Carbon dioxide Is a Cost-effective Contrast Medium to Guide Revascularization of TASC A and TASC B Femoropopliteal Occlusive Disease

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Background: Iodine contrast medium (ICM) is considered gold standard in endovascular revascularization procedures. However, nephrotoxicity and hypersensitivity to ICM are causes that limit its indiscriminate use. Carbon dioxide (CO2) contrast angiography has been used as an alternative in patients with formal contraindication to ICM. However, no studies to the present date have compared in a randomized and prospective way, outcomes of revascularization procedures performed with either ICM or CO2 in patients eligible for use of both contrasts.

Methods: Between April 2012 and April 2013, 35 patients with peripheral arterial disease with arterial lesions classified as Trans-Atlantic Inter-Society Consensus A or B (identified on preoperative angio computed tomography scan) and adequate runoff underwent femoropopliteal revascularization by endovascular technique in a prospective, randomized, and controlled study. Patients were randomized into 2 groups: CO2 group and ICM group, according to the contrast media selected of the procedure. We evaluated the following outcomes in both groups: feasibility of the procedures, complications, surgical outcomes (ankle-brachial index [ABI]), glomerular filtration rate using the Cockcroft–Gault formula, relationship between the volume of injected iodine and postoperative creatinine clearance, quality of the angiographic images obtained with CO2, costs of the endovascular materials, and finally, cost of contrast agents.

Results: We were able to perform the proposed procedures in all patients treated in this series (ICM group and CO2). There were no CO2-related complications. No procedures required conversion to open surgery. Clinical results were satisfactory, with regression of ischemia and increased levels of ABI in both groups. Variations in creatinine clearance levels showed a numerical increase in the CO2 group and a decrease in ICM group, however, with no statistically significant difference between the delta clearance in each group. All CO2 arteriograms of the supragenicular arteries were graded as good or fair by both observers with high interobserver image quality concordance. There was no statistical difference between endovascular material costs between the groups, but the contrast cost was significantly lower in CO2 group ($P < 0.001$).

Conclusions: The use of CO2 in patients with no restriction for ICM is an alternative that does not limit the feasibility of the procedures. Similar outcomes were observed with CO2 when compared with the gold standard contrast (ICM) regarding quality of images produced, with no associated changes in creatinine clearance or hypersensitivity reactions and also allows a reduction in contrast-related costs in angioplasty procedures.
INTRODUCTION

Oclusive arterial disease of the extremities is a common condition, affecting 3–10% of patients <70 years and up to 20% of individuals over this age group. In cases of critical limb ischemia and limiting intermittent claudication unresponsive to clinical treatment and exercise, revascularization is the treatment of choice and it can be accomplished by open surgery or endovascular therapy depending on the extent of lesions and clinical conditions of the patient. According to Trans-Atlantic Inter-Society Consensus (TASC), in TASC A and TASC B lesions, the endovascular approach is considered more cost-effective, with better long-term outcomes.

Currently, the use of iodine contrast medium (ICM) is considered gold standard in endovascular revascularization procedures. However nephrotoxicity and hypersensitivity to ICM are causes for concern that limit its indiscriminate use. Furthermore, although the cost of the ICM represents only a fraction of the overall expenses in endovascular procedures, it is not irrelevant.

Carbon dioxide (CO2) contrast angiography has been used as an alternative to ICM. Although the use of CO2 as a contrast agent was first described in 1970, it did not receive much attention until the 2000s, when the endovascular treatment became mainstream and the use of ICM presented a limitation to treat patients with renal impairment.

The use of CO2 is currently considered an alternative for aortic, aortoiliac, and femoropopliteal therapies in patients with formal contraindication to ICM (mainly renal impairment or iodine-related hypersensitivity). However, to our knowledge, no studies to the present date have compared in a randomized and prospective way, outcomes of revascularization procedures performed with either ICM or CO2 in patients eligible for use of both contrast media.

Attempting to evaluate if CO2 is effective for the treatment of TASC A and B lesions, we elaborated this prospective and randomized study to compare the feasibility, quality of the angiographic images, clinical outcomes, and the relative costs of TASC A and B lesions treated using CO2 and ICM as contrast mediums.

METHODS

Between April 2012 and April 2013, 35 consecutive patients with peripheral arterial disease with arterial lesions classified as TASC A or B (identified on preoperative angio computed tomography scan) and adequate runoff underwent femoropopliteal revascularization by endovascular technique in a prospective, randomized, and controlled study. This study was approved by the Ethics Committee for Analysis of Research Projects on Human Experimentation at our institution. None of these patients exhibited severe chronic obstructive pulmonary disease, kidney or heart failure, pregnancy, or TASC C or D lesions.

Patients were randomized into 2 groups, CO2 group and ICM group, according to the contrast media selected for the procedure. All patient signed informed consent terms agreeing on the use of either contrast medium. Randomization was performed by computer-generated list immediately before the beginning of the surgery.

Table 1 shows the demographic, clinical, and laboratory profile of patients in our study sample, submitted to either ICM or CO2.

All procedures were performed in an endovascular suite operating (Philips Allura Xper FD, Netherlands) room under general anesthesia with cardiac monitoring, invasive arterial pressure monitoring, and bladder catheterization. In the CO2 group, a 40° Trendelenburg tilt was maintained throughout the procedure.

The patients underwent femoral popliteal angioplasties by the same surgical team (4 surgeons) using a constant surgical technique throughout the study.

Ipsilateral puncture of the common femoral artery was used as access in 34 of the 35 patients. In 1 case, due to the accidental loss of the ipsilateral puncture, a contralateral approach was used.

A standard surgical technique was used in all cases. After arterial puncture and insertion of a 6French introducer access sheath, systemic heparinization was performed followed by initial angiography with the selected contrast media. The lesion was crossed using catheters and hydrophilic guidewires, followed by dilatation with balloon angioplasty and new control angiography to evaluate the need for stenting. At the end of the procedure, heparinization was reversed, and local manual compression was carried out for 30 mins after removal of the introducer.

Immediately after the operation, all patients were referred to the intensive care unit for at least 24 hr, as routine in our hospital, and received intravenous fluids following a fixed protocol for renal protection, despite the contrast media used. The protocol for renal protection included intravenous fluids before the procedure added with endovenous acetylcysteine and intravenous fluids maintenance for 24 hr. Thereafter the patient remained hospitalized for the time needed, with daily monitoring of renal function, blood count, and electrolytes for at least 72 hr.
CO2 as a cost-effective contrast medium

Table I. Demographic and clinical profile of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CO2 group (N = 19)</th>
<th>ICM group (N = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age, mean (SD)</td>
<td>65 (23)</td>
<td>67 (11)</td>
<td>0.573b</td>
</tr>
<tr>
<td>Age, range</td>
<td>37–82</td>
<td>55–92</td>
<td></td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>13 (68.4)</td>
<td>13 (81.3)</td>
<td>0.460a</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>23</td>
<td>24</td>
<td>0.1999b</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>9 (47.4)</td>
<td>12 (75)</td>
<td>0.096c</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>16 (84.2)</td>
<td>15 (93.8)</td>
<td>0.608a</td>
</tr>
<tr>
<td>History of tobacco use, n (%)</td>
<td>7 (36.8)</td>
<td>8 (50)</td>
<td>0.433a</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>18 (94.7)</td>
<td>12 (75)</td>
<td>0.156a</td>
</tr>
<tr>
<td>Intermittent claudication, n (%)</td>
<td>1 (5.3)</td>
<td>4 (25)</td>
<td>0.156a</td>
</tr>
<tr>
<td>TASC A, n (%)</td>
<td>14 (73.7)</td>
<td>11 (68.8)</td>
<td>&gt;0.99a</td>
</tr>
<tr>
<td>TASC B, n (%)</td>
<td>5 (26.3)</td>
<td>5 (31.3)</td>
<td>&gt;0.99a</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation.

*Fisher’s exact test.

bStudent’s t test.

The CO₂ injection was performed manually, without any specific pump system. A cylinder with medicinal CO₂, a particle filter (Millex-Durapore hydrophilic 0.22 µm pore) and a 3-way stopcock were used for aspiration of CO₂ and the entire procedure was held inside a bowl with saline solution. After capturing the required volume of CO₂, an additional 3–5 mL of saline solution was aspirated into the syringe to provide a water seal while the tip was kept down. This way, a physical barrier was created between the room air and CO₂ content, which is independent of manual compression and is safe of air contamination. Ten and 20 mL syringes were used for the intra-arterial contrast injection, performed into the femoral introducer or through an end hole catheter.

The injection of ICM was performed manually in 10 mL syringes using 3 mL of iodinated contrast media and 7 mL of saline solution per injection.

The endovascular materials (sheaths, guidewires, and stents) used in all procedures were provided by Cook Medical Inc. The material used in each intervention and the volumes of ICM or CO₂ were precisely recorded for further analysis. The ICM used in all cases was Omnipaque (Iohexol) 300, nonionic low osmolar contrast, routinely used in our service.

All the procedures were recorded on digital versatile disc for further analysis by 2 observers who did not take part in the intervention and had no experience with the use of CO₂. The recorded angiographies were separated into 2 groups according to the anatomical location of the lesion, above-knee (femoral-popliteal) and below-knee (tibial and peroneal arteries). Each film was analyzed separately by the 2 observers.

Observers attributed a score for each image evaluated ranging from 1 to 3. The score 1, considered poor, was attributed when there was significant loss of definition in the vessels and/or collateral circulation which precluded the procedure; score 2, considered fair, was attributed when there was some loss of definition in the vessels and/or collateral circulation but did no hinder intervention; and score 3, considered good, was observed when there was good contrast in the vessels and collateral circulation.

An individual analysis was carried out for each intervention, evaluating costs related to the contrast media and endovascular material used (puncture needles, sheaths, angioplasty balloons, catheters, insufflating syringes, and stents). It is relevant to emphasize that because ICM is required for balloon filling during angioplasties, we added the price of one 20 mL flask of ICM to all the patients in the CO₂ group who demanded no, or <20 mL of iodinated contrast. In 2 CO₂ cases that required the use of >20 mL of ICM, costs equivalent to 2 flasks of 20 mL were added to the overall expenses.

We evaluated the following outcomes in both groups: feasibility of the procedures, complications, surgical outcomes (ankle-brachial index [ABI] index), glomerular filtration rate using the Cockcroft–Gault formula, relationship between the volume of injected iodine and postoperative creatinine clearance, quality of the angiographic images obtained with CO₂, cost of the endovascular materials, and cost of contrast agents.

Statistical Analysis

Categorical variables were described as absolute frequencies and percentages. The distribution of numerical variables was investigated by histograms and normality Shapiro–Wilk tests, analyzed separately in each group. Numerical data were described by means and standard deviations or medians and interquartile ranges (first quartile—third quartile) in the case of non-normally distributed data.

Categorical variables were compared between groups by Fisher’s exact tests, because of the small sample size. Quantitative variables were compared by Student’s t-test or nonparametric Mann–Whitney tests in the case of non-normal distribution.

The relationship between volume of iodine and delta clearance were assessed using the Pearson and Spearman coefficients of linear correlation.
Statistical analysis was performed using SPSS (SPSS for Windows, Version 17.0, released in 2008; SPSS Inc., Chicago). The level of significance used was 5%.

RESULTS

We were able to perform the proposed procedures in all patients treated in this series (ICM group and CO2). Conversion to open surgery was not necessary in any of the cases. There were no CO2 related complications. One fatal event was observed as a result of myocardial infarction, occurring within 30 days of the intervention in the CO2 group. No statistically significant differences between the groups were observed for the demographic, clinical, and laboratory profile analyzed in Table I.

Clinical results were satisfactory, with regression of ischemia and increased levels of ABI in both groups. In the CO2 group, the median ABI levels increased from 0.5 to 0.97 and in the ICM group, from 0.44 to 0.91, with an overall average improvement of 94% and 106% in the CO2 and ICM groups, respectively, without statistically significant difference between the groups.

The mean injected volume of CO2 required for each procedure was 70.07 mL (range 24–180 mL). The mean volume of ICM used per patient was 31.29 mL (range 12–51 mL).

In the CO2 group, 9 patients with TASC A lesions required implantation of 1 stent, and in 5 patients, 2 stents were deployed. For treatment of the TASC B patients, 2 stents were required in 1 case, no stent in 1 case, and 1 stent was used in 3 cases.

Considering the ICM group, 7 patients with TASC A lesions required 1 stent deployment, and in 4 cases, 2 stents were necessary. Four patients with TASC B lesions required implantation of 2 stents, and in 1 case, only 1 stent was necessary.

In 4 patients from the CO2 group (2 TASC A patients and 2 TASC B), the use of iodine was necessary for completion of the procedure. These cases occurred in the beginning of the series and iodine use was justified by difficulty in visualizing refill after occlusion. In 2 cases, the volume of ICM used was inferior to 10 mL, and in the other 2 cases, less than 25 mL. The duration of the procedures did not exceed 2 hr in either of the groups.

Variations in creatinine clearance levels are shown in Table II where we observe a numerical increase in the group CO2 (from 69 to 83 mL/min) and a decrease in ICM group (from 73.9 to 72.5 mL/min).

We analyzed the variation in creatinine clearance levels using delta clearance, which was positive in the CO2 group and negative in the ICM group, however, with no statistically significant difference between them.

The relationship between the volume of injected iodine and progression of creatinine clearance was studied.

There is evidence that the greater the volume of ICM, the smaller the delta clearance. This relation cannot be verified by tests because of the small sample size. The Pearson correlation coefficient calculated for the data has a value of −0.289, indicating a negative and weak correlation.

We also calculate the Spearman correlation coefficient, which assumed value of −0.193 (P = 0.344), also indicating a weak and negative correlation.

The evaluation of CO2 arteriographies by the 2 observers is presented in Table III. Figure 1 shows an example of CO2 arteriogram.

All CO2 arteriograms of the supragenicular arteries were graded as good or fair by both observers with high interobserver image quality concordance. Similarly, for infragenicular arteries only 2 images were graded as poor (2 infragenicular images were lost and could not be validated).

All the iodine arteriograms were graded as good by both observers.

The costs of the endovascular materials and contrast media used in both groups are outlined in Table IV.

The endovascular material costs were similar in both groups, however the ICM cost was significantly more expensive than the CO2 cost.

### Table II. Variation in creatinine clearance levels in the preoperative and postoperative period

<table>
<thead>
<tr>
<th>Creatinine clearance level</th>
<th>CO2 Median (interquartile interval)</th>
<th>ICM Median (interquartile interval)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>69.0 (49.0–120.2)</td>
<td>73.9 (56.0–85.9)</td>
<td>0.960</td>
</tr>
<tr>
<td>Postoperative</td>
<td>83.0 (73.0–122.0)</td>
<td>72.5 (56.7–94.5)</td>
<td>0.116</td>
</tr>
<tr>
<td>Delta&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.0 (−6.0 to 27.0)</td>
<td>−2.00 (−9.65 to 11.4)</td>
<td>0.185</td>
</tr>
</tbody>
</table>

<sup>a</sup>Nonparametric Mann–Whitney test.
<sup>b</sup>Delta clearance = creatinine clearance postoperative – creatinine clearance preoperative.
DISCUSSION

The high nephrotoxicity and antigenicity of iodinated contrasts, has restricted the use of this agent in patients with renal impairment or iodine-related hypersensitivity. Therefore, CO₂ has been increasingly used in surgical practice, especially in individuals with renal impairment. Aiming to investigate the possibility of a wider use for CO₂, in this study, we sought to establish the effectiveness of CO₂ compared with iodinated contrast, in patients with femoral popliteal TASC A and B lesions, who presented no contraindication to ICM. For this, we assigned the contrast media randomly to all patients referred for endovascular therapy.

Our results showed that, the use of the CO₂ did not affect the feasibility or the outcomes of the procedures. All procedures performed with CO₂ were successful and a rise in ABI was observed in all cases. Although there are few reports of complications with the use of intra-arterial CO₂ in our series, no adverse events were observed that could be related to this particular contrast media, corroborating with other larger series previously published.12

There were no cases of postoperative acute renal failure in either of the study groups. In the CO₂ group, a numerical increase in postoperative creatinine clearance levels was observed, contrasting with a decrease in these levels in the ICM group; however, these differences were not statistically significant in both cases. We then analyzed the delta clearance between the groups and despite the numerical variation, the difference was not statistically significant, probably because of the reduced number of studied patients. Future studies with larger numbers of patients may demonstrate the protective effect of CO₂ even in patients with normal renal function. 

We have shown here that when performed by experienced physicians, the use of CO₂ provides angiographic imaging quality comparable to that produced with iodinated contrast medias, enabling the successful completion of the endovascular procedures. With mastery of the technique and improvement of imaging equipment, it is possible to obtain high-quality images in areas previously considered unsuitable13 for CO₂, such as below-knee arteries.

The cost of the endovascular material used in procedures performed with the CO₂ was similar to those performed with ICM. Expenses varied according to the anatomy of the treated lesion and was more

<table>
<thead>
<tr>
<th>Observer</th>
<th>Supragenicular</th>
<th>Infrogenicular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Fair</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>4</td>
</tr>
</tbody>
</table>

Fig. 1. Supragenicular CO₂ angiography.
strongly related to the need for stent deployment rather than the contrast agent used, demonstrating that CO₂ does not increase intervention costs.

The costs specifically related with intravascular contrast agents were significantly smaller in the CO₂ group, despite the inclusion of a 20-mL flask of ICM in all cases. It is worth noticing that in the procedures performed exclusively with CO₂, higher osmolarity iodine contrast agents (that are 60% cheaper) could have been used for balloon filling, enabling a further reduction of costs.

If we extrapolated the savings that could be achieved with the use of CO₂ to the 10 thousand angioplastic procedures that are performed annually by the public and private healthcare systems in Brazil, a considerable decrease in the overall costs of the treatment of leg ischemia could be accomplished.

In conclusion, the use of CO₂ in patients with no restriction for ICM is an alternative that does not limit the feasibility of the procedures. In this preliminary data, similar outcomes were observed with CO₂ when compared with the gold standard contrast (iodine) regarding quality of images produced, with no associated changes in creatinine clearance or hypersensitivity reactions and with a possible reduction in contrast-related costs in angioplasty procedures.

Further studies, with more patients, are welcome to support our findings of CO₂ as a noninferior contrast agent when compared with iodine.

### REFERENCES


