Automated Carbon Dioxide Digital Angiography for Lower-Limb Arterial Disease Evaluation: Safety Assessment and Comparison With Standard Iodinated Contrast Media Angiography

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ABSTRACT: Introduction. Carbon dioxide (CO_2) has been validated as a contrast agent in a large series of studies. A particular advantage of CO_2 over iodinated contrast medium (ICM) is the absence of nephrotoxicity and allergic reactions. One of the limitations of CO_2 angiography is the difficulty of CO_2 manual injection due to its compressibility. The manual gas injection does not permit optimal control of the gas output. Development of an automated CO_2 injector has overcome these problems. **Aim.** This study compares the feasibility, safety, and diagnostic accuracy of automated CO_2 digital subtraction angiography (DSA) in comparison with ICM-DSA in the evaluation of critical limb ischemic (CLI) patients. **Methods.** We performed DSA with both CO_2 and ICM on 40 consecutive CLI patients and directly compared the two techniques. Sixteen females and 24 males participated in the study (mean age, 71.7 years). We assessed the diagnostic accuracy of CO_2 in identifying arterial stenosis in the lower limb, with ICM-DSA used as the gold standard. **Results.** The overall diagnostic accuracy of CO_2-DSA was 96.9% (sensitivity, 99.0%; specificity, 96.1%; positive predictive value, 91.1%; negative predictive value, 99.6%). Tolerable minor symptoms occurred in 3 patients. No allergic reactions or significant decline in renal function were observed in patients receiving the CO_2 injection. **Conclusion.** Carbon dioxide DSA is a valuable and safe alternative to traditional ICM-DSA for evaluating CLI patients. This modality should be considered as the standard choice for CLI patients undergoing angiographic evaluation who are known to have renal insufficiency or contrast allergy.

Carbon dioxide (CO_2) has been used for diagnostic purposes in humans since the early 1900s.[1,2] It is currently used as an alternative to iodinated contrast media (ICM) in several diagnostic and interventional procedures.[3-8] Studies have shown potential benefits in the use of CO_2 over ICM for digital subtraction angiography (DSA) vascular imaging.[3-5] Carbon dioxide is an inexpensive gas that is widely available, providing cost savings compared with traditional ICM. It is highly soluble in blood (20 times more soluble than oxygen) and is rapidly eliminated by the lungs in the first pass, allowing the injection of almost unlimited quantities of gas provided that adequate time for elimination is allowed between injections.[9] Carbon dioxide has no known inherent nephrotoxicity, making it desirable for evaluating patients with evidence of renal dysfunction.[3,5,9,10] Additionally, there is no potential for allergic contrast reactions. Because of the low viscosity of CO_2 (400 times less than ICM), smaller angiographic catheters may be used, and the filling of severely diseased stenotic vessels may be enhanced.[11] During the injection, the gas displaces the column of blood and acts as a negative contrast agent. The small change in density between a blood vessel containing blood and a blood vessel containing gas can

be demonstrated using DSA. The CO_2 x-ray absorption is roughly one-tenth of the absorption obtained with diluted iodine.[4,11,12] For these reasons, both the injection process and the radiologic set-up must be optimized to yield good-quality angiographic images.[13-15] Various authors have described their experience with catheter-based angiography using CO_2 as the radiographic contrast agent for the evaluation of arterial and venous diseases. These reported uses have included diagnostic evaluations of the abdominal[8,13-15] and extremity vessels,[6,16-18] renal transplants,[19] tumors,[20] and hemodialysis access sites.[7] Therapeutic interventions such as balloon angioplasty,[21,22] stent placement,[18,21,22] caval interruption procedures,[23,24] and transjugular intrahepatic portosystemic shunts[25] using CO_2 as the contrast agent have also been reported. Despite these encouraging results, the use of CO_2 as a contrast agent in the evaluation and treatment of peripheral arterial disease (PAD) has not been as prevalent as expected. There are various explanations for this occurrence. The use of a gas rather than a liquid contrast agent changes some steps in the process of angiography that may be unfamiliar to vascular interventionalists. The injection of a gaseous element, which is mostly performed by hand, requires a long training period, and the vascular image results are not

Table 1. Population characteristics.

Female gender	16 [40%]
Age [years]	71.7 ± 7.2
Diabetes	24 [60%]
Hypertension	23 [57.5%]
Coronary artery disease	9 [22.5%]
Hypercholesterolemia	28 [70%]
Transient ischemic attack	4 [10%]
Chronic obstructive pulmonary disease	5 [12.5%]
Smoker	17 [42.5%]
Creatinine ≥1.3 mg/dL	20 [50%]
Creatinine ≥2 mg/dL	11 [27.5%]
Data presented as mean ± standard deviation or number (percentage).	

Table 2. Peripheral arterial disease prevalence.

Fontaine Stage	Patients	Rutherford Stage	Patients
I	0	0	0
IIa	8 [20%]	1	8 [20%]
IIb	22 [55%]	2	9 [22.5%]
III	8 [20%]	3	13 [32.5%]
IV	2 [5%]	4	8 [20%]
		5	2 [5%]
		6	0

Table 3. Carbon dioxide angiography diagnostic accuracy in the above-the-knee, below-the-knee, and overall districts.

	ATK	BTK	Overall
Sensitivity	100 [93.5-100]	97.9 [88.9-99.9]	99.0 [94.7-100]
Specificity	96.2 [92.4-98.5]	95.8 [88.3-99.1]	96.1 [93.0-98.1]
PPV	88.7 [78.1-95.3]	94.0 [83.5-98.7]	91.1 [84.2-95.6]
NPV	100 [97.9-100]	98.6 [92.3-100]	99.6 [97.8-100]
Accuracy	97.1 [94.1-98.8]	96.7 [91.7-99.1]	96.9 [94.6-98.5]

ATK = above the knee; BTK = below the knee; PPV = positive predictive value; NPV = negative predictive value.

always ideal due to the mechanical behavior and the small radiological absorption coefficient of the gaseous contrast medium.[4-11,26] Expert operators insist that a long period of empirical training is required to obtain good-quality images. This training is necessary to acquire the skill to control the hand injection and to become accustomed to the natural properties of CO_2 to obtain optimal gas filling of the vessels, particularly in the distribution of the vessels below the

knee.[16,17,26] The main limitation of CO_2 use in angiography is the unreliability of the CO_2 injection; its compressibility and possible contamination with air can lead to a potentially fatal complication.[27] The development of an automated CO_2 injector (Angiodroid, Angiodroid SRL) has addressed these problems. This automatic gas injector with low-pressure automatic line washout may limit the risk of liquid jet injury and optimize vessel imaging through an optimal regulation of the amount and flow of the injected gas.[26]

The aim of this study was to compare the feasibility, safety, and diagnostic accuracy of automated CO_2-DSA with standard ICM-DSA in the evaluation of PAD.

Methods

Patients. During an 8-month period, from September 2012 to April 2013, a total of 40 CLI patients underwent lower-limb angiography with both ICM and CO_2 contrast agents to directly compare the two techniques. Sixteen female and 24 male patients participated; their mean age was 71.7 years (range, 50-82 years). The baseline clinical characteristics of the treated patients are shown in Tables 1 and 2. Medical illnesses included the following: diabetes in 24 patients; chronic renal insufficiency in 31 patients; hypertension in 23 patients; stable coronary artery disease in 9 patients; mild chronic obstructive pulmonary disease (COPD, stage I GOLD classification) in 5 patients; and cerebrovascular disease in 4 patients. Exclusion criteria were: COPD stage II, III, or IV GOLD classification; severe ischemic limb ulcers or frank gangrene (category 6 Rutherford classification); atrial and ventricular septal defects; or pulmonary arteriovenous malformation. Study approval was obtained from the local ethics committee, and informed consent was obtained from each patient at the time of the investigation. The patients who consented to participate in the study had angiography performed with both CO_2 and ICM to directly compare the two techniques. CO_2-DSA was performed before ICM-DSA in the same procedure.

CO_2 and ICM digital angiography. All patients received the same preparation they would receive for iodinated angiograms. Angiography was performed via femoral arterial puncture. CO_2 was delivered using the Angiodroid CO_2 injector via a straight selective 4 Fr catheter positioned at three different levels: common iliac artery, common femoral artery, and popliteal artery. The volume of gas injection was chosen considering the injection site: between 40 mL (popliteal artery) and 60 mL (iliac and femoral arteries) of CO_2 were used per injection at 300-400 mm Hg of pressure. In each patient, we performed an average of 6 CO_2 injections. The total average volume of CO_2 used was 240 ± 80 mL. For lower-extremity procedures, elevation of the extremity often enhanced the quality of the images by taking advantage of the lower density of CO_2 compared to blood. DSA images were obtained in an anteroposterior (AP) projection and in both oblique projections. At least 2 minutes

Table 4. Carbon dioxide digital subtraction angiography diagnostic accuracy in the 9-district model.

	CIA	EIA	CFA	PFA	SFA	PA	ATA	PTA	PEA
Sensitivity	100 [29-100]	100 [59-100]	100 [48-100]	100 [29-100]	100 [88-100]	100 [59-100]	92.3 [64-100]	100 [84-100]	100 [77-100]
Specificity	100 [91-100]	90.9 [76-98]	97.1 [85-100]	97.3 [86-100]	90.0 [55-100]	97.0 [84-100]	96.3 [81-100]	100 [82-100]	92.3 [75-99]
PPV	100 [29-100]	70.0 [35-93]	83.3 [36-100]	75.0 [19-99]	96.8 [83-100]	87.5 [47-100]	92.3 [64-100]	100 [84-100]	87.5 [62-98]
NPV	100 [91-100]	100 [88-100]	100 [90-100]	100 [90-100]	100 [66-100]	100 [89-100]	96.3 [81-100]	100 [82-100]	100 [86-100]
Accuracy	100 [91-100]	92.5 [80-98]	97.5 [87-100]	97.5 [87-100]	97.5 [87-100]	97.5 [87-100]	95.0 [83-99]	100 [91-100]	95.0 [83-99]

PPV = positive predictive value; NPV = negative predictive value; CIA = common iliac artery; EIA = external iliac artery; CFA = common femoral artery; PFA = profunda femoral artery; SFA = superficial femoral artery; PA = popliteal artery; ATA = anterior tibial artery; PTA = posterior tibial artery; PEA = peroneal artery.

were allowed between injections to ensure complete excretion of CO_2. All studies were performed using the GE Innova DSA system (GE Medical Systems) with a postprocessing software for CO_2 images. A high-mA (90 mA) and low-kV (70 kV) technique was used. Because of the quick passage of the CO_2 through the blood stream, increased frame rates were generally required to acquire pictures (7 frames/s is a typical setting for most systems). Iodinated contrast medium angiography was performed using iodixanol 320 mg/mL (Visipaque; GE Healthcare) via 4 Fr Pigtail catheter positioned at the abdominal aortic bifurcation. Between 15-20 mL of iodixanol were used per injection and the total volume average of contrast medium used was 150 ± 50 mL. Patients were questioned at the time of the study regarding any symptoms experienced during or following the CO_2 and ICM injections. Following the investigation, the patients were observed for 48 hours and any clinical incidents were recorded.

Nine-territory lower-limb angiography model. For the comparison of the two investigative methods, we used a 9-territory angiographic model. Six territories were included in the first district above the knee (ATK: common iliac artery, external iliac artery, common femoral artery, profunda femoral artery, superficial femoral artery, and popliteal artery). Three territories were included in the second district below the knee (BTK: anterior tibial artery, posterior tibial artery, and peroneal artery). Evaluation and comparison of ICM-DSA and CO_2-DSA were conducted independently by two operators who did not perform the arteriography procedure. A stenosis was considered significant if it was greater than 50% by visual estimate.

Statistical analysis. Descriptive statistics (counts and percentages, means ± standard deviations) are presented for patients' demographic and clinical characteristics. The change in serum creatinine level pre-DSA and post-DSA was evaluated with a paired 2-tailed Student's t-test. The performance of CO_2-DSA for diagnosis of significant stenosis compared with the gold-standard ICM-DSA method was determined with regard to sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and corresponding 95% confidence intervals (CIs). Because the values of the sample proportions were very close to 1, we did not use the normal approximation to compute CIs. The Clopper-Pearson interval was used, and the exact method was based directly on the binomial distribution. The main analysis was performed at the level of ATK, BTK, and overall districts. Secondary analyses were performed at the level of the 9 districts taken individually. The data were collected and reviewed in Microsoft Excel, and statistical analysis was performed with SPSS 13.0 (SPSS, Inc).

Results

The two investigative methods were compared by analysis of the nine territories in the entire group of 40 patients with a total number of 360 evaluated segments. Table 3 shows an overall diagnostic accuracy of 96.9% for CO_2-DSA, using ICM-DSA as the gold standard (sensitivity, 99.0%; specificity, 96.1%; PPV, 91.1%; NPV, 99.6%). The diagnostic accuracy was 97.1% in the ATK district (sensitivity, 100%; specificity, 96.2%; PPV, 88.7%; NPV, 100%) and 96.7% in the BTK district (sensitivity, 97.9%; specificity, 95.8%; PPV, 94.0%; NPV, 98.6%). The diagnostic accuracy values of CO_2-DSA in the 9 districts taken individually are shown in Table 4.

No significant decline in renal function was observed in patients with a normal basal creatinine value (average, 0.10 mg/dL), but the average increase in serum creatinine level was 0.24 mg/dL ($P<.001$) in patients who were considered most at risk (serum creatinine level ≥2 mg/dL). Tolerable minor symptoms, including foot pain, occurred in 3 patients, and 1 patient experienced nausea. No cardiovascular events were noted while monitoring the patients during and after the CO_2 injections. No life-threatening complications occurred during the use of CO_2-DSA. No allergic reactions were noted following CO_2 injection, although 3 patients experienced reversible cutaneous erythema after ICM injection.

Discussion

Carbon dioxide has several attractive properties as an intravascular contrast agent. It is non-allergenic, eliminating the possibility of fatal hypersensitivity reactions.[27-29] Allergic reactions requiring some form of medical intervention may complicate up to 5% of all conventional angiography investigations.[28,29] Both ionic and non-ionic ICM can cause fatal allergic reactions.[30] Pretreatment with high–dose corticosteroids can prevent contrast-related anaphylactic reactions, but CO_2-DSA eliminates the need for such pretreatment. In this study, 3 patients (7.5%) experienced diffuse cutaneous erythema after ICM injection, which resolved with the administration of intravenous corticosteroids.

In addition, there is no evidence in either clinical experience or animal studies to suggest that CO_2 is nephrotoxic.[31] Deterioration in renal function following ICM arteriography has been reported to occur in up to 11% of all patients; most of these patients are diabetic, with laboratory evidence of renal insufficiency.[32,33] Iodinated contrast medium arteriography led to the need for permanent dialysis in 8% of patients with a serum creatinine >1.8 mg/dL or blood urea nitrogen >30 mg/dL.[34] Because chronic renal insufficiency with or without diabetes is present in many patients with symptomatic PAD, the risk of inducing renal failure in this patient population has precluded the use of arteriography. Although the advantage of using CO_2-DSA in patients with renal dysfunction is clearly demonstrated in the literature, and although patient hydration, bicarbonate infusion, and N-acetylcysteine have been used in an attempt to reduce the nephrotoxic effects of iodinated contrast, contrast nephrotoxicity remains an issue.[35,36] In this study, no significant decline in renal function was found in patients with a normal basal creatinine value (average, 0.10 mg/dL), but the average increase in serum creatinine level was 0.24 mg/dL (P<.001) in patients considered most at risk (serum creatinine level ≥2 mg/dL). Because both contrast agents were administered in the same session, the increase in serum creatinine levels was attributed to the use of ICM, since there is no evidence in clinical experience or animal studies of nephrotoxicity associated with CO_2 use.

The properties of CO_2 allow it to be used effectively in patients with renal failure and patients who are allergic to ICM. These properties obviate the need for preangiography hydration in patients in whom cardiac and renal (or other metabolic) dysfunctions coexist. CO_2 can be used in sequential studies on consecutive days, as is frequently required for completion of endovascular procedures.

Many interventionalists expressed concern about the adequacy of imaging using CO_2 in the lower extremities, particularly in smaller BTK vessels. Several studies have reported the use of CO_2 as an alternative to ICM agent with a good diagnostic quality in lower-limb arteries located ATK.[37-39] In a study by Rolland et al, the imaging quality of CO_2-DSA was comparable to ICM-DSA at the pelvis in 93% and at the thigh in 74% of 120 arteries studied.[39] The same quality was achieved distally in only half of the cases. Oliva et al found no significant differences in the mean stenosis values obtained with CO_2 or ICM in any segment for any of the observers;[37] however, imaging of BTK vessels using CO_2 has not been reported to show such favorable results.[40-42] In our series, CO_2 angiography showed a diagnostic accuracy of 97.1% in the ATK district and 96.7% in the BTK district (Table 1). There are several reasons for these results: the prevalence of patients with a complete occlusion of the proximal vessels, the site of the CO_2 injection, the use of the CO_2 delivery system, and the use of CO_2-dedicated postprocessing software.

In the referenced studies, inadequate opacification of the BTK vessels by CO_2 could be related to the high prevalence of patients with complete occlusion of the proximal vessels, which causes slow distal flow. In patients in whom aortic injection of CO_2 was used for bilateral lower-limb evaluation, there was a fragmentation of the CO_2 gas column, which degrades the image quality, especially in the BTK arteries.[17] In our study, the CO_2 was administered selectively in the lower limbs and in the presence of a complete artery occlusion by placing the catheter proximal and as close as possible to the occlusion. Several authors[16,39] have suggested selective arterial injection in cases of suboptimal opacification due to fragmentation. Hawkins and Caridi suggested that the catheter should be placed as close as possible to the lesion to improve the filling of the vessel with the gas.[43]

Another issue to consider is that CO_2 was delivered intravascularly by a hand injection with a 50 mL syringe in most studies. Because CO_2 gas in compressible syringes is loaded under pressure from CO_2 cylinders, these syringes contain indeterminate amounts of CO_2. In contrast to liquid injections, in which the rate of delivery remains constant, the rate of CO_2 delivery increases exponentially toward the end of injection.[9] In our opinion, this produced inconsistent CO_2 delivery, and consequently, poor vessel filling.

The high value of overall diagnostic accuracy of CO_2-DSA evidenced by our study (96.9%) was determined by using automated injection of the gas. This automated injection allowed us to take full advantage of the physical characteristics of the gas, drastically reducing the risks associated with manual injection. The automated CO_2 angiography was safer due to the internal circuit of the injector, which maintained positive pressure to prevent the introduction of air from outside the system. The CO_2 procedure was fully automatic, repeatable, and independent of the operator. Once the volume and pressure parameters were set up, the injector automatically handled the injection of the gas toward the infusion line.

As a final point, the use of CO_2 as an intraarterial contrast agent also required the use of digital subtraction technology. This technology detects a very low concentration of contrast agent by subtracting the presence of soft tissue before
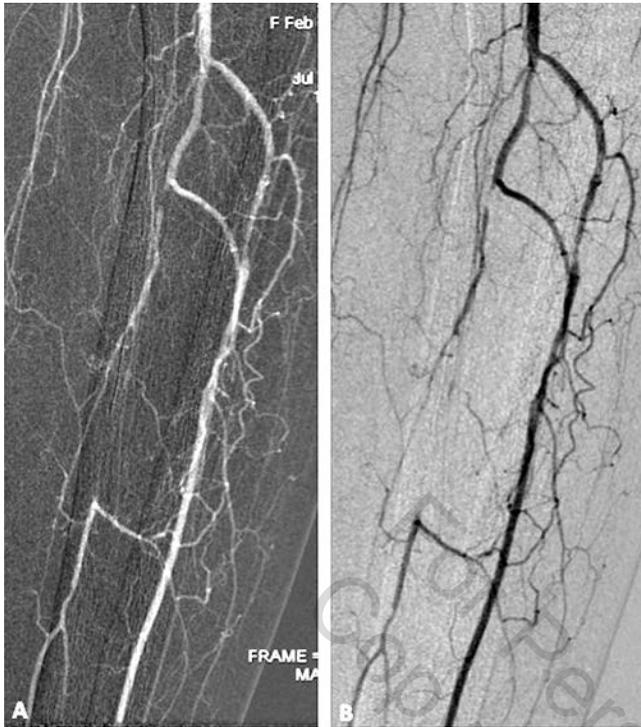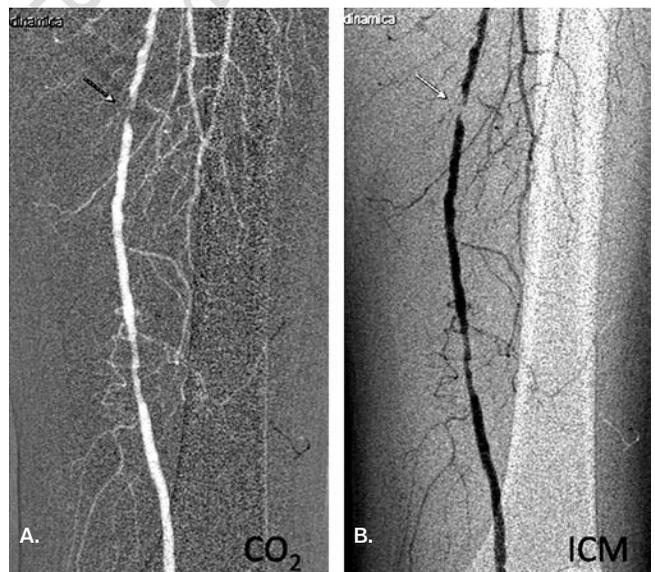
FIGURE 1. Below-the-knee imaging comparing (A) carbon dioxide (CO_2) angiography and (B) iodinated contrast media (ICM).

FIGURE 2. Femoropopliteal bypass imaging comparing (A) iodinated contrast media (ICM) and (B) carbon dioxide (CO_2) angiography.

contrast injection and enhancing the postcontrast images through manipulation and amplification of a digitized radiographic image. Current angiography procedures are now set up with CO_2 postprocessing "stacking" software. CO_2 produces contrast by causing complete displacement of the blood column in the vessel. In each x-ray acquisition, the CO_2 will sometimes fail to opacify the entire field during the same run. For postprocessing visualization of the entire vasculature, "stacking" techniques are used to stack the individual images on top of each other to form a single composite image.[9] The ability to stack these images is essential for obtaining a final picture that delineates the true anatomy. By employing some of the strategies previously mentioned, excellent imaging of the lower extremities can be obtained (Figures 1, 2, and 3)

Finally, consideration must be given to the ability of the automated CO_2 procedure to be painless for the patient. The definition and control of injection pressure allows the operator to maintain an acceptable pressure of the gas injection into the artery. Excessive pressure normally causes pain for the patient in the manual procedures, because it is basically impossible to control low pressure values. In our study, only 3 patients experienced transient foot pain after CO_2 injection. CO_2 as a contrast agent is very inexpensive; however, the cost of the injector is several thousand euros, and the cost of the connectors that transmit CO_2 from the injector to the catheter must also be considered.

FIGURE 3. Superficial femoral artery imaging comparing (A) carbon dioxide (CO_2) angiography and (B) iodinated contrast media (ICM).

As technology advances, this imaging will likely continue to improve, making CO_2 arteriography a valuable tool in the armamentarium of the vascular interventionalist when evaluating the lower extremities. This approach represents a potential imaging alternative, or supplement, to standard contrast agents for patients who are candidates for an endovascular procedure but are at high risk for contrast–related complications.

Conclusion

CO_2-DSA using the Angiodroid automated delivery system is a safe alternative technique for the evaluation of patients with PAD of the lower limbs. Adequate opacification of the ATK and BTK arteries can be obtained with proper injection technique. We suggest that CO_2 should be used as the initial contrast agent for the evaluation of PAD in patients with renal failure and iodine contrast allergy. For infrapopliteal segment opacification, we recommend selective injection as close to the target artery as possible. To maximally optimize imaging, the proceduralist must take advantage of the special properties of CO_2. This requires some changes in angiographic techniques from contrast preparation to image postprocessing.

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