Carbon Dioxide as a contrast agent to guide vascular interventional procedures

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Learning objectives

To discuss the rationale of using of Carbon Dioxide (CO2) as a contrast agent in angiographic and vascular interventional procedures in patients with formal contraindications to Iodinated Contrast Medium (ICM).

To illustrate chemical and physical properties of CO2 with the aim of its use as contrast agent, outlining its value and limitations.

To present some clinical cases in which CO2 angiography was performed.
Background

Iodine contrast medium (ICM) is considered gold standard in endovascular procedures. However, contrast-induced-nephrotoxicity and hypersensitivity to ICM may limit its use in endovascular procedures. (1)

In the general population, the incidence of nephrotoxicity related to ICM is about 0.6-2.3% (4); patients with renal insufficiency or other risks factors (elderly age, diabetes, low cardiac ejection rate, hypotension, anaemia, use of nephrotoxic drugs, high volume of ICM needed for the procedure) are at high risk to develop this condition. (5)

As far as it concerns hypersensitivity to ICM, the patient can manifest a light, moderate or severe allergic reaction; severe allergic reactions rarely occur, but are dramatic and controlled with difficulty. (23) (24)

Carbon Dioxide (CO2) has been proposed as an alternative contrast agent in patients with formal contraindications to ICM, and CO2 angiography has been reported to be feasible and safe in several different procedures. (1) (2) (3) (21) (22)

CO2 was used for the first time in 1914 in order to show up retroperitoneal structures (6). Later, in 1950s, several studies demonstrated that CO2 was safe and well tolerated by patients when used as a contrast agent in the venous circulation through peripheral venous injections (2). Moreover, intravenous injection of CO2 was used for many years to detect pericardial effusion. (3) (7)

Nowadays, CO2 angiography has become widely used as a contrast agent for vascular imaging (aortography, visceral and peripheral vessels angiography) and to guide endovascular procedures (angioplasty and stent placement, transcatheter embolization, endovascular abdominal aortic aneurysm repair and transjugular intrahepatic portosystemic shunt procedure), thanks to the availability of high-resolution DSA and a reliable gas delivery system. (14) (15) (19)

A thorough understanding of the unique physical properties of CO2 is necessary for the safe and effective performance of CO2 angiography for both diagnosis and intervention. (16) (17) (20)

Thus, the present work offers an overview on CO2 properties and angiography technique, also presenting some cases of procedure guided by CO2 angiography.
Findings and procedure details

CO2 angiography has to be considered whenever possible in patients at risk of contrast nephrotoxicity or contrast reaction to ICM (3). In particular, CO2 is indicated in patients with reduced renal function (serum creatinine > 1.5 g/dl) that must undergo diagnostic or therapeutic angiography. It may also be used in combination with ICM in order to reduce the amount of ICM. (2) (3) (22) Finally, CO2 may be used in patients with cardiac failure that must undergo angiography. (3)

Patients can have more than one risk factor. (3)

Chemical and physical properties of CO2 to be known for CO2 angiography

CO2 is a colorless and odorless gas, thus, not distinguishable from air. Consequently, a perfect sealing of the delivering system is crucial, as a leakage of CO2 may be undetectable. CO2 is approximately 20 times more soluble in blood than oxygen. When injected into the blood, CO2 bubbles completely dissolve within 2-3 minutes, combining with water to produce carbonic acid. Carbonic anhydrase catalyzes the conversion of CO2 to bicarbonate (HCO3-) and protons in the blood stream; then, bicarbonate reverts to CO2 before being expelled out of capillaries into the lung, so CO2 is eliminated breathing. (2) (9) For this reason, 2-3 minutes should elapse between two CO2 injections.

When injected into a vessel, CO2 does not mix with blood and so it does not become diluted by collateral flows as it happens to ICM. (2) (10) Moreover, being lighter than blood plasma, it floats above the blood. This characteristic has to be considered when performing CO2 angiography, as ventral or dorsal location of the vessel to be imaged may considerably affect the image formation. Gas buoyancy is an advantage when it is necessary to display the anterior visceral vessels but is theoretically disadvantageous for posterior vessels, such as the renal and internal iliac arteries. (3) This property of the gas is not a problem when the vessel to be imaged is smaller than 10 mm in diameter because the gas bubbles tend to displace the blood in greater than 80% of the lumen. (2) When injected into a large vessel (aorta or inferior vena cava) of a supine patient, CO2 bubbles flow along the superior part of the vessel, with incomplete blood displacement along the inferior portion. (10) Because of their ventral point of origin, the celiac and superior mesenteric arteries fill well with small volumes (< 30 cc) of CO2. Instead, because of the dorsal position of the kidney relative to the aorta where CO2 is injected, the distal renal arteries do not fill well, owing to the buoyancy of the gas. Imaging may be improved by moving vessels of interest into nondependent locations. For example, filling of a renal artery may be improved by elevating the side of interest so that the gas rises into that
vessel. Likewise, elevation of the legs to 15-20°, enhances gas flow and filling of the distal arteries in the lower extremity. (2) (11) (18)

CO2 is compressible; during injection, it is compressed into the catheter while it expands in the vessel as it exits the catheter. Clearing the fluid of the catheter by using 3-5 cc of CO2 before injection reduces the explosive delivery, which may contribute to discomfort during the injection.

CO2 is approximately 400 times less viscous than iodinated contrast medium. The low viscosity accounts for an easy manual injection, that can also be achieved with small diameter catheter, or between the catheter and the guidewire. Also, low viscosity offers a better filling of collateral vessels for both arterial and venous occlusive diseases.

CO2 is less dense than ICM and has a low intrinsic contrast. Thus, CO2 angiography requires digital subtraction for gas imaging; (3)

The compressibility and low viscosity of the gas accounts for the greater sensitivity of CO2 as a contrast agent in detecting the source of bleeding (gastrointestinal tract and traumatic bleeding), as compared with ICM. In fact, CO2 is able to pass through small vascular breaches; this characteristic, together with gas intrinsic ability to expand into low pressure districts, produces a rapid discharge of CO2 in gastro-intestinal cavities interested by bleeding, and this is easily recorded with DSA angiography as a typical bubble.

**CO2 angiography technique**

**Patient preparation**

No specific patient preparation is required for CO2 angiography. The standard preparation for catheter angiography is used. Patients with a history of allergy to ICM do not require steroid preparation, if angiography is performed using only CO2. Patients with renal impairment have to be hydrated with intravenous normal saline before the procedure in case iodinated contrast is needed. (3) Heavy sedation should be avoided during CO2 angiography, as respiratory depression and hypotension caused by air contamination may be mistaken for adverse effects of the sedatives and/or analgesics. All patients undergoing CO2 angiography should be monitored with ECG and pulse oximetry; blood pressure, respiratory and heart rates should also be monitored. A significant change in any monitoring parameter suggests either that the doses of CO2 were excessive or that air contamination has occurred.

**Material preparation**
The CO2 delivery system should be filled with 99.99% laboratory-grade CO2 from a disposable cylinder. The cylinder is supplied with highly pure gas, a valve, a regulator, a gas gauge, and a metal diaphragm with the regulator set at 18 psi. (See FIGURE 1)

Because the risk of injection of large volumes of CO2, the catheter should not be directly connected to the CO2 cylinder, which contains a large volume of CO2 at very high pressure. CO2 may be delivered into a vessel by use of a handheld syringe or by the plastic bag system. (See FIGURE 2, FIGURE 3)

The plastic bag is connected to the carbon dioxide cylinder through a 0.2 micrometer filter. The 3-way stopcock between the cylinder and the bag allows filling and emptying of the bag with carbon dioxide to remove residual air from the bag. The bag is connected to the connecting tube where the injection syringe is located. The 3-way stopcock just distal to the check valve permits flushing and the injection of contrast medium into the catheter.

When a syringe is used, it should be filled directly from a CO2 cylinder. CO2 should not be aspirated into the syringe because this may cause air contamination. When the syringe has been filled with CO2, its pressure should be reduced to the atmospheric level by quickly opening and closing the stopcock. The CO2-filled syringe should not be left on the table with the stopcock open before injection because the CO2 in the syringe is rapidly replaced with air. The syringe method is inconvenient when multiple injections are necessary. The collection bag is filled with CO2 and is connected to the reservoir port of the fluid management system. This system has airtight connections with the check valves, the injection port, the bleed-back port, and the catheter port. The check valves reduce the need for stopcock manipulation, which in turn reduces the risk of air contamination. The bag must be tightly connected to the reservoir port of the delivery system to prevent air contamination. The bleed-back port near the catheter port allows normal saline or contrast medium injections. If CO2 is to be injected with a guide wire in the catheter, a Y-connector is connected to the injection port. The bag should be filled and emptied with CO2 3 times before the final filling to remove air from the bag.

The injection rate depends on the diameter, length, and flow of the vessels being imaged. For an abdominal aortogram 60-100 cc of CO2 is injected. When imaging aortic branches (celiac, superior mesenteric, renal arteries) 20-40 cc is used; in case of arteries of the lower extremity, 40-60 cc is used. Finally, in case of an inferior vena cavogram, 30-40 cc of CO2 is injected. Because of the low viscosity of the gas, CO2 may be injected through a 3-Fr microcatheter for selective and superselective angiography and for selective arterial embolization.

**CO2 Imaging**

Digital subtraction imaging may be particularly helpful when performing CO2 angiography, due to the low density of this gas. (8) If available, a 1024 X 1024 digital subtraction angiographic system and magnification technique should be used. (2) (3)
Stacking software for integrating a series of images has solved problems associated with the breakup of CO2 bubbles after injection.

Modern digital angiographic equipment with 1024x1024 matrix and rapid digital data manipulation has greatly increased the ability to utilize CO2 as a contrast agent. High acquisition frame rates are generally recommended when using CO2 and this has led to concern about radiation dose to the patient. In practice, contemporary image summation software integrates several frames, thereby minimizing the effects of breakup of the gas bolus and permitting the use of standard frame rates (2 frames/second) with satisfactory results. With the current technique there has been a tendency toward a reduction in radiation dose when CO2 is used. (3)

Rapid delivery of a large volume of gas, gas expansion and bolus fragmentation tend to lead to shorter image acquisitions with CO2. (3) The major source of reduction in radiation dose is a decrease in the number of frames acquired during each angiographic run. (3) Respiratory motion and peristalsis may become significant problems, in particular for visceral artery CO2 angiography. Additional mask images should be obtained to decrease motion artifacts by using new mask imaging subtraction. Intravenous administration of glucagon at the dose of 0.5-1 mg before CO2 injection improve intra-abdominal CO2 angiography by decreasing peristalsis and reducing bowel gas artifacts. (2) Superselective CO2 injection into the arterial branch with gas reflux can also improve the quality of the images.

Rapid exposures (4 to 6 frames per second) should be obtained, and superselective injection of CO2 as close to the target vessel as possible should be performed to optimize CO2 imaging.

**Advantages**

CO2 causes no allergic reaction as it is a natural product. (2) Therefore, CO2 is an ideal alternative to ICM for patients who have a history of allergic reactions. (2) (8) No steroid preparation is needed when CO2 is used.

CO2 causes no renal toxicity. (2) (8) Experimental and clinical findings (1) (2) (3) indicate that the selective injection of CO2 into the aorta or into the renal artery is safe and causes no renal injury, even in patients with diabetes or compromised renal function. Therefore, the gas can be considered the best contrast agent for renal artery angioplasty and stent placement.

CO2 causes no hepatic toxicity. The use of CO2 as a contrast agent for celiac, splenic, superior mesenteric, and hepatic arteriograms for patients with a variety of disorders causes no injuries to the hepatic parenchyma.
Unlimited amounts of CO2 may be used for vascular imaging because the gas is effectively eliminated by means of respiration keeping in mind to allow sufficient time for its clearance. (2)

CO2 may be used to reduce the volume of ICM used for all procedures. (3) (2)

CO2 angiography may allow for a reduction in radiation dose compared with equivalent procedures performed using ICM. (3) The major source of reduction in radiation dose is a decrease in the number of frames acquired during each angiographic run. (3)

Contraindications and adverse effects

Complications resulting from intravascular CO2 injection may be several, but are generally rare (2). They often relate to an incorrect application of technique that may result in air contamination and cause serious complications (vapor lock in the pulmonary artery with consequent hypotension), or to an inadvertent injection of excessive volumes of CO2. When air contamination occurs, fluoroscopy of the chest shows gas bubbles in the pulmonary artery that persists for longer than 30 seconds. If hypotension develops, the patient should be placed in the Trendelenburg and left lateral decubitus positions. If possible, air should be aspirated from the pulmonary artery using a catheter. (12)

In supine patients, the gas may be trapped anteriorly in an abdominal aortic aneurysm. (3) This can result in the nondependent inferior mesenteric artery filling with CO2, which can produce stasis and ischemia. For the same reason CO2 aortography and celiac arteriography may cause nausea and pain lasting 2-3 minutes. No specific treatment is required. Placing the patient in a left- or right-side-up position may relieve the pain. A decrease in the doses of CO2 usually reduces the frequency and severity of pain.

Excess CO2 trapped occurring in the apex of an aneurysm should be simply removed by aspiration via the angiographic catheter. (3)

Seizures, loss of consciousness, brief respiratory arrest, or some combination of these complications have been described in some patients when CO2 refluxed into the cerebral arteries. (13) (14) Therefore, arterial CO2 injections are not performed above the diaphragm. (2) (3) Injection of CO2, especially for runoff of the lower extremities, can cause pain, secondary to adventitial distension from large gas volumes and possibly contamination of the gas with rust particles and acid due to corrosion in the gas cylinder. (3) Using disposable gas cylinders, decreasing the amount of CO2 with selective injection and stacking technique, passing the gas through a blood filter before filling the syringes, minimizes these effects and helps in reducing the pain. (3)

There are no absolute contraindications to the use of CO2.
CO2 should not be used as an arterial contrast agent in sites above the diaphragm (thoracic aorta and arteries above the diaphragm) because of the risk of spinal, coronary, and carotid artery gas embolism. (13) (14)

CO2 should not be used in patients with an intracardiac septal defect (CO2 bubbles injected into the venous system may enter the systemic circulation via the patent foramen ovale or intracardiac septal defects) or a pulmonary arteriovenous malformation because of the possibility of paradoxical gas embolism.

CO2 should be used with caution in patients with pulmonary insufficiency or pulmonary hypertension because a diagnostic dose of CO2 may cause an increase in pulmonary arterial pressure. (15)

**Clinical Applications**

CO2 may be used as a contrast agent for diagnostic arteriography, venography, and various vascular interventions, including angioplasty and stenting of visceral and peripheral vessels, and endovascular aneurysm repair (EVAR) particularly for patients with renal insufficiency and for patients who have a history of hypersensitivity to iodinated contrast medium. (2) (3) (14) (19) (22)

A case of a patient with impaired renal function and a renal artery stenosis in which diagnostic CO2 angiography and subsequent treatment with angioplasty and stenting was performed using this technique is shown in FIGURE 4.

A case of aortic aneurysm repair with CO2 angiography is shown in FIGURE 5.

A case of external iliac artery stenosis before and after a PTA intervention and stenting demonstrated at CO2 angiography is shown in FIGURE 6.

**Tips and tricks**

- Clearing the fluid of the catheter by using 3-5 cc of CO2 before injection reduces the explosive delivery, which may contribute to discomfort during the injection.

- Because the gas is buoyant, imaging may be improved by moving vessels of interest into nondependent locations. For example, filling of a renal artery may be improved by elevating the side of interest so that the gas rises into that vessel. Likewise, the legs may be elevated to improve flow of the gas into the distal arteries. (2) (11)

- Elevation of the lower extremities to 15-20° above the level of the angiographic table, in conjunction with the intra-arterial injection of 100-200 µg of nitroglycerin, enhances gas flow and filling of the distal arteries. (11)

- Proximal arteries can be imaged by refluxing CO2 from a peripheral injection.
• Intravenous administration of glucagon at the dose of 0.5-1 mg before CO2 injection improve intra-abdominal CO2 angiography by decreasing peristalsis and reducing bowel gas artifacts. (2)
Fig. 1: Figure 1: Equipment for CO2 injection. Images a, b, c, d illustrate 4 steps to prepare the injection system, putting the luer lock syringe (S) into the appropriate space, in the right way.

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Fig. 2: Figure 2: Images e, f, g illustrate CO2 delivery system, filled with 99,99% laboratory-grade CO2 from a disposable gas cylinder (C). S = luer lock syringe

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Fig. 3: Figure 3: Images h and i show the monitor with its parameters dose, pressure and slope. Red arrow indicates the key to press to start the injection. Image l shows the "injection test" of CO2 out of the patient in sterile physiological solution.

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**Fig. 4:** Figure 4:A) A significant left proximal renal artery stenosis (red arrow) depicted by a CO2 angiography in patient with arterial hypertension associated with impaired renal function. Guide catheter (Cobra 6F) and guidewire (0.014") are placed in the left renal artery;B) Final CO2 angiography showed optimal result of renal stenting implantation (red arrow).

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**Fig. 5:** We present a case of patient with aortic abdominal aneurysm with short proximal neck. The final angiography (CO2) showed correct aortic endoprosthesis implantation (Cook endoprosthesis characterized by "suprarenal anchoring barbs") in the presence of the regular placement of prosthetic elements, patency of the renal arteries and absence of any endoleaks. (A and B, C and D: images before and after digital reconstruction)

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Fig. 6: CO2 angiography shows a significant external iliac-artery stenosis (red arrow); Final result after iliac stent implantation (red arrow) depicted by «conventional» (Iodine contrast medium -ICM) angiography.

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Conclusion

CO2 angiography is a feasible and safe procedure, that can be successfully used to guide diagnostic angiography and interventional procedures. (1) (2) (3) (21)

This may be particularly useful in patients with allergy to ICM or impaired renal function in order to avoid or reduce the use of ICM. (16) (17) (20)
References


