Carbon dioxide (CO\textsubscript{2}) has been used for diagnostic purposes in humans since the early 1900s.\textsuperscript{1,2} It is currently used as an alternative to iodinated contrast media (ICM) in several diagnostic and interventional procedures.\textsuperscript{3-8} Studies have shown potential benefits in the use of CO\textsubscript{2} over iodinated contrast medium (ICM) for digital subtraction angiography (DSA) vascular imaging.\textsuperscript{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.\textsuperscript{9} Carbon dioxide has no known inherent nephrotoxicity, making it desirable for evaluating patients with evidence of renal dysfunction.\textsuperscript{3,5,9,10} Additionally, there is no potential for allergic contrast reactions. Because of the low viscosity of CO\textsubscript{2} (400 times less than ICM), smaller angiographic catheters may be used, and the filling of severely diseased stenotic vessels may be enhanced.\textsuperscript{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\textsubscript{2} x-ray absorption is roughly one-tenth of the absorption obtained with diluted iodine.\textsuperscript{4,11,12} For these reasons, both the injection process and the radiologic set-up must be optimized to yield good-quality angiographic images.\textsuperscript{13-15} Various authors have described their experience with catheter-based angiography using CO\textsubscript{2} as the radiographic contrast agent for the evaluation of arterial and venous diseases. These reported uses have included diagnostic evaluations of the abdominal\textsuperscript{8,13-15} and extremity vessels,\textsuperscript{5,16-18} renal transplants,\textsuperscript{19} tumors,\textsuperscript{20} and hemodialysis access sites.\textsuperscript{7} Therapeutic interventions such as balloon angioplasty,\textsuperscript{21,22} stent placement,\textsuperscript{18,21,22} caval interruption procedures,\textsuperscript{23,24} and transjugular intrahepatic porto-systemic shunts\textsuperscript{25} using CO\textsubscript{2} as the contrast agent have also been reported. Despite these encouraging results, the use of CO\textsubscript{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.
always ideal due to the mechanical behavior and the small radiological absorption coefficient of the gaseous contrast medium. 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 CO₂ to obtain optimal gas filling of the vessels, particularly in the distribution of the vessels below the knee. The main limitation of CO₂ use in angiography is the unreliability of the CO₂ injection; its compressibility and possible contamination with air can lead to a potentially fatal complication. The development of an automated CO₂ 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.

The aim of this study was to compare the feasibility, safety, and diagnostic accuracy of automated CO₂-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 CO₂ 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 CO₂ and ICM to directly compare the two techniques. CO₂-DSA was performed before ICM-DSA in the same procedure.

**CO₂ and ICM digital angiography.** All patients received the same preparation they would receive for iodinated angiograms. Angiography was performed via femoral arterial puncture. CO₂ was delivered using the Angiodroid CO₂ 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 CO₂ were used per injection at 300-400 mm Hg of pressure. In each patient, we performed an average of 6 CO₂ injections. The total average volume of CO₂ 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 CO₂ compared to blood. DSA images were obtained in an anteroposterior (AP) projection and in both oblique projections. At least 2 minutes

### Table 1. Population characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>16 (40%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.7 ± 7.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24 (60%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (57.5%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>28 (70%)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Creatinine ≥1.3 mg/dL</td>
<td>20 (50%)</td>
</tr>
<tr>
<td>Creatinine ≥2 mg/dL</td>
<td>11 (27.5%)</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation or number (percentage).

### Table 2. Peripheral arterial disease prevalence.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients</th>
<th>Rutherford Stage</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIa</td>
<td>8 (20%)</td>
<td>1</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>IIb</td>
<td>22 (55%)</td>
<td>2</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>III</td>
<td>8 (20%)</td>
<td>3</td>
<td>13 (32.5%)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (5%)</td>
<td>4</td>
<td>8 (20%)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2</td>
<td>5 (5%)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>ATK</th>
<th>BTK</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100 (93.5-100)</td>
<td>97.9 (88.9-99.9)</td>
<td>99.0 (94.7-100)</td>
</tr>
<tr>
<td>Specificity</td>
<td>96.2 (92.4-98.5)</td>
<td>95.8 (88.3-99.1)</td>
<td>96.1 (93.0-98.1)</td>
</tr>
<tr>
<td>PPV</td>
<td>88.7 (78.1-95.3)</td>
<td>94.0 (83.5-98.7)</td>
<td>91.1 (84.2-95.6)</td>
</tr>
<tr>
<td>NPV</td>
<td>100 (97.9-100)</td>
<td>98.6 (92.3-100)</td>
<td>99.6 (97.8-100)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>97.1 (94.1-98.8)</td>
<td>96.7 (91.7-99.1)</td>
<td>96.9 (94.6-98.5)</td>
</tr>
</tbody>
</table>

ATK = above-the-knee; BTK = below-the-knee; PPV = positive predictive value; NPV = negative predictive value.
were allowed between injections to ensure complete excretion of CO₂. All studies were performed using the GE Innova DSA system (GE Medical Systems) with a postprocessing software for CO₂ images. A high-mA (90 mA) and low-kV (70 kV) technique was used. Because of the quick passage of the CO₂ 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 ioxanol 320 mg/mL (Visipaque; GE Healthcare) via 4 Fr Pigtail catheter positioned at the abdominal aortic bifurcation. Between 15–20 mL of ioxanol 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 CO₂ 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 CO₂-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 CO₂-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 CO₂-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 CO₂-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 CO₂ injections. No life-threatening complications occurred during the use of CO₂-DSA. No allergic reactions were noted following CO₂ 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 CO₂-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 CO₂ 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 arte-riography 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 CO₂-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 CO₂ use.

The properties of CO₂ 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. CO₂ 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 CO₂ in the lower extremities, particularly in smaller BTK vessels. Several studies have reported the use of CO₂ 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 CO₂-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 CO₂ or ICM in any segment for any of the observers;³⁷ however, imaging of BTK vessels using CO₂ has not been reported to show such favorable results.⁴⁰⁻⁴² In our series, CO₂ 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 CO₂ injection, the use of the CO₂ delivery system, and the use of CO₂-dedicated postprocessing software.

In the referenced studies, inadequate opacification of the BTK vessels by CO₂ 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 CO₂ was used for bilateral lower-limb evaluation, there was a fragmentation of the CO₂ gas column, which degrades the image quality, especially in the BTK arteries.³⁷ In our study, the CO₂ 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 authors³⁶⁻³⁹ 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 CO₂ was delivered intravascularly by a hand injection with a 30 mL syringe in most studies. Because CO₂ gas in compressible syringes is loaded under pressure from CO₂ cylinders, these syringes contain indeterminate amounts of CO₂. In contrast to liquid injections, in which the rate of delivery remains constant, the rate of CO₂ delivery increases exponentially toward the end of injection.⁹ In our opinion, this produced inconsistent CO₂ delivery, and consequently, poor vessel filling.

The high value of overall diagnostic accuracy of CO₂-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 CO₂ 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 CO₂ 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 CO₂ 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
contrast injection and enhancing the postcontrast images through manipulation and amplification of a digitized radiographic image. Current angiography procedures are now set up with CO₂ postprocessing “stacking” software. CO₂ produces contrast by causing complete displacement of the blood column in the vessel. In each x-ray acquisition, the CO₂ 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. 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 CO₂ 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 CO₂ injection. CO₂ 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 CO₂ from the injector to the catheter must also be considered.
As technology advances, this imaging will likely continue to improve, making CO₂ 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

CO₂ 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 CO₂ 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 maximaly optimize imaging, the proceduralist must take advantage of the special properties of CO₂. This requires some changes in angiographic techniques from contrast preparation to image postprocessing.

References

30. Gharekhani F, Torabian S. Comparison of allergic adverse effects...


