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CO₂ angiography is enjoying resurgence in terms of use given the significant increase in endovascular procedures and the need to reduce usage of iodinated contrast and contrast-induced nephropathy, in patients with or without pre-existing renal disease. Nevertheless, it is an underused tool due to handed-down dogma re lack of practical applicability, concerns re complications and imaging quality. A narrative review is undertaken looking the scope, applicability, technique and modern advances in technology related to CO₂ angiography. Literature searches were undertaken within Pubmed/EndNote, Google Scholar, Google and Bing search engines. A description is provided of local practice at the author's institution.

The author describes the institutional use of manual CO₂ angiography (MCDA) in peripheral arterial interventions, endovascular aneurysm repair (EVAR) and provided an overview of their practice in this context.

There been significant recent advance in CO₂ angiography that merit greater uptake in current interventional and endovascular practice. CO₂ angiography should be considered a routine adjunct to EVAR.

Introduction

Carbon dioxide (CO₂) exists all around us in the atmosphere, trapped in rocks, dissolved in water and, in the modern industrial era, as a product of the internal combustion engine from fossil fuel oxidation. This simple gas has found its way into medical usage including medical lasers^{1,2} and, of vascular relevance, as a (negative) contrast medium for angiography^{3,4}, yet another case of medical serendipity in 1971 when inadvertently injected air (rather than iodinated contrast) allowed visualisation of the coeliac axis⁵. Nevertheless, despite advances in imaging technology, the recognised need for reduction in use of iodinated contrast media (ICM) to avoid contrast-induced nephropathy (CIN)⁶ driving technological advances such as image fusion, angiographic imaging still relies mostly on usage of high-osmolality ICM. CO₂ (digital subtraction) angiography allows vascular imaging with a recognised ICM-sparing effect, yet, the typical non-user's argument remains "the equipment is too cumbersome", "it is very difficult to undertake", or

"the equipment is too expensive", often without actually having seen or used any such. With the current improvement in CO₂-delivery systems, digital subtraction angiography techniques in this context⁷, the overall process of CO₂ angiography has become both affordable and convenient, as indicated further in this review.

Materials and Methods

Technical applications

CO₂ has been used for different forms of angiography, besides conventional intra-arterial imaging. It has been applied in magnetic resonance angiography⁸, and also central venous imaging. Historically, its application was for retroperitoneal imaging⁷, and via the right atrium to diagnose pericardial effusion⁷.

Clinical scope

CO₂ angiography has been used for many specific indications, such as diagnosis of aortocaval fistula⁹ besides standard aortography and arteriovenous fistula imaging⁷, diagnosis of haemorrhage¹⁰, trauma imaging and mesenteric angiography⁷, assessment of transplanted kidney vasculature¹¹, imaging for renal arterial denervation¹², tumour embolisation⁷. On the venous front, CO₂ has been used for cavography prior to inferior vena cava filter placement in intensive care^{13,14}, and (wedged) hepatic venography^{7,15}, splenoportography and TIPSS⁷. It has also been used guide superior vena cava interventions. Other therapeutic interventions guided by CO₂ angiography include foreign body retrieval, catheter-directed thrombolysis, endovascular aneurysm repair⁷, peripheral arterial interventions.

It is not advised for supra-diaphragmatic arterial use in order to avoid neurotoxicity and cardiac arrhythmias⁷ though it has been used for experimental cerebral angiography¹⁶.

Delivery systems

Currently, dedicated modern delivery systems exist that facilitate CO₂ angiography. Of note are the Angiodroid System (Angiodroid Srl, Bologna, Italy) and- used currently by the author- the CO₂mmander system (CO₂mmander II System, AngioAdvancements, FL, USA).

The Angiodroid system is a dedicated automatic CO₂ injector (Figure 1A), conceptually similar to the pumps that inject ICM. It is an expensive device costing in excess of €28,000. Usage of the Angiodroid system has been described for peripheral automatic carbon dioxide angiography (ACDA) in diabetic arteriopathies with concurrent CKD¹⁷, using injection pressures typically 20mmHg above the patient's systolic blood pressure.

The CO₂mmander system is a compact, self-contained manual carbon dioxide angiography (MCDA) unit with a mouse pad-sized footprint, with a disposable 10L (compressed) CO₂ cartridge (CO₂mmander II System, AngioAdvancements, FL, USA) (Figure 1B).

This is comparatively cheaper at €3543 (including €34 for the gas canister). Gas outflow is via a disposable one-way, four-point system (inlet from system → filling



Figure 1A: Overview of the Angiodroid ACDA injector system (new model). Image provided courtesy of Platform 14 Medical Devices (distributors), 65 Bath Road, Stroud, Gloucestershire, UK GL5 3LA.



Figure 1B: Overview of the CO₂mmander MCDA system (current). Image provided courtesy of Mermaid Medical (UK) Limited (distributors), 16 Dover Road, Southport, Merseyside PR8 4SY.

syringe → injecting syringe → outlet tubing connecting to angiography catheter; AngiAssist, AngioAdvancements). This is critical in creating a system that once set up is constantly air-free.

Technique

CO₂ effectively becomes a contrast medium by displacing blood from the region of interest. Traditionally, MCDA has been undertaken using a 'jugaar' /home-made approach consisting of a system of tubes with junctions created by 3-way stopcocks with attached 50ml syringes leading out from a CO₂ cylinder into an angiographic catheter placed at the vascular region of interest¹⁸. Such simplistic solutions

have been traditionally reasonably effective, delivering a hand-injected contrast injection¹⁹⁻²¹ sometimes with common-sense adjuncts for displacing bowel gas for example²². Though automated injectors have been around^{23,24}, and interim modifications attempted²⁵, it has only been recently that devices such as the Angiodroid have been mass produced for general availability to endovascular/interventional operators.

Essentially the tubing system needs to be purged of all air. For aorto-iliac angiography it is useful to have the patient in a head-down tilted position to allow the CO₂ to move upwards *i.e.* caudal, and also minimise spillage into the supra-diaphragmatic aorta. CO₂ angiography is contraindicated in the aortic arch for fear of cerebral gas embolism/ neurotoxicity, and thus typically limited to being undertaken in the infra-diaphragmatic abdominal aorta.

For peripheral imaging, an end-hole catheter (4F/5F) is used, and upto 30mls of CO₂ injected. Most operators are of the opinion that imaging is of reasonable quality in the iliofemoral segments down to the knee, but image quality may deteriorate in the crural vessels needing ICM supplementation, or quality improvement adjuncts like blood-CO₂ mixture injections as described¹⁸. Imaging parameters sometimes need modifying²⁶, and it may become necessary to increase the fluoroscopic dosage and also the frame rate (upto 5-6 fps) during image acquisitions. Post-processing can further improve image quality obtained. Other adjuncts including pitch-shifting have been described¹⁸.

Results

CO₂ can be used for imaging during arterial and venous vascular procedures. Arterial indications include endovascular aneurysm repair (EVAR)²⁷, fenestrated/ branched EVAR (FEVAR/BEVAR) with or without iliac branch adjuncts. It can also be used for peripheral angiography, though operators should remind themselves that crural CO₂ injections can be painful for the patient. In our experience, aortoiliac injections have not caused any discomfort to our patients, usually attributable to the 'explosive' delivery of the gas.

At our institution we undertake MCDA for all angiographic procedures- EVAR or peripheral- for all patients with CKD; some of us now use it routinely for all EVARs.

In such cases, initial angiography is done with CO₂, if any doubt with the actual position of the renal arteries (especially in patients with hostile necks) then we use low-volume/high-flow-rate boluses of iodinated contrast (Visipaque) to finalise the renal arterial position prior to endograft deployment. Typically this reduces Visipaque usage to <10mls, as we use CO₂ for all subsequent runs including completion angiography. At EVAR, 60mls of CO₂ are injected either by hand or via a pump for an aortogram, in particular to highlight the renal arterial anatomy. For iliac runs, 30mls can be used. The real-world issue that arises is that of the operator not believing one's eyes, and thus from a pragmatic standpoint a small bolus of iodinated contrast may be merited, in particular if a patient has small renal arteries. We typically use low volume high flow rates of ICM, *e.g.* 6mls @ 30mls/sec. Nevertheless, application of pre-procedure planning insights and use of CO₂ angiography still minimise the amount of iodinated contrast used. Both end-hole or side-hole catheters may be used, and for iliac angiography at EVAR we use CO₂ 'sheathograms' (Figure 2A) with good effect, and even the completion angiogram can be undertaken using CO₂ (Figure 2B).



Figure 2A: Iliac sheathogram at EVAR. An Ovation endoprosthesis is noted deployed proximally.



Figure 2B: Completion MCDA at EVAR using a pigtail catheter. Coeliac and superior mesenteric angiograms can be noted as well as the renal arteries. No endoleaks are seen.

A gap of about 60 seconds is recommended between each injection (though some recommend longer intervals), keeping in mind that even in the right atrium, 5mls of CO₂ will take 45 seconds to clear, and this accelerates to 15 seconds in the pulmonary outflow vessels⁷.

Acceptable image quality has been obtained at the femoropopliteal (Figure 3A-i, ii), crural (Figure 3B) and even pedal (Figure 3C) segments.

MCDA is now our default approach for all peripheral interventions in patients with CKD, and whilst it is also our default for use during EVAR in patients with >CKD3, some operators at our institution are now using it routinely for all patients undergoing EVAR to promote a kidney-sparing procedure and reduce the possible long-term deterioration in renal function. This allows us to undertake EVAR with <10mls of ICM, and completely ICM-free peripheral interventions.

Discussion

CO₂ can now be delivered into the vascular region of interest without the cumbersomeness associated it with previously, though the use has been previously described by occasional enthusiasts²⁸. CO₂ application at EVAR or FEVAR is not new²⁹⁻³¹; in our own institution it is now routine to use it for all EVAR patients with CKD or contrast allergy³², and there are moves to use it routinely even in those who do not have CKD given that even such patients are susceptible to CIN. Imaging quality varies between fixed C-arm and mobile C-arm and that must be borne in mind, particularly for the renal runs. If there is any doubt then small doses of iodinated contrast may be used just for the renal runs, and this still allows us to complete a standard infrarenal EVAR with <10mls of ICM (typically Visipaque). Completion angiograms are of excellent quality, and whilst endoleaks will be revealed on CO₂ angiography³³, an absence of any type I/III endoleak is particularly reassuring. It is our view that if there is no endoleak with CO₂ then there will be no endoleak later, and that has been our experience in general. CO₂ seems very effective for completion angiography at EVAR as there is no more loss into the aneurysm sac and the graft and iliac anatomy are very clearly delineated (Figure 2).

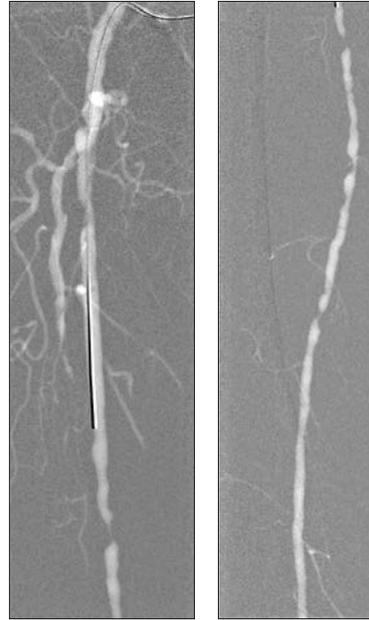


Figure 3A: MCDA at the (i) femoral bifurcation (ii) femoropopliteal station. The common femoral bifurcation is denoted and stenotic areas clearly defined.

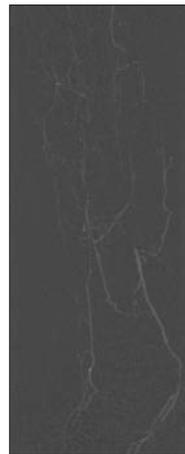


Figure 3B: MCDA at the crural station. The distal anterior and posterior tibial vessels are noted to re-form just above the ankle with filling via collateral vessels which are also clearly visible.

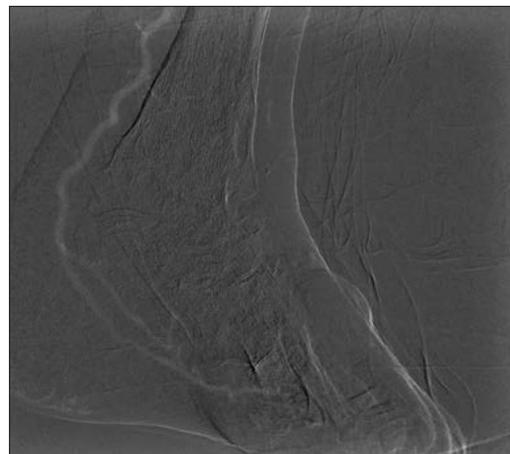


Figure 3C: MCDA at the pedal station outlining a prominent posterior tibial artery continuing on to the plantar aspect of the foot.

There is a certain learning curve to handling manual injection of CO₂ given its compressible nature- an issue eliminated by automated systems- but in our view this is a short process unlike what has been represented in the literature³⁴, much like hand injections with standard contrast. Getting the syringe pressures right is more of an issue with aortography rather than in more distal vessels because of the need to control larger volumes.

A concern that remains is that of non-occlusive mesenteric ischaemia (NOMI)³⁵; complications described may be due to embolic *i.e.* mechanical effects rather than a direct chemical effect, given that is likely that dedicated one-way tubing may not have been used, allowing inadvertent air entry into the delivery system. Furthermore, CO₂ is 28 times more soluble in blood than oxygen⁷, which adds further doubt to its role in the pathogenesis of NOMI. The potential risk for neurological complications are a concern³⁶, though experimental studies suggest that CO₂ used for cerebral angiography does not exert any directly toxic effects^{16,37}; however, other authors are clear in mentioning that CO₂ is absolutely contraindicated for cerebral angiography⁷. Milder complications such as abdominal pain and diarrhoea have also been described¹⁷, though a direct causal relationship is difficult to ascertain.

CO₂ will not provide the typical contrast-clarity provided on standard DSA, and thus IVUS has been used an imaging adjunct for percutaneous angioplasty in the iliac³⁸ or femoropopliteal and crural segments³⁹, particularly in those patients where iodinated contrast is absolutely contraindicated. With appropriate imaging tweaks we feel that IVUS is not really necessary, though still a useful tool if one has it.

Safety has never been an issue⁴⁰; even with the volumes used during aortography even our cursory review of patient capnography has shown no real change in readings. The key is to maintain reasonable intervals between injections. A comprehensive write-up on this issue by noted CO₂ angiography enthusiasts and pioneers Hawkins and Cho is recommended for those wishing to increase their knowledge on this diagnostic /therapeutic technical adjunct even further⁴¹.

In conclusion, whilst there has been recent emphasis in advances in radiation dosage reduction, less attention is paid to reduction to reduction of contrast dosage.

CO₂ angiography provides a ready alternative that has been now around for decades- with available 21st century updates- that provides reliable imaging for use in patients at risk of CIN, those with contrast allergy, and perhaps should be really brought into the interventional operator's armamentarium for routine use.

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