Clinical Research

Carbon Dioxide as Contrast Medium to Guide Endovascular Aortic Aneurysm Repair

Cynthia de Almeida Mendes,1,2 Alexandre de Arruda Martins,1,2 Marcelo Passos Teivelis,1 Sergio Kuzniec,1 Andrea Yasbek Monteiro Varella,1 and Nelson Wolosker,1 Morumbi, Jardim Ângela, São Paulo, and Brazil

Background: Iodine contrast medium (ICM) is considered to be gold standard in endovascular procedures, but its nephrotoxicity and hypersensitivity limit the widespread use. Carbon dioxide (CO2) is considered as an alternative for endovascular procedures in patients with contraindication to ICM. However, no studies have compared the outcomes of endovascular aneurysm repair (EVAR) performed with ICM or CO2 among patients with no contraindication to ICM.

Methods: From May 2012 to April 2014, 36 patients with abdominal aortic aneurysms underwent EVAR in a prospective, randomized, and controlled study. Patients were randomized into 2 groups, CO2 or ICM group.

Results: We were able to perform the proposed procedures in all patients in this study. There were no conversions to open surgery and no CO2-related complications. Endovascular material costs, duration of surgery, and time of fluoroscopy were similar between groups, and the cost of the contrast media was smaller in the CO2 group than in the ICM group. Among CO2 group procedures, 62.5% of the patients needed ICM complementary use.

Conclusions: The use of CO2 as a contrast medium for EVAR is an alternative in patients with no restriction for ICM, with similar outcomes when compared to ICM, regarding duration of surgery, duration of fluoroscopy, and endovascular material costs. Using CO2, there were no changes in creatinine clearance and no risk of hypersensitivity reactions; moreover, there was a reduction in contrast-related costs for EVAR procedures. However, in our study, additional use of ICM to visualize the internal iliac artery was needed in most procedures.

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a common condition, with a prevalence rate of 5.7% in the population. Although there is a rationale for medical treatment,1 surgery is considered the best treatment. Endovascular aneurysm repair (EVAR) has emerged as a less invasive and less morbid treatment option when compared with conventional open surgery. In the United States, the overall use of EVAR2 has risen sharply in the past 10 years (5.2–74% of the total number of AAA repairs), although the total number of AAAs remains stable at 45,000 cases per year.3

The use of iodine contrast medium (ICM) is currently considered the gold standard in endovascular procedures, but its nephrotoxicity and hypersensitivity reactions limit its widespread use.4–6

Carbon dioxide (CO2) was initially described as an endovascular contrast media in 1970 by Hawkins et al. However, since it is a gaseous contrast agent with some application particularities, its use was not widespread until the 2000s, when the endovascular treatment became mainstream and the use of ICM presented as a limitation to treat patients with renal impairment.
Currently, CO₂ can be considered an alternative for aortic, aortoiliac, and femoropopliteal procedures only in patients with formal contraindication to ICM (renal impairment or iodine-related hypersensitivity). However, to our knowledge, no studies have compared the outcomes EVAR performed with either ICM or CO₂ in patients eligible for use of both contrast media by a randomized and prospective approach. Attempting to evaluate if CO₂ is as effective as ICM for EVAR in patients with no contraindication to ICM, we elaborated this prospective study to compare feasibility, quality of the angiographic images, clinical outcomes, and relative costs of EVAR using CO₂ or ICM as contrast mediums, and here we show our results.

METHODS

From May 2012 to April 2014, 36 patients with infrarenal aortic aneurysms (identified on preoperative angioCT scan) and normal renal function underwent EVAR 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. Regarding the cases anatomy, none of the included patients had proximal aortic neck with angle greater than 60°, or length less than 20 mm neither thrombus or calcification in more than 50% of the proximal aortic neck. Clinical exclusion criteria were chronic obstructive pulmonary disease, severe heart failure (on whom surgery was contraindicated because they were deemed to be very high risk on clinical grounds), or kidney failure (creatinine clearance less than 30 mL/min estimated using the Cockcroft–Gault formula). Clinical exclusion criteria were chronic obstructive pulmonary disease, severe heart failure (on whom surgery was contraindicated because they were deemed to be very high risk on clinical grounds), or kidney failure (creatinine clearance less than 30 mL/min estimated using the Cockcroft–Gault formula), pregnancy or patients who had the aortic anatomy described previously.

All patients signed an informed consent form agreeing on the use of either contrast medium.

Patients were randomized into 2 groups, CO₂ and ICM groups, according to the primary contrast media used in the procedure. Randomization was performed by a computer-generated list immediately before the beginning of the surgeries, in a one-to-one ratio.

All procedures were performed on an endovascular suite operating room (Philips Allura Xper FD, Netherlands). This equipment has a specific CO₂ mode for performing procedures with CO₂ as contrast.

The patients were operated under general anesthesia with cardiac monitoring, invasive arterial pressure monitoring, and bladder catheterization.

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

Surgical procedures were performed using conventional technique for EVAR with bilateral oblique inguinal incisions, followed by a bilateral dissection of the common femoral arteries. We finished the procedure with femoral artery suture, hemostasis, and closure of the incision in multiple layers.

As routine in our hospital, all patients were referred to the intensive care unit immediately after the operation for at least 24 hr and received intravenous fluids following a fixed protocol for renal protection regardless of the contrast media used. The protocol for renal protection included intravenous fluids preprocedure in addition to endogenous acetylcysteine, followed by intravenous fluid maintenance for 24 hr. Thereafter, patients remained hospitalized for the time needed to recover (at least 72 hr), with daily monitoring of renal function, blood count, and electrolytes dosage.

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 to aspirate CO₂; this was performed inside a bowl filled with saline solution. After acquiring the required volume of CO₂, an additional 5 mL of saline solution was aspirated into the syringe to provide a water seal, whereas the needle 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 protected from air contamination. Twenty or 60 mL syringes were used for the intra-arterial CO₂ injection, performed using a femoral introducer or through an end-hole catheter.

ICM injection was performed manually with 10-mL syringes using 3-mL iodinated contrast media and 7-mL saline solution per injection. During the final control aortography in the ICM group, an injection pump was used, with a half-to-half dilution of ICM and saline solution. The ICM used in all cases was Omnipaque 300 (Iohexol), a nonionic low osmolar contrast agent routinely used in our studies.

The endovascular material (sheaths, guidewires, stents, and endoprosthesis) used in all procedures was provided by Cook Medical Inc®. The endoprosthesis used in all cases was Zenith Flex®. The volumes of ICM and CO₂, duration of the procedure, duration of X-ray exposure, and the endovascular material used in each intervention were precisely recorded for further analysis.

In cases where it was necessary to perform internal iliac artery embolization, renal angioplasty, iliac angioplasty, or when it was necessary to use a proximal
cuff, we considered these as associated procedures, and all the material that was used was also accounted.

All procedures were recorded on DVD for further analysis of the angiographic images. Two observers, also vascular surgeons, who did not take part in the intervention and had no experience with the use of CO2 analyzed the data. Each film was analyzed separately by the 2 observers.

The images obtained with CO2 were analyzed separately for: renal arteries, internal iliac arteries, and final control angiography.

Observers attributed a score for each image ranging from 1 to 3. A score of 1, considered poor, was assigned when there was significant loss of definition in the vessels, which precluded the procedure; a score of 2, considered fair, was assigned when there was some loss of definition in the vessels but did not hinder intervention; and a score of 3, considered good, was assigned when there was good contrast in the vessels.

Each intervention was analyzed evaluating contrast media costs and endovascular material used (puncture needles, sheaths, guidewires, catheters, balloon, and endoprosthesis). It is important to emphasize that since ICM is required for balloon prosthesis, we added the price of one 20-mL ICM flask to the total procedural cost for patients in the CO2 group who demanded less than 20 mL or no ICM.

We evaluated the following outcomes in both groups: feasibility of the procedures; surgical outcomes; complications; total duration of the procedures and fluoroscopy time; glomerular filtration rate using the Cockcroft–Gault formula11 before and 3 days after the procedure; quality of the angiographic images obtained with CO2; endovascular materials costs; and the costs of the contrasts.

Statistical Analysis
Categorical variables were described using absolute frequencies and percentages and compared between groups by Fisher’s exact or Pearson’s chi-squares tests. Numerical variables were analyzed for their distribution within Shapiro–Wilk and boxplot graphs separately. Variables with normal distribution (volume CO2, body mass index, age, and creatinine before and after surgery) were described by means and standard deviations and compared with Student’s t-tests. The homogeneity of variance was checked by Levene’s tests. The other numerical variables were described by medians and interquartile ranges and compared by nonparametric Mann–Whitney test. The minimum and maximum values were calculated for all variables.

The level of significance was 5%.

RESULTS
We were able to perform the proposed procedure in all patients treated in this series (ICM group and CO2 group). Conversion to open surgery was not necessary in any of the cases. However, in the CO2 group, 10 of the 16 cases required ICM supplementation to finish the procedure.

The clinical results were good, achieving exclusion of aneurysms from circulation in all cases. There was no mortality in this study, and the patient who stayed in hospital the longest was discharged on postoperative day 4.

The demographic and clinical profiles of the patients are presented in Table I.

No significant differences were observed for the demographic and clinical profiles of patients between the groups.

Contrast volumes used in both groups are summarized in Table II. Among the 16 patients in the CO2 group, 10 (62.5%) received iodine supplement.

The total duration of surgery and fluoroscopy time are also summarized in Table II.

The use of CO2 as a contrast did not increase the duration of surgery or fluoroscopy time.

In the CO2 group, the treated aneurysms had a medium landing zone (distance from the lowest renal artery to the aneurysm neck of the aorta) of 28.1 mm (range, 20–42 mm) and medium angulation neck of 42.3° (range, 21–60°). The medium diameter of the treated aneurysms was 65 mm (range, 52–85 mm). In this group, associated procedures were necessary to adequately complete EVAR for 8 patients. All these procedures, except the one patient who needed a loop snare, were previously predicted and not due to complications during the procedures. In 5 of these 8 patients, embolization of the right internal iliac artery was necessary; in 1 patient, embolization of the left internal iliac artery and external iliac artery angioplasty (the same case) were necessary; in another patient, renal artery angioplasty was performed; and in the last of the 8 patients, after unsuccessful attempts to catheterize the contralateral limb, it was necessary to use a loop snare to capture the contralateral femoral guide.

One case in the CO2 group had the left internal iliac artery covered unintentionally by the iliac endograft limb because we could not adequate visualize the origin of that artery. Since the right internal iliac artery remained patent, there was no clinical repercussion in the postoperative period.

In the ICM group, the medium landing zone of the treated aneurysms was 28.6 mm (range, 20–40 mm) and angulation neck of 40.7° (range, 23–60°). The medium diameter of the treated aneurysms was
63 mm (range, 50–88 mm). In this group, 6 cases required associated procedures to complete EVAR: 1 needed proximal cuff insertion, 3 needed embolizations of the left internal iliac artery, and 2 needed embolizations of the right internal iliac artery. These additional procedures were also planned prior the surgery, with exception of the proximal cuff.

The follow-up time of the study varied from 9 to 55 months, and there were no reinterventions in either groups. As routine in our service, we made an angioCT scan 1 month after the procedure in all patients. We found 2 type II endoleaks in the CO2 group and 1 type II endoleak in ICM group that were conservatively managed.

Patients creatinine clearance levels (using Cockcroft–Gault formula) both presurgery and postsurgery are illustrated in Table III.

There was no significant change in renal function in the ICM and CO2 groups in the postoperative period.

The evaluation of CO2 angiographies concerning the number of images from each location evaluated by each of the 2 observers is illustrated in Table IV.

Analyzing images produced with CO2, we noticed the greatest amount of “poor” notes by both observers for internal iliac arteries.

In the CO2 group, 10 of the 16 cases required ICM supplementation. The supplementation with ICM was performed when the image produced with CO2 had significant loss of definition of the vessels, which precluded the safe completion of the procedure. In 5 of these cases, the only difficulty was to assess 1 internal iliac artery. In 3 cases, we needed ICM to assess 1 internal iliac artery and to assess the final angiography. In 2 cases, the iodinated contrast was used to assess only the final arteriography.

Figures 1 and 2 illustrate images obtained using CO2 as contrast during EVAR.

The endovascular materials costs and contrast media costs used are outlined in Table V.

The endovascular material costs were similar in both groups; however, the contrast media cost in the ICM group was significantly more expensive than that observed in the CO2 group.

**DISCUSSION**

ICM is currently considered the gold standard for performing endovascular procedures, although it is a nephrotoxic contrast with high antigenicity.

<table>
<thead>
<tr>
<th>Table I. Demographic and clinical profile of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO2 group, n = 16</td>
</tr>
<tr>
<td>Age average (SD)</td>
</tr>
<tr>
<td>Age range</td>
</tr>
<tr>
<td>Gender male (%)</td>
</tr>
<tr>
<td>BMI average (Kg/m²)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>History of tobacco use (%)</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
</tr>
<tr>
<td>Cardiac failure (%)</td>
</tr>
<tr>
<td>Coronary disease (%)</td>
</tr>
<tr>
<td>Additional procedures (%)</td>
</tr>
</tbody>
</table>

BMIs, body mass index.
\(^a^\)Student’s t-test.
\(^b^\)Fisher’s exact test.
\(^c^\)Pearson’s chi-squared test.

<table>
<thead>
<tr>
<th>Table II. Operative details</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO2 group</td>
</tr>
<tr>
<td>CO2 volume</td>
</tr>
<tr>
<td>Iodine volume</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
</tr>
</tbody>
</table>

\(^a^\)Mann–Whitney nonparametric test.
Knowing that CO₂ is a therapeutic alternative for patients with contraindications to ICM, we aimed to investigate the possibility of a more widespread use for CO₂. In this study, we attempted to establish the effectiveness of CO₂ compared with iodinated contrast in patients with AAA who presented no contraindication to ICM. For this, we assigned the contrast media randomly.

Complications with the use of intra-arterial CO₂ are possible, but in our study, no adverse events were observed, corroborating with other larger studies previously published. Regarding severe chronic obstructive pulmonary disease patients, CO₂ might in fact not be a good alternative, because of the CO₂ retention risk, so injecting large amounts of CO₂ might be problematic.

Previous studies have used CO₂ for performing EVAR but in patients with renal dysfunction. A retrospective cohort compared the use of CO₂ and ICM to perform EVAR in patients with chronic renal failure and considered the CO₂ safe but with an increase in operative time and fluoroscopy time. In a retrospective analysis, Criado et al. using CO₂ for EVAR in 114 patients found a lower operative and fluoroscopy time compared with the ICM. We observed that is possible to perform EVAR exclusively with CO₂ or with the supplemental use of small amounts of ICM in patients with no contraindication to ICM. For this, we assigned the contrast media randomly.

Table III. Variations in creatinine clearance levels in the preoperative and postoperative period

<table>
<thead>
<tr>
<th></th>
<th>CO₂</th>
<th>ICM</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear creat pre</td>
<td>53.9 (41.9–86.5)</td>
<td>82.6 (56.8–100.6)</td>
<td>0.080</td>
</tr>
<tr>
<td>Clear creat post</td>
<td>79.4 (49.2–96.4)</td>
<td>91.7 (58.2–110.2)</td>
<td>0.226</td>
</tr>
<tr>
<td>Delta clear</td>
<td>11.1 (−3.1 to 22.6)</td>
<td>11.7 (−5.1 to 19.5)</td>
<td>0.799</td>
</tr>
</tbody>
</table>

Clear creat pre, creatinine clearance preoperative; clear creat post, creatinine clearance postoperative.

*aNonparametric Mann–Whitney test.

Table IV. Evaluation of the images produced with CO₂ by the observers, divided by location

<table>
<thead>
<tr>
<th></th>
<th>Observer 1</th>
<th>Observer 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor</td>
<td>Fair</td>
</tr>
<tr>
<td>Internal iliac artery angiography, n = 24 (%)</td>
<td>8 (33.3)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Renal artery angiography, n = 17 (%)</td>
<td>1 (5.8)</td>
<td>6 (35.2)</td>
</tr>
<tr>
<td>Final angiography, n = 12 (%)</td>
<td>2 (16.6)</td>
<td>8 (66.6)</td>
</tr>
</tbody>
</table>

n, number of images.

Table V. Costs of endovascular materials and contrast media

<table>
<thead>
<tr>
<th>Group</th>
<th>CO₂</th>
<th>ICM</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular material</td>
<td>11,483.8 (10,884.8–12,557.7)</td>
<td>10,984.8 (10,898.4–11,888.8)</td>
<td>0.567</td>
</tr>
<tr>
<td>Median (interquartile interval)</td>
<td>10.12</td>
<td>25.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contrast media</td>
<td>10.12 (10.12)</td>
<td>(25.0–50.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values in American dollars.

*aNonparametric Mann–Whitney test.
expected not to alter the renal function, since it is used in patients with renal impairment exactly because of its absence of nephrotoxicity. There are many studies describing the nephrotoxicity of ICM, and in this study, we propose that this deleterious effect was not significant because of the low volume of ICM used (medium 35.5 mL) and due to the renal protection therapy performed in all patients in the perioperative period.

The use of CO₂ by experienced physicians provides angiographic imaging quality comparable to that produced with iodinated contrast media, enabling successful completion of the endovascular procedures, with the use of no or very little ICM.

The manual injection of CO₂ without the need for pumps or injection systems is considered safe and makes its use more affordable and easily reproducible.

In 8 procedures of CO₂ group, ICM supplementation was necessary to identify the internal iliac artery. In all of these cases, despite performing maneuvers to change position and the use a higher volume of CO₂, we need to use ICM to identify these arteries.

Because of the gaseous characteristics of CO₂, it tends to “float” on the anterior wall of the large arteries and visualization of branches with posterior origins in the vessel are more difficult with this type of contrast. This difficulty can be predicted in the preoperative CT. In cases with favorable anatomy (nonposterior origin of the hypogastric artery) CO₂ is sufficient; conversely, in cases where the location of the internal iliac artery is more posterior, ICM supplementation may be necessary.

In all the cases in the CO₂ group, we could identify the lowest renal artery using CO₂, and we were able to perform safe release of the main body of the stent graft. To accomplish this, we must position the tip of a diagnostic VS1 catheter near the ostium of the lowest renal artery, in the position estimated by the preoperative CT scan, and then inject CO₂ at the presumed location. With this technique, we obtained good quality images of all renal arteries and did not need supplemental ICM in any case. Control aortography at the end of the procedure was performed with only CO₂ in 11 patients in this group. This is a technique that has proved to be quite sensitive in another study seeking to identify endoleaks. However, in 5 procedures, in which we did not considered safe to finish the procedure only with the image produced with CO₂, we need ICM supplementation to safely assess the absence of endoleaks after final ballooning and to ensure patency of the arterial tree. Iodine contrast confirmed that no endoleaks were present and that arteries were patent.

The endovascular material costs used in the procedures performed with the CO₂ were similar to those performed with ICM. The presence of associated procedures (not the type of contrast used) was a predictor of the variation in costs. The costs specifically related with intravascular contrast agents were significantly lower in the CO₂ group, despite the inclusion of a 20 mL flask of ICM in all cases for the balloon filling. The contrast agent used had no significant burden on
costs and the use of CO₂ did not increase intervention costs. For daily practice, it has already been demonstrated the safety of CO₂ use in patients with chronic kidney failure and AAA, and our study added this information in patients without kidney failure.

We conclude that it is possible to perform EVAR with only CO₂ in patients with no contraindication to ICM with nonposterior origin of the hypogastric artery. The supplementation of small amounts of ICM, especially for evaluating the origin of the internal iliac artery when its origin is located posteriorly may be necessary which can be foreseen with criterions analyses of the preoperative CT angiography. This information is very important in patients that have some contraindication to ICM and are candidates to EVAR with CO₂. If the origin of the internal iliac artery is posterior posteriorly some preparation and care must be taken before the procedure, since we can predict the need of iodine supplementation.

CO₂ utilization leads to similar outcomes when compared with the gold standard contrast (iodine) regarding duration of surgery, time of fluoroscopy, and endovascular material costs, with no associated changes in creatinine clearance. Moreover, we did not observe any risk of hypersensitivity reactions, and we found a reduction in contrast-related costs in EVAR procedures.

CO₂ use in patients with no contraindication to ICM may decrease overall costs, and, when supplementation with iodine is necessary, the burden of nephrotoxicity may be diminished, as its volume is significantly lowered. Owing to relatively small patient number, no patients with hostile aortic anatomy and absence of a longer follow-up in the renal function, further studies are welcome to support our findings.

REFERENCES


