ml's of CO2 are rapidly hand-injected. IVC diameter as measured with CO2 is not statistically different from iodinated contrast as long as pincushion distortion is corrected for. Rather that dealing with this inconvenience, it is best to advance the calibration marks on the pigtail to the middle of the field after the IVC'gram, perform a digital radiograph, and use this image to correct for magnification. We found no compromise in blood pressure or O2 saturation in patients following CO2 injection, except in a patient with severe pulmonary hypertension. Caution should be exercised when injecting large intravenous boluses of CO2 into patients with pulmonary hypertension.

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FOURTEEN-YEAR EXPERIENCE
WITH CO₂ DSA

University of Florida
I.F. Hawkins, M.D., J.G. Caridi, M.D., and K. Weingarten, M.D.

This exhibit outlines our experience with CO₂ at the University of Florida since 1971 and developments with CO₂ DSA since 1981.

To date, we have used CO₂ in over 120 animals and 1,000 patients with remarkably good results and a very low complication rate. Recent developments in delivery systems – dedicated power injector and plastic bag hand delivery system – coupled with advances in DSA imaging ("Image Stacking") has resulted in CO₂ being our contrast agent of choice in patients with renal failure and allergy, and is being used presently for routine angiographic and interventional studies.

EVOLUTION OF ARTERIAL CO₂ IMAGING

Film Suboptimal

1971

BENIGN RENAL CYST
FILM SUBTRACTION

DSA Enhanced "Low Density" CO₂
Produces Diagnostic Images

1991

280 lb ↑ BP
PHILIPS EEM 4500

LARGE LLQ SARCOMA
TOSHIBA DSA 20 HM354
ADVANTAGES OF CO₂

- No allergic potential.
- No renal or hepatic toxicity.
- Low viscosity permits use of very small catheters.
- No or minimal discomfort.
- Unlimited Volumes of CO₂ can be delivered if multiple low volume injections are made since CO₂ is eliminated by the pulmonary circulation in a single pass.
- Very inexpensive (300cc Cost less than 5¢).

INDICATIONS

Can be injected into ANY luminal structure

- Arterial.
- Venous.
- Biliary Tree.
- GU Tract.
- Fistulas.
- Improved detection of arterial bleeding.
- Wedge portogram for tips.
- Most interventional procedures.

ABSOLUTE CONTRAINDICATION

Don't expose brain to CO₂

Use arterially ONLY below diaphragm until the safety of CO₂ in the cerebral circulation has been demonstrated.

RELATIVE CONTRAINDICATION

Severe Pulmonary Disease
(CO₂ may be retained)
SAFETY

- From 1957-1971, 100cc's of CO\textsubscript{2} were routinely injected into right atrium for the detection of pericardial effusion.
- In 1971, patients injected were all with right side up (CO\textsubscript{2} traps in right atrium).
- CO\textsubscript{2} underwent extensive animal testing (both intravenously and intra-arterially) before it was used on humans.
- Large volumes (up to 10 liters) were injected into dogs at a rate of 100cc/min.
- Bendib injected 200cc into the right atrium in 1600 cases with no complications.

ANIMAL EXPERIENCE

at the University of Florida

- CO\textsubscript{2} eliminated from lungs in one pass (2-3 sec). CO\textsubscript{2} injected in IVC with DSA Imaging. 3 Rats.
- CO\textsubscript{2} opacifies inferior vena cava with large volume Aortic Injection. CO\textsubscript{2} appears to flow from artery to vein. 100 cc/sec., total volume 100-800cc. No untoward effects. 10 canines.
- Excessive volumes in very short time (1000-5000cc in several minutes) resulted in death of 3 canines.
- No neurological deficit in 10 canines with arch and selective carotid and vertebral injections. No apparent spinal cord toxicity. 100cc injected in aorta in 10 prone canines.
- Significant neurological defects seen in 20 rats. Blood brain-barrier disrupted. Selective carotid injections with tuberculin syringe may have caused "explosive" delivery.
- No significant evidence of renal ischemia injecting 10x estimated normal dose selectively into 14 canines. No decrease in flow or function 24 hours post injection. Mild A.T.N. was seen in one canine where kidney was vertically positioned (higher than the injection site).
- No evidence of hepatic toxiticy in 12 rabbits with large volume aortic injection.
- CO\textsubscript{2} totally displaced blood permitting clear angioscopic viewing without danger of fluid overload. 20 canines.
CO₂ DELIVERY
Very Difficult

- Compressible.
- Invisible.
- Heavier than air.

COMPRESSIBILITY

Danger of delivering excessive volume.

CO₂ cylinder contains 3.3 million cc's at very high pressure.

CO₂ regulator malfunction

= =

Massive volume with possible flooding of vascular system

= "Vapor Lock"

= Death

DANGER OF REGULATOR MALFUNCTION!
HIGH PRESSURE CYLINDER IMMEDIATELY DISCHARGES 1.5 MILLION CCs INTO SYRINGE OR PATIENT.

INADVERTENT INJECTION OF LARGE VOLUME OF CO₂ FILLS RIGHT HEART WITH POSSIBLE "VAPOR LOCK"
COMPRESSIBILITY CAN CAUSE "EXPLOSIVE DELIVERY"

(CO\textsubscript{2} Delivery in an inconsistent manner)

POSSIBLE:

- Reflux into unwanted area (e.g. CEREBRAL).
- Distention of vascular structure "Pain?"
- Potential arterial wall injury.

WHY EXPLOSIVE DELIVERY

- Due to catheter resistance, pressure is required to remove fluid from catheter.
- Resistance results in compression of CO\textsubscript{2}.
- At the instant the fluid exits the catheter, the CO\textsubscript{2} expands rapidly resulting in "Explosive" delivery.

EXPERIMENTAL BENCH TESTING WITH 1.5-4.1 F CATHETERS USING HAND AND MECHANICAL SYRINGE SHOWS = 95\% OF CO\textsubscript{2} DELIVERED IN LAST 1/2 SECOND.

INVISIBILITY

- Invisible air can displace or mix with CO\textsubscript{2} unless a "closed system" is used.
- Reusable CO\textsubscript{2} cylinders have contained water, rust, and Methane.

Use Disposable Medical-Grade CO\textsubscript{2} Cylinders
Plastic Bag
Hand Delivery System
1994

(can be assembled using standard IV bags, syringes, connecting tubes, and check valve fitting stopcocks)

System uses same principle learned during the development of the computer controlled injector.

PLASTIC BAG RESERVOIR
(1500 cc)

- If bag is flaccid, CO₂ is not compressed.
- CO₂ must be aspirated from bag with syringe.
- Bag incrementally collapses.
- Connecting tube and 1-way stopcock keeps CO₂ in bag.

FILL PLASTIC BAG WITH PURE CO₂

- Use disposable cylinders. (Reusable cylinders have contained H₂O & rust.)

- Source we use consists of:
  - Disposable CO₂ Cylinder.
  - Preset Regulator (15 psi).
  - Automated Valve.
  - 0.2 Micron Filter.
  - Luer Lock Fittings.

NEVER connect cylinder directly to patient - possible inadvertent injection of massive volumes of CO₂.
CLOSED DELIVERY SYSTEM

Eliminates Air Contamination
Connects to Plastic Bag

COMPONENTS:

A. Delivery Syringe (20-60cc) and
   3-way fitting with two, 1-way
   check valves.
B. Purge syringe 3cc (used to
   clear blood from catheter) in-line,
   1-way check valves prevent back
   flow of blood into catheter.
C. Connecting tube between two
   fittings increases distance from
   X-ray reducing operator exposure.

PROCEDURE:

1) After bag is filled with CO₂, 1-way
   stopcock is connected to delivery
   fitting.
2) CO₂ is aspirated and injected into
   closed system 5-6x to purge any
   residual air in tubing.
3) After 3cc syringe is purged, system is
   attached to angiographic catheter.

4) 3cc of CO₂ forcefully injected clearing
   blood from catheter. 1-way, 3cc Syringe
   stopcock is closed.
5) Desired amount of CO₂ injected with
   delivery syringe.
6) Repeat injection. CO₂ injected at will—
   no repeat purging is necessary.

KEY to "Non-Explosive" controlled delivery is clearing the blood from the catheter.

KEY to clearing is check valves:

- Prevent back flow of blood into catheter after purge cycle.
- Eliminate stopcock manipulation.
  ✔ (No possibility of delivering CO₂ incorrectly.)
  (Permits rapid aspiration and injection of CO₂.)

RESULTS:

- > 100 Patients for all indications.
- Studies diagnostic in majority of patients.
- No complications.
- No possibility of delivering excessive
  volumes of CO₂.
- Closed system reduces possibility of
  air contamination.
- CO₂ is easily delivered "Non Explosively."
Intravascular Ultrasound

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Instrumentation

Manufacturers:

Boston Scientific:
- rotating transducer, rotating mirror
- 10, 15, 20, 30 MHz
- coronary, peripheral, intracardiac

Hewlett-Packard:
- rotating transducer
- 12.5, 20, 30 MHz
- coronary, peripheral, intracardiac, Doppler

Endosonics:
- phased array 20 MHz
- coronary

Role of IVUS in vascular disease

Arterial:
- occlusive
- aneurysmal
- dissection

Venous:
- thrombotic
- occlusive
- filter-related
Arterial: occlusive

- quantify stenosis
- characterize plaque, thrombus
- image post-treatment results
  - residual stenosis %
  - elastic recoil
  - dissection flap
  - thrombus formation
  - results of 2nd stent, atherectomy

Arterial: aneurysmal

- lumen & wall diameters
- mural thrombus
- branch vessel origins
- aneurysm neck length
- pseudoaneurysm origin

Arterial: dissection

- proximal/distal extent
- branch vessel involvement
- total vessel diameter
- true & false lumina diameters
- re-entry points
- treatment planning
- fenestration, stent-graft results
Venous:

- thrombotic: monitor lysis
- occlusive: intrinsic vs. extrinsic
  - SVC syndrome: +/- thrombus
  - May-Thurner syndrome
  - monitor PTA results: +/- stent

Venous:

- indications for IVUS pre-filter
  - hx severe contrast reaction
  - renal insufficiency
  - pregnancy
  - patient’s weight exceeding table limit

Venous:

- pre-deployment vena cava analysis
  - +/- thrombus
  - renal vein #, location
  - deployment site
  - vena cava diameter at site
Venous:

- post-deployment result
- filter placement
- axis orientation in cava
- orientation of legs

IVUS Investigations:

- 3-dimensional reconstruction
- forward-looking transducers
- real-time treatment monitoring
Intravascular Ultrasound
Summary Points

1. Axial spatial resolution (near-to-far discrimination) is greater than lateral spatial resolution (side-by-side discrimination). The closer the transducer is to the vessel wall, the greater the spatial resolution of the image.

2. Most small vessel imaging, up to femoropopliteal size, is done with a 20 MHz or larger transducer frequency. Larger vessels, such as aortoiliac and vena cava are better imaged at lower frequencies, such as 10 or 12.5 MHz to obtain a larger field of view.


4. Endosonics makes a phased array transducer, with 64 elements, which has lower spatial resolution than the rotating transducers, but avoids the potential problem of cable binding in tortuous vessels which occasionally affects rotating transducers. Whereby rotating transducers pass eccentrically over a wire in a sidetosaddle or monorail fashion, phased array transducers can pass coaxially over a guidewire.

5. Doppler capability is available as an option in the H-P system, and a Doppler wire is available in Europe. Endosonics offers a transducer incorporated in the catheter shaft just proximal to a coronary angioplasty balloon, to provide more rapid pre- and post-PTA analysis. A 0.035 inch transducer has been inserted through a balloon catheter guidewire lumen to monitor PTA in real time.

6. The average price for imaging machinery is $100,000. Catheters cost on the average between $350 and $575.

7. IVUS is equal to and more accurate than contrast angiography in measuring vessel sizes, and can measure vessel diameters in any direction, unlike the two-dimensional aspect of contrast angiography which allows only a single diameter per projection.

8. IVUS is being used more frequently to assess coronary arteries for exact sizing before PTA or stent placement, and to assess the deployed stent’s position, size and adequacy of apposition against the vessel wall. Optimizing these factors may reduce acute stent thrombosis, restenosis, and may permit discharge of the patient without systemic anticoagulation.

9. Detailed IVUS-derived lumen, plaque, and artery wall measurements have been made to study the mechanism of iliac balloon angioplasty. The most important factor in successful PTA is an increase in cross-sectional area of the original lumen. The next most important factor is the creation of new lumen by intimal or intimal-medial dissection, and the third factor is compression of plaque to about 2/3 its
original surface area. Surprisingly, there is only minimal increase in vessel wall outer diameter.

11. In elastic (larger) arteries, intima is hyperechoic, and the predominantly elastic fibers in the media are equally echogenic, as is adventitia. Muscular arteries tend to have more distinguishable layers, with echogenic intima and internal elastic lamina, while the predominantly smooth muscle media is hypoechoic, and the outer adventitia is echogenic.

Plaque has been characterized as well: fatty plaque tends to be hypoechoic, fibrous plaque is more echogenic, and calcification is brightly echogenic and casts shadows. This information may be helpful in treatment planning, e.g. whether to increase balloon size or resort to stent placement after a technically unsuccessful initial PTA.

Thrombus signal depends on its red blood cell composition: the greater the RBC concentration, the more echogenic. IVUS has not yet proven to be accurate in determining thrombus age.

12. IVUS is helpful in aneurysm stent-graft planning, and intra-procedure monitoring. It provides information on neck length, branch vessel locations and size, quality of stent-graft deployment, residual flow in aneurysm post-treatment, and final lumen size and patency. There is similar value to IVUS when planning stent or stent-graft deployment for dissections.

13. In venous occlusive disease, IVUS may be helpful in distinguishing an intrinsic stenosis from intraluminal thrombus or extrinsic compression. In particular, intraoperative IVUS may help in planning the specific type of thoracic outlet surgery required.

14. IVUS is helpful as an alternative to contrast cavography before filter placement in several patients: as a means of reducing radiation exposure in pregnant women, and as a means of imaging the vena cava in patients who cannot undergo standard cavography because they are too heavy to be accommodated on fluoroscopy tables, and must have their filter placed using C-arm fluoroscopy on an OR table.

15. Three-dimensional reconstruction may be performed by reconstructing images obtained while manually retracting the transducer along the length of vessel studied. In the CVIS system the transducer motion is performed by an automatic pullback device (a motor drive which retracts the catheter at a fixed speed to optimize the image acquisition).

16. Forward-viewing IVUS may aid in maintaining intraluminal position while crossing occlusions. This device produces a series of slices, representing discreet distances in front of the transducer, displayed simultaneously on a monitor.

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