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Contrast alternatives for iodinated contrast allergy and renal dysfunction: Options and limitations

Gregory J. Nadolski, MD, and **S. William Stavropoulos, MD,** *Philadelphia, Pa*

Diagnostic angiography and vascular interventions make routine use of iodinated contrast material (ICM). Patients with renal disease or contrast allergy pose limitations on the use of ICM. In such cases, alternative contrast media may be used to carry out the procedure. Current alternatives include carbon dioxide, gadolinium, and dilute ICM. Each of these alternatives has its own unique features and limitations. In the present review article, the current alternatives to ICM are explored, with a focus on the applications and restrictions of each. (J Vasc Surg 2013;57:593-8.)

Patients with impaired renal function or contrast allergy pose a challenge to the safe and effective performance of diagnostic angiography and vascular interventions using iodinated contrast media. Despite the development of low and iso-osmolar iodinated contrast material (ICM) and the institution of hydration protocols, patients with chronic kidney disease (CKD), especially those with concomitant diabetes, remain at risk for contrast-induced nephropathy (CIN).[1,2] Contrast allergies are another potential barrier to the use of iodinated contrast for vascular interventions.[3,4] Although premedication with steroids and antihistamines allows iodinated contrast to be used safely in many allergic patients, occasionally patients present for procedures without having taken effective prophylaxis or having failed premedication in the past. Given the prevalence of the scenarios in which ICM poses potential serious risk to the patient, a strong interest remains in the use of alternative contrast media. Our purpose is to briefly review ICM contrast allergies and nephrotoxicity and then to review the applications and limitations of alternatives to full-strength iodinated contrast, which include carbon dioxide (CO_2), gadolinium, and dilute iodinated contrast, for patients with CKD and iodinated contrast allergies.

From the Division of Interventional Radiology, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania.

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Reprint requests: Dr S. William Stavropoulos, Division of Interventional Radiology, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104 (e-mail: stav@uphs.upenn.edu).

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IODINATED CONTRAST

Reviews devoted solely to the chemical and physical properties of iodinated contrast have been published.[5-8] In brief, all ICMs in current use are modifications of a 2,4,6-tri-iodinated benzene ring and are classified based on the physical and chemical properties of osmolality, ionization in solution, and chemical structure. Four classes of contrast are commercially available: ionic monomers, nonionic monomers, ionic dimers, and nonionic dimers. Additionally, agents can be classified by their osmolality relative to blood and typically are described as high, low, or iso-osmolar. Once administered intravascularly, these agents are rapidly distributed in the body and are excreted largely unmetabolized in the urine.

Allergic reactions to ICM. Allergic reactions to ICM occur. They typically are described as anaphylactoid because they have the features of type 4 hypersensitivity reactions but do not occur through an immunoglobulin E-mediated pathway in most cases. In fact, the exact mechanism remains unknown.[9] Mild anaphylactic reactions to high-osmolar ionic contrast occur between 4% and 12%, whereas such reactions occur in only 0.7% to 3% of patients receiving low-osmolar nonionic contrast.[10,11] Severe anaphylaxis is estimated to occur between 0.1% to 0.4% with ionic contrast material and 0.02% to 0.04% with nonionic contrast material.[10,12] Attempts to reduce contrast reactions with steroid prophylaxis (classically prednisolone 32 mg given 12 and 2 hours before the procedure) are beneficial for mild and moderate reactions but less so for severe anaphylaxis.[13,14] Additionally, breakthrough reactions occur in some patients.[4]

Contrast-induced nephropathy. Contrast-induced nephropathy is defined as acute kidney injury attributable to the administration of iodinated contrast. The exact definition of acute kidney injury for diagnosing CIN and the temporal relationship of contrast administration are still debated. Some data support an absolute rise in serum creatinine ≥0.5 within 48 hours to be a reasonable definition.[15,16] Contrast-induced nephropathy likely is the result of direct tubule toxicity and hypoxia caused by reduced blood flow and subsequent generation of reactive oxygen species.[17] The incidence of CIN is related to the dose of ICM, the route of administration (intra-arterial > intravenous), and patient factors, of which CKD with an estimated glomerular filtration rate (eGFR) <60 mL/min is the most important.[17,18] Studies have tried to identify the maximum amount of CM that can safely be injected during percutaneous coronary interventions, suggesting possible limits of ICM dose in grams of iodine equal to the eGFR or keeping the ratio of the CM volume to the creatinine clearance <3.7. However, a safe dose of ICM has not been established for patients with CKD.[19] Multiple meta-analyses regarding prevention of CIN have been conducted using hydration protocols and various oral medications thought to be renal protective. Most authors conclude that intravenous hydration is of some benefit. Comparison of hydration protocols and oral agents is beyond the scope of this review. For a more detailed review, see van der Molen et al.[2,19]

ALTERNATIVE CONTRAST AGENTS

Carbon dioxide

Principles of carbon dioxide and its advantages. Carbon dioxide (CO_2) is a highly soluble, invisible gas. When injected into vessels, it briefly displaces the blood before it is rapidly dissolved and eliminated through exhalation.[20] The unique properties of CO_2 give it several advantages over other contrast media. Foremost, CO_2 is nonallergenic and nonnephrotoxic, making it safe for use in patients with either contrast allergy or kidney disease.[21-25] Essentially unlimited volumes of CO_2 can be used, assuming sufficient time is allowed for the gas to be eliminated from the body. Carbon dioxide even is safe in patients with chronic lung disease with CO_2 retention, as long as additional time is taken between injections to allow for the gas to be cleared by the lungs.[26] Further benefits include its low viscosity relative to blood, which can aid in the detection of subtle bleeding.[27] Carbon dioxide's low viscosity additionally can improve visualization of small collateral vessels and aid in identifying distal reconstitution in patients with peripheral arterial disease.[21] Lastly, medical-grade CO_2 is very inexpensive compared with iodinated contrast and is readily available.

Limitations and complications of CO_2. However, CO_2 is not without limitations. Given the possibility of neurotoxicity, CO_2 cannot be injected or allowed to enter the cerebral circulation.[28] Thus, CO_2 should be used only for infradiaphragmatic arteriography. Central venography above the diaphragm is still permissible with CO_2 and, in fact, may be more sensitive for detecting central venous stenosis.[26] The rare complication of air trapping, or vapor lock, is another limitation. If an excessive volume of CO_2 is injected at once or the blood–gas interface is reduced, normal dissolution of CO_2 into the bloodstream may not occur. The undissolved bolus of gas may then impede blood flow and produce ischemia.[29] Nondependent locations such as aortic aneurysms, the pulmonary outflow tract, and the mesenteric vessels are most at risk.[30] Typically, vapor lock can be broken by changing the patient's position or by aspiration of the CO_2. If CO_2 arteriography is being used near or in a vessel at risk for vapor lock, periodic fluoroscopy between injections is advisable. If residual gas is seen between injections, the patient's position should briefly be changed to move the CO_2 bolus into a different vessel to allow dissolution.[31] The theoretical risk of air trapping increases with introduction of less soluble gases from room air contamination and the use of nitrous oxide as an inhaled anesthetic. Nitrous oxide may dissolve out of the soft tissues and into the intravascular CO_2 bolus, rapidly increasing its volume and its potential to create a vapor lock.[29]

Another barrier is ease of use. Because a dedicated CO_2 injector or bag delivery system is not available in the United States, practitioners may be unfamiliar with administration of CO_2. Most physicians use a system of tandem three-way stopcocks or a three-way stopcock and a flow switch (Fig 1). Contamination with less soluble room air could occur if a stopcock or flow switch is left open.[26] Because both gases are invisible, contamination of CO_2 with room air is impossible to detect. Special attention must be given to purging syringes of air and, once filled with CO_2, not allowing valves to be left open. Carbon dioxide has been shown to accurately measure vessel diameter (Fig 2). However, improper injection of CO_2 can lead to errors in measurement.[21,32] CO_2 is buoyant relative to blood and therefore rises to the nondependent portion of the vessel. If insufficient volumes of CO_2 are injected into large vessels, the operator may underestimate the true size of the vessel (Fig 3). Alternatively, if the bolus is delivered in an explosive manner, the operator may overestimate vessel diameter.[33]

Optimizing image quality with CO_2. Unfamiliar users may be uncertain of how to optimize image quality for their procedures. With the development of digital subtraction angiography and image stacking software, use of CO_2 as a contrast agent has became a viable option. Hawkins[21] first reported his pioneering use of CO_2 as an intravascular contrast agent in the early 1980s. Most modern angiography suites come with preinstalled settings to optimize image quality for CO_2 angiography. Typically, inversion opacification software is used with a frame rate of three to six per second using a 60-ms exposure time.[26] To prevent explosive delivery of CO_2, blood should be purged from the catheter with CO_2 before subtraction angiography is performed. A less explosive injection will reduce patient discomfort and thus motion artifact. Proper injection rate also reduces fragmentation of the CO_2 bolus, which, when combined with the buoyancy of CO_2, can give the illusion of a stenosis.[34] If fragmentation occurs, image stacking may be used to improve image quality. If stacking is unavailable or does not resolve the problem, a repeat angiogram with a longer injection (and larger volume of CO_2) can be performed.[26] Vessel-specific protocols for CO_2 arteriography are beyond the scope of

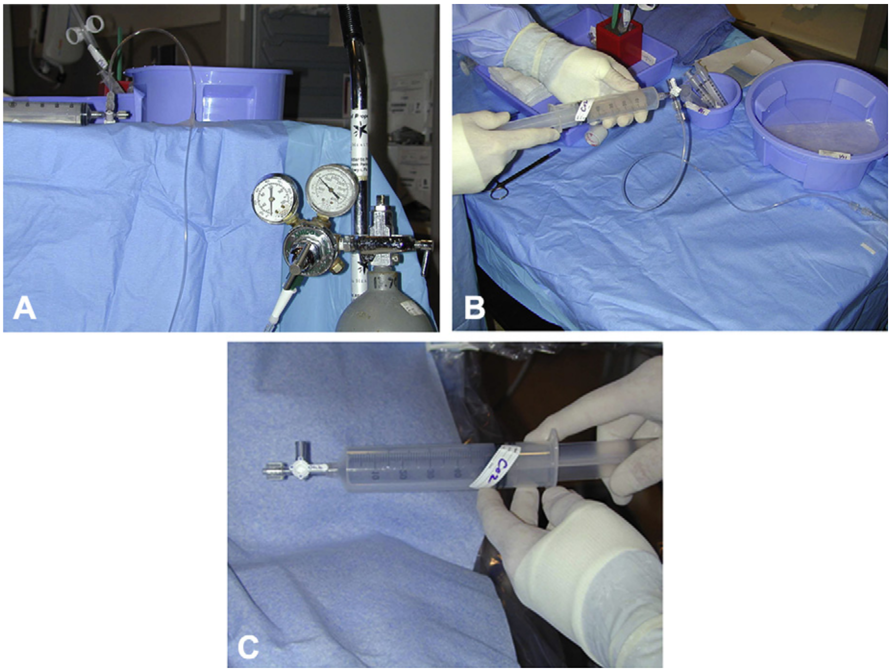

Fig 1. A, Tandem three-way stopcocks with extension tubing and 60-mL syringe used to administer carbon dioxide (CO_2) for angiography. **B,** Filling the syringe with CO_2. **C,** Disconnect syringe from tubing that is connected to the CO_2 canister. Close three-way stopcock. The syringe is not ready to connect to the diagnostic catheter.

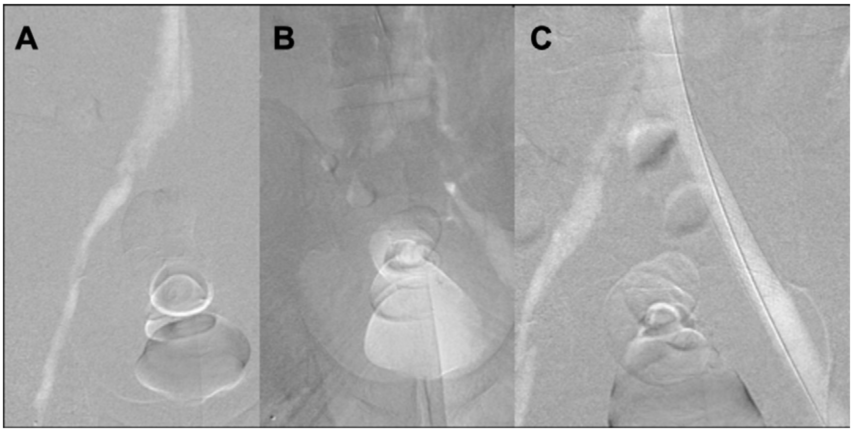

Fig 2. Diagnosis of May-Thurner syndrome and treatment using carbon dioxide (CO_2). Cavogram and bilateral iliac venogram demonstrate normal right iliac vein **(A)** and extrinsically compressed left common iliac vein **(B)**. Accurate estimation of vessel size for stent placement can be obtained with CO_2. Poststent venogram demonstrates brisk flow into the inferior vena cava with appropriately sized and properly apposed stent in the left common iliac **(C)**.

this review. A detailed protocol for aortogram with runoff can be found in Hawkins et al.[26]

Dilute iodinated contrast

Advantages and use of angiography in patients with CKD. Another alternative for patients with CKD undergoing vascular interventions is dilute ICM. The principal advantage of using diluted ICM is the operator's familiarity with administration during diagnostic angiography and endovascular procedures. Its use has primarily been studied in dialysis fistulography and venous mapping. In 28 patients undergoing venous mapping, Won et al[35] demonstrated no significant difference in eGFR at baseline and 4 days after receiving 10 to 15 mL of iodinated contrast diluted 1:1 with

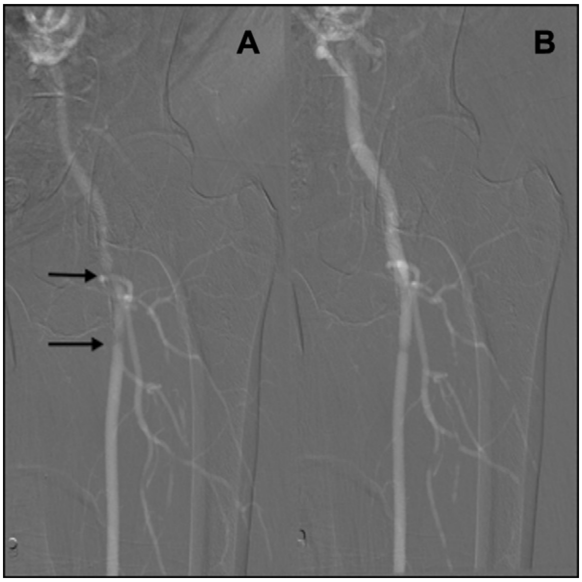

Fig 3. Leg arteriogram demonstrating pseudostenosis. **A,** Left leg arteriogram depicting stenosis in left common femoral artery and proximal left superficial femoral artery (*arrows*). **B,** Repeat arteriogram with the patient's leg elevated and with more forceful injection showing the suspected lesion in the common femoral artery was a pseudostenosis, while the stenosis of the superficial femoral artery was overestimated. Both occurred due to poor injection technique and underfilling of the vessel.

Fig 4. Use of carbon dioxide (CO_2) in conjunction with dilute contrast. Aortogram with CO_2 identifies single left renal artery (*white arrow*) and large hypervascular left renal mass (*black arrow*). Dilute contrast was used for selective renal arteriogram before embolization of the mass (image not shown).

saline. In this study, only one patient developed CIN, which resolved within 1 week.[35] Similarly, patients with stage 4 kidney disease (eGFR <30 mL/min) undergoing fistulography and intervention who are hydrated with a weight-based bicarbonate protocol and receive <20 mL of ICM diluted 1:2 with normal saline have a reported CIN incidence of 5.5%.[36]

Limitations of dilute contrast. Several limitations of dilute ICM exist. First, it cannot be used as an alternative in patients with anaphylactic allergy to ICM. Second, the operator is still limited with regard to the total volume of contrast that can safely be used without putting patients at risk for CIN. Lastly, if overly dilute, the contrast may not be rendered optimal image quality in large vessels within the abdomen or thorax. Given the limited advantages of dilute ICM, we typically reserve its use for extremity angiography, fistulography, and selective arteriography as a supplemental tool for use with CO_2 (Figs 4 and 5).[37]

Gadolinium

Nephrogenic systemic sclerosis and the limited role of gadolinium. Gadolinium once was heralded as an alternative contrast agent in patients with CKD. Since its association with the disease nephrogenic systemic fibrosis (NSF) in 2006, its use as an angiographic agent in patients with CKD has appropriately declined rapidly.[38]

Nephrogenic systemic fibrosis is an illness that presents with firm, erythematous, and indurated plaques of the skin associated with subcutaneous edema involving the extremities.[39] It can progress to flexion contractures with limited range of motion, pain, paresthesias, and/or severe pruritus. Currently, no effective treatment of NSF is available.[39] Knowledge of NSF's pathogenesis, risk factors for acquiring it, and its exact relationship to gadolinium is still not completely elucidated.[39,40] Studies suggest that slow excretion of gadolinium-based contrast media in patients with severe renal impairment allows lower-stability gadolinium chelates to dissociate, releasing free gadolinium, which incites the disease.[41]

The overall incidence of NSF is difficult to assess but may be as high as 3% to 7% in patients with severe CKD.[42] In a study of 33 patients presenting with NSF, all patients had eGFR <15 mL/min at the time of gadolinium administration. Four of these patients had received gadolinium during arteriography.[40] Although the incidence is low and the exact relationship between gadolinium and NSF is not fully known, its use in patients with severe CKD (eGFR <15 mL/min) is not recommended by the United States Food and Drug Administration and the American College of Radiology.[43] Furthermore, studies have shown gadolinium chelates to be nephrotoxic in patients with stage 3 and 4 CKD (eGFR <60 mL/min) when used in equivalent X-ray attenuating doses with a reported incidence of gadolinium CIN of 1.9%.[1,44,45] In fact, the use of gadolinium as an alternative contrast agent in patients with any

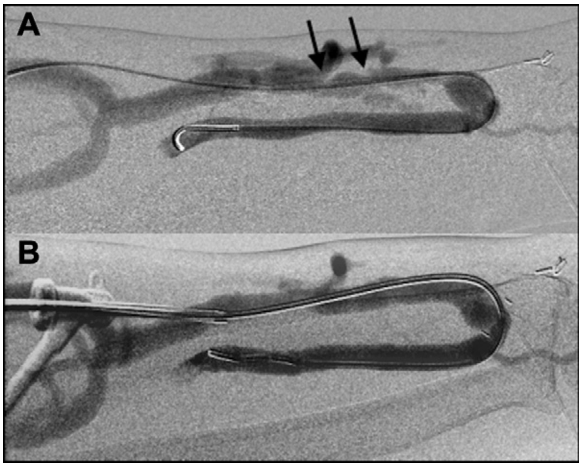

Fig 5. Use of dilute contrast to supplement carbon dioxide (CO_2) in upper extremity fistulogram performed in a patient with residual renal function. Retrograde access to the fistula was achieved directed toward arterial anastomosis. The radial artery was selected with a Binkert catheter. **A,** Fistulogram performed using dilute iodinated contrast material demonstrating two tandem stenoses in the perianastomotic vein (*black arrows*). **B,** Postangioplasty fistulogram with dilute iodinated contrast material (ICM) demonstrating no residual stenosis. The remainder of the fistulogram, including central venography, was completed using CO_2 (image not shown).

degree of renal impairment is not advised by several consensus groups.[1,44] In summary, the application of gadolinium as an ICM alternative for angiography is essentially limited to patients with normal renal function who have anaphylactic reaction to ICM.

Limitations of gadolinium in patients with normal renal function. Even in this scenario, gadolinium has several challenges and limitations. The physical properties of gadolinium are different from those of iodine, and the contrast produced by gadolinium chelates using standard angiographic settings is similar to that of dilute contrast. Adjustments to the peak voltage of the X-ray source can result in contrast similar to that of full-strength ICM.[46] Gadolinium is in such low concentration in current commercially available chelates that it cannot be visualized under fluoroscopy. Thus, all test injections must be performed using digital subtraction angiography. The total volume of gadolinium chelate injected is typically limited to 0.3 mmol/kg to prevent nephrotoxicity (approximately between 42 and 56 mL for a 70-kg man depending on the chelate used).[1,47]

SUMMARY

Impaired renal function and allergic reactions can limit the typical use of ICM for diagnostic arteriography and vascular interventions. Several alternatives, each with its unique benefits and limitations, exist for use in these scenarios. Patients with normal renal function but contrast allergy ideally should receive appropriate prophylaxis, and ICM can be used. If prophylaxis cannot be administered or has been ineffective in the past, CO_2 is our preferred alternative contrast, with gadolinium being reserved for arteriography of the arch vessels. In the setting of CKD, our preferred alternative contrast is CO_2, which may be supplemented with a limited volume of ICM, which can be diluted to provide a greater volume. We do not recommend the use of gadolinium in patients with CKD.

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Analysis and interpretation: SS, GN
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Writing the article: SS, GN
Critical revision of the article: SS, GN
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