The Current Status of the Use of Carbon Dioxide in Diagnostic and Interventional Angiographic Procedures

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Abstract
Since the first description of carbon dioxide (CO₂) angiography the indications for using CO₂ have been changing and the applications of CO₂ angiography evolving. This review covers the contemporary role of CO₂ angiography. CO₂ angiography can be considered according to whether it is likely to be better, equivalent to or worse than conventional iodinated contrast medium (ICM). Areas where CO₂ angiography offers distinct advantages over ICM will be emphasized. The limitations to using CO₂ and specific caveats will be discussed. The basic physical properties of CO₂ and avoidance of the complications of gas angiography will be considered. CO₂ gas is cheap, non-allergenic, and is not nephrotoxic. Unfortunately it is not a panacea, angiographic quality is reduced, it is not tolerated by every patient, and it cannot be used in every location. It is important to be pragmatic and to use conventional contrast or alternative imaging rather than struggling with suboptimal CO₂ angiography.

Key words: Aortic stent-graft placement—Carbon dioxide—Contrast media—Embolsation—Hemorrhage, gastrointestinal—IVC filter—Peripheral vascular diseases, radiography—Renal intervention—Wedge hepatic venography

A Brief History of CO₂ Angiography
The initial radiological use of CO₂ gas was to outline retroperitoneal structures [2]. Subsequently intravenous injections were used to delineate the right heart to detect pericardial effusions [3]. Hawkins pioneered the use of CO₂ as an intravascular contrast agent and interest developed because it represented a safe, effective, inexpensive alternative to the relatively toxic ionic contrast agents available at that time. Despite this, CO₂ angiography has never been widely used.

This is due to two factors. Firstly angiographic image quality is limited due to the low intrinsic contrast of CO₂ gas and secondly there is a perception that gas contrast is difficult to use. Some indications for CO₂ angiography are less relevant due to improved safety and reduction in the price of ICM. Some of the newer contrast agents appear to be less nephrotoxic and may prove to be safe in patients with impaired renal function. There is some evidence that the nonionic agent io-dixanol (Visipaque) reduces the risk of contrast-induced nephropathy compared with iohexol [4]. Many “high-risk” patients are spared ICM and catheter angiography in favor of noninvasive imaging. Ultrasound and magnetic resonance angiography (MRA) will rightly become first line for many diagnostic angiographic procedures but at present do not readily permit vascular intervention.

Modern angiographic equipment is capable of high resolution and image summation. Many angiographic units incorporate software packages specifically designed for CO₂ angiography. This has increased the scope for CO₂ angiography. Currently there are several novel applications in both diagnostic and interventional vascular radiology in which CO₂ offers definite advantages over alternative techniques. CO₂ angiography also has an important role to play in any patient not suited to ICM and in those patients with a contraindication to MRA.

Physiology and Safety of CO₂
CO₂ gas is a colorless, odorless, noncombustible and compressible end product of cellular metabolism. CO₂ is 20 times more soluble in blood than oxygen. Basal CO₂ production is about 250 ml/min and increases about 5-fold during exercise. There are large quantities of CO₂ present in the body either dissolved or in the form of bicarbonate ions. Due to the action of carbonic anhydrase intra-arterial CO₂ diffuses into erythrocytes and is carried on hemoglobin to the lungs where it is cleared with little effect on pH or pO₂. An excellent resume of the physiology of CO₂ metabolism can be found in Nunn’s Applied Respiratory Physiology [5].
CO₂ does not cause idiosyncratic allergic reactions and has no deleterious effect on renal function even in those with pre-existing renal impairment [6]. This has been confirmed in studies on canine kidneys, which demonstrated no change in blood flow, function, or histology following exposure to intra-arterial CO₂ [7].

Imaging Principles and Delivery of CO₂

The fundamental principle of a gaseous contrast agent is to reduce the attenuation of the blood vessel compared with soft tissue and fat. Appropriate angiographic inversion opacification software should be used. Frame rates of 3–6/ sec are commonly used, although 2/sec has been used satisfactorily with no increase in radiation dose [8]. Conventional liquid contrast agents mix with blood and are carried by blood flow. CO₂ is extremely buoyant and displaces rather than mixes with blood. The gas will float if the column of blood is not completely displaced. It is 400 times less viscous than iodinated contrast. These properties can be advantageous in certain procedures.

Injecting CO₂ Gas

Pure medical-grade CO₂ must be used. Disposable cylinders are recommended as corrosion has been reported in reusable cylinders. A closed delivery system and strict protocols are needed to prevent contamination with room air. Air embolism could lead to thrombosis and ischemia. CO₂ can be delivered by hand or pump injector. Dedicated gas injectors deliver known volumes of dry CO₂ at a uniform flow rate with electrocardiographic gating if required. However, they are expensive to buy and have significant ongoing consumable costs. In practice hand injection is equally effective.

Hand injection of CO₂ is very easy due to its low viscosity and even large vessels can be opacified. Techniques for the manual delivery of CO₂ are well described [9–11]. CO₂ must never be delivered direct from the gas cylinder or from syringes at greater than atmospheric pressure as potentially dangerous volumes could be injected. When using pressurized syringes the simple expedient of briefly opening the tap prior to use reduces the pressure to atmospheric pressure. The angiographic catheter is purged of saline prior to injection. This ensures smooth rapid injection rather than explosive delivery which breaks up the gas bolus.

Intra-arterial injection of CO₂ may produce symptoms including paresthesia in the legs, abdominal pain, tenesmus, and nausea. Diaz et al. found pain led to the discontinuation of 18% of examinations when high volumes and flow rates were used [12]. In practice warning the patient what to expect, giving a test injection of 20 ml, and reducing volume and flow rates minimizes side effects and improves tolerance.

Artifacts

_Bohus Fragmentation_

The CO₂ gas bolus displaces the blood from a section of the blood vessel. As CO₂ passes through bifurcations the bolus tends to break up into discrete bubbles and image stacking needs to be employed to obtain diagnostic-quality images. Pseudostenosis artifact is consequence of gas fragmentation and buoyancy and can be very convincing (Fig. 1). Where there is doubt, stenoses need to be confirmed by reviewing the run on the console: if the morphology of the stenosis changes with each frame it should be regarded with suspicion.

_Underfilling of Dependent Vessels_

If blood is not completely displaced the gas will float on the surface this may be particularly evident in patients with abdominal aortic aneurysm. In our experience posterior vessels such as the renal arteries are less readily demonstrated. This can normally be overcome by pointing the catheter toward the target vessel without resorting to decubitus positioning or other postural maneuvers.

Hazards of CO₂ Angiography

_CO₂ in Respiratory Failure_

In patients with chronic type 2 respiratory failure there is a theoretical risk of exacerbating CO₂ retention. For these patients CO₂ is still safe to use but decreasing the volume per injection and increasing the time interval between injections is recommended [13]. In practice injections of 50 ml/min are equivalent to a 20% increase in basal CO₂ production and are unlikely to be clinically significant. In Leeds we have monitored end tidal CO₂ concentrations in anesthetized patients undergoing endovascular stent-grafting and transjugular intrahepatic portosystemic shunt (TIPS) procedures and shown only minor transient physiologically insignificant changes following the CO₂ injection (unpublished data). It is possible that these changes may even be the result of the accumulation of CO₂ due to the period of apnea during angiography.

_Neurotoxicity_

Neurotoxicity represents the most serious safety concern in the use of intravascular CO₂. Direct injection of CO₂ into the carotid arteries of rats resulted in breakdown of the blood–brain barrier and ischemic cerebral damage [14]. Ehrman et al. reported neurologic sequelae when CO₂ was thought to have refluxed into the vertebral arteries of three patients (two had seizures and one became unconscious) [15].

This represents the most important limitation to the use of CO₂ angiography. For this reason intra-arterial CO₂ should not be used above the diaphragm and it is absolutely contraindicated for cerebral and upper limb angiography.
Likewise intravenous CO₂ should not be used in the presence of a right-to-left intracardiac shunt.

Vapor Lock

Vapor lock is caused by trapped CO₂ gas interfering with normal blood flow. Large volumes of intracardiac CO₂ can potentially prevent the venous return to the heart. In reality this risk only applies to venography and the volumes of CO₂ injected are too low to cause this [16]. When there is stasis nitrogen may diffuse into the trapped CO₂. As nitrogen is much less soluble than CO₂ a nitrogen bubble would be much more dangerous with potential nitrogen emboli causing “the bends.” Similarly the simultaneous use of CO₂ and nitrous oxide anesthesia should be avoided. The nitrous oxide can diffuse into the CO₂ bubble and dilute it making the bubble less soluble in plasma and increasing the potential to cause a vapor lock. Vapor lock of the mesenteric arteries has been reported to cause transient intestinal ischemia [17]. This is most likely to occur in the context of abdominal aortic aneurysms with CO₂ accumulation in the aneurysm sac. In practice whether the problem of vapor lock is due to CO₂ or nitrogen it can easily be avoided by aspirating any trapped CO₂ through the angiographic catheter.

Applications of CO₂ Angiography

CO₂ angiography should be considered in the following circumstances: (1) when patients have a history of severe contrast reaction and cannot be investigated by MRI or ultrasound; (2) in applications where CO₂ confers definite advantages over ICM or other forms of imaging (Table 1).

Procedures Simplified by Using CO₂

The following procedures are either easier to perform with CO₂ angiography or using CO₂ confers benefits to the patient.

Guidance for Transjugular Intrahepatic Portosystemic Shunt (TIPS) Procedures

The most difficult element of a TIPS procedure is targeting the portal vein. Various strategies have been described including arteriography, percutaneous portal vein puncture, and ultrasound guidance. The portal vein is usually readily demonstrated by CO₂ wedged hepatic venography. Due to its low viscosity CO₂ readily passes through the hepatic sinusoids, and thus is much more effective in opacifying the portal vein than conventional contrast (Fig. 2A). This has been shown to increase technical success rates and reduce procedure time [18]. Using CO₂ reduces the contrast load and the need for transhepatic and arterial punctures in patients who often have coagulopathy and impaired renal function.

Caveats for Wedged Hepatic Venography

It is often possible to demonstrate the portal vein with a relatively small injection of CO₂. Fatal liver capsule laceration has been reported as a rare complication of CO₂ wedged hepatic venography [19]. We have not seen this complication in 8 years’ experience of using CO₂ guidance. This may be related to performing small test injections under fluoroscopy prior to performing an angiographic run. Overall the risk seems to be overshadowed by the benefits of simplifying the TIPS procedure.

A further potential pitfall when using CO₂ wedged hepatic venography is preferential opacification of a patent umbilical vein. This is usually readily recognized by its origin from the left portal vein and unusual course (Fig. 2B).
Acute Gastrointestinal Hemorrhage

When CO₂ enters the bowel it rapidly expands giving a very characteristic “bubble” (Fig. 3). Improved detection of acute arterial bleeding has been reported in both gastrointestinal hemorrhage and post-traumatic bleeding using CO₂ angiography. Because of this distinctive appearance it is not uncommon for a CO₂ flush arteriogram to demonstrate the source of bleeding (Fig. 3). In an unstable patient speed is of the essence and this can markedly simplify angiography and expedite treatment. On occasion CO₂ will reveal bleeding that is not demonstrable on conventional angiography. Examinations include the low viscosity of the gas allowing it to pass through vessels in spasm and small arterial tears. CO₂ acts as a vasodilator and it is possible that this combined with the tendency to expand and displace blood is helpful in revealing intermittent bleeding. Patient tolerance and the acquisition of diagnostic-quality examinations is also an issue especially in a group of patients who are usually agitated and hemodynamically unstable.

In a series of 27 patients with suspected arterial bleeding in the gastrointestinal tract Back et al. reported detecting bleeding sites in 44% with CO₂, compared with only 14% detected using ICM [10]. In a smaller series Sandhu et al. performed CO₂ mesenteric arteriograms on 15 patients with acute gastrointestinal hemorrhage and found that the images were more difficult to interpret as a result of increased patient movement. They reported that CO₂ was inferior to conventional contrast in detecting hemorrhage and in demonstrating nonbleeding vascular abnormalities. However, in anesthetized patients diagnostic-quality mesenteric angiograms were consistently obtained [20].

Clearly this there is no level 1 evidence on which to base practice. In reality CO₂ angiography and conventional angiography are complementary techniques. A pragmatic approach is to perform a CO₂ flush arteriogram at the start of angiography for acute gastrointestinal bleeding. If this is tolerated and the quality of the CO₂ angiogram is satisfactory then use it for selective angiography. If it is not then use conventional contrast. Our experience suggests that if highly selective angiography is necessary then conventional contrast is usually required.

Endovascular Stent-Grafting in Abdominal Aortic Aneurysm

Patients undergoing endovascular aneurysm repair (EVAR) are usually elderly and frequently have impaired renal function. Typically repeated angiograms are performed during positioning, deployment, and at completion and can involve high doses of contrast. This increases the risk of contrast-induced nephropathy and prolongation of the hospital stay. In an attempt to reduce the contrast burden Bush et al. used unenhanced CT, MRA, intravascular ultrasound (IVUS), transabdominal US, and CO₂ angiography for planning, stent-graft placement, and detection of endoleaks. Using this regime they placed 20 stent-grafts without ICM [21]. It should be remembered that CO₂ angiography is very cheap and IVUS very expensive. Gahlen et al. reported placing stent-grafts in three high-risk patients with infrarenal...
nal abdominal aortic aneurysm using CO₂ alone via a pump injector. No complications occurred and the renal function remained stable in all three patients [22]. In our initial experience of 15 patients we were able to use CO₂ alone in 13 (87%) with conventional contrast needed in only 2 (13%) [8]. If the operator is familiar with using CO₂ the majority of abdominal aortic stent-graft procedures can be performed with CO₂ angiography alone (Fig. 4).

Caveats to Using CO₂ During EVAR

There has only been one reported complication directly attributable to the use of CO₂. Stent-graft release was commenced following satisfactory positioning angiography. During check angiography the renal arteries failed to opacify. They were mistakenly thought to be covered by the stent-graft which was subsequently deployed too distally. It is thought that this may have occurred because the angiographic catheter was pushed anteriorly by the graft [8]. As always, if there is any doubt regarding position it is simple to confirm the position with conventional contrast.

Detection of Endoleaks Following EVAR in Abdominal Aortic Aneurysm

CO₂ angiography readily demonstrates endoleaks, probably for the same reasons that it is able to show gastrointestinal bleeding. It is likely that the fact that CO₂ displaces blood contributes to the detection of small, low-flow type II endoleaks which are occult on other forms of imaging (Fig. 5) [8].

Procedures with a Relative Advantage of Using CO₂

Angiography in Patients with Impaired Renal Function or History of Severe Contrast Reaction

These were key indications for CO₂ angiography but their importance has decreased due to the advent of MRA. They may reduce further if iodinated contrast agents can be demonstrated to be safe in patients with impaired renal function. It is clear that adequate hydration is the single most important measure in patients with impaired renal function who require angiography. CO₂ remains important in patients with a history of idiosyncratic anaphylactoid contrast reactions or pulmonary edema who should not be hydrated. In addition CO₂ is much cheaper than conventional contrast agents and remains advantageous if it is tolerated and gives satisfactory angiographic results. Isosmolar agents, such as ioxilan, typically give much better views of the calf vessels in patients with critical limb ischemia as they do not cause pain during injection.

Renal Artery Intervention

Patients with renal transplants are particularly vulnerable to ICM-induced nephrotoxicity due to pre-existing microvascular disease and from episodes of rejection and drug toxicity [23]. CO₂ offers an advantage over ICM as unlimited amounts can be used and can be injected directly into the main renal artery without fear of deterioration in renal function.
Additionally there are technical advantages to using CO₂ during renal artery intervention. It is particularly suited to use with low-profile systems, especially when using long catheters from the radial artery approach [24]. Due to its low viscosity it is readily injected through a 0.035-inch lumen catheter around a 0.018-inch guidewire by using a Tuohy-Borst adapter (Fig. 6). This allows confirmation of the intraluminal position of the guidewire after passing through the stenosis. If using low-profile 4 Fr systems for stenting the position of the stent can be verified immediately before deployment by exchanging for a 0.014-inch guidewire and injecting around this. The CO₂ will typically reflux into the aorta. Similarly postprocedural angiography can be performed either by removing the wire and injecting with the balloon in the renal artery or by replacing the 4 Fr catheter.

Renal artery angioplasty and stenting can be successfully performed using CO₂ with small quantities of ICM to aid when imaging is suboptimal. Caridi et al. deployed 23 stents in 17 patients with 100% technical success rate. Small volumes of supplementary ICM were required in 5 patients because CO₂ imaging was inadequate due to respiratory or bowel motion artifact [25]. In our local experience roughly 85% of renal artery stents are performed using CO₂ alone [8]. Failures occur in those patients who cannot tolerate intra-arterial injection of CO₂ and in a small proportion in whom the image quality is unsatisfactory. As stated previously, if the images are suboptimal or the patient is distressed by CO₂ there should be no hesitation to changing to iso-osmolar ICM.

Upper Limb Venous Diagnosis and Intervention

CO₂ venography of the upper limb is reported to be more accurate than ICM in the detection of stenoses in the subclavian and brachiocephalic veins. Superior-quality images of the central veins are attributed to the less viscous nature of CO₂ that allows it to fill more collaterals and travel more rapidly than ICM (this may also reduce the movement artifact). Injection into veins on the dorsum of the hand is painful and therefore the antecubital veins are preferred [26]. CO₂ has been used successfully in planning and performing upper limb venous interventions including placing central venous catheters, central vein percutaneous transluminal angioplasty, and stent placement [13]. Optimal images of the central veins are obtained using centrally placed catheters. Many of these patients will be on renal dialysis in which case the benefit of using CO₂ is only financial unless there is another contraindication to ICM.

Vascular Malformations

CO₂ is not routinely used for the assessment and treatment of vascular malformations. A single report in the literature suggests that due to the buoyancy and low viscosity of CO₂ in high-flow arteriovenous malformations it provides more detailed information of the arteriovenous connections whilst planning embolization than does ICM and detects residual postembolization communications that ICM does not [27].
Applications Where CO₂ Has No Advantage Except in Patients with ICM Allergy

Lower Limb Angiography

Peripheral arteriography can be performed with CO₂ alone but in general patients find it less comfortable than conventional contrast. This is particularly true of patients with critical ischemia, who may find even small volumes of CO₂ impossible to tolerate. This group of patients benefit particularly from noninvasive imaging, especially MRA. When angiography is essential an iso-osmolar agent such as io-
dixanol is generally painless when injected and maximizes the chance of obtaining diagnostic images.

CO₂ angiography is reported to be as accurate as ICM in detection of stenoses [28]. The calf runoff vessels are most difficult to image and opacification is improved with selective injections into each leg [29]. Some authors recommend elevation of the legs and the use of nitroglycerin to improve suboptimal filling in the crural arteries. In our experience the principal difficulties occur due to bolus fragmentation and misregistration due to movement secondary to patient discomfort. In these circumstances such maneuvers are seldom
effective and MRA is the best modality for demonstration of the calf vessels.

Peripheral Arterial Intervention
There is limited descriptive literature regarding interventions in the lower limb with CO₂. Frankhouse et al. successfully performed 25 interventions in the iliac, femoropopliteal and infrapopliteal segments. Eight procedures were performed with CO₂ alone, while 17 required small amounts of ICM [30]. Eschelman et al. reported 15 interventions in 13 lower limb arteries with technical success in 93%. Seven were performed with CO₂ alone. Small volumes of ICM were used in the remainder to confirm positioning before intervention and to improve the quality of angiography after the procedure [31]. Our experience suggests that the majority of peripheral angioplasty and stenting can be performed with CO₂ alone. Despite this we seldom use CO₂ angiography for routine peripheral intervention and reserve it for those cases in which ICM is strongly contraindicated [8].

Inferior Vena Cava Filters
CO₂ can be used effectively to place inferior vena cava (IVC) filters. The operator needs to be aware of certain differences in technique and interpretation. More numerous and selective injections may be required to outline the anatomy (especially the right renal vein, which is a posterior structure usually lying inferior to the left renal vein and does not readily fill with CO₂). Accessory renal veins are less likely to be demonstrated, and IVC thrombus can go undetected [32].

Applications in which CO₂ May Be Unhelpful

Embolization
CO₂ can be used to guide coil embolization but cannot be used to inject particulate or liquid embolic agents. We have performed a variety of embolization procedures on internal iliac, lumbar, and superior mesenteric arteries using CO₂ guidance either prior to aortic stent-graft placement or in patients with gastrointestinal tract hemorrhage.

Difficulties were encountered assessing occlusion of the target vessel as the low viscosity of the gas and the tendency to expand meant that it readily passed through coil nests. In general coils are placed until the operator feels that the vessel is likely to thrombose [8].

Fibroid embolization has been performed successfully in a woman with a history of ICM allergy. CO₂ was used for guidance and small quantities of gadolinium were mixed with the polyvinyl alcohol particles for embolization [33].

Hemodialysis Access Grafts
There is limited literature on the use of CO₂ for assessing hemodialysis access sites as ICM can be used safely in patients with established renal failure on dialysis. Almost by definition these patients have renal function which is beyond salvage and so the benefit of using CO₂ is questionable. A single study has evaluated CO₂ in the imaging of hemodialysis access grafts. It was found to overestimate stenoses at the graft—venous anastomosis. As already mentioned, adverse effects have been reported when attempting to evaluate the arterial—graft anastomosis by the reflux technique (significant transient neurologic sequelae). This was attributed to the reflux of CO₂ up the arm and into the vertebral arteries [15].

Summary
CO₂ angiography should be viewed as a complementary angiographic technique. CO₂ angiography has distinct advantages over conventional iodinated contrast in certain circumstances due to its physical properties. It is excellent for wedged hepatic venography, guiding TIPS, and the detection of acute gastrointestinal hemorrhage and endoleaks. MRA and ultrasound have largely replaced the need for CO₂ angiography in the assessment of peripheral arterial disease. The need for CO₂ in patients at risk of contrast-induced nephropathy may reduce further with the promising improvements in the safety profiles of the iso-osmolar contrast agents. CO₂ remains the best alternative in patients with a history of severe contrast reaction in whom MRA is contraindicated. As with any technique there are limitations and contraindications, and as long as these are remembered CO₂ angiography is a valuable addition to the vascular radiologist’s armamentarium.

References