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CO_2-EVAR: An innovative approach to Automated Carbon Dioxide Angiography during Endovascular Abdominal Aortic Aneurysm repair

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Abstract

Objectives

CO_2-angiography in endovascular aortic repair (CO_2-EVAR) has been proposed for treatment of AAA especially in patients with chronic kidney disease and/or allergy to iodinated contrast medium (ICM). Issues regarding the standardization of the technique, such as visualization of the lowest renal artery (LoRA) and the best quality image in angiographies performed from pigtail or introducer-sheath, are still unsolved.

Aim of the study was to analyze different steps of CO_2-EVAR, in order to create an operative protocol to standardize the procedure.

Methods

Patients undergoing CO_2-EVAR were prospectively enrolled in 5 European centers from 2018 to 2021. CO_2-EVAR was performed using an automated injector (Pressure:600mmHg; Volume:100cc); a small amount of ICM was injected in case of difficulty in LoRA visualization or other doubts. LoRA visualization and image quality (1=low, 2=sufficient, 3=good, 4=excellent) were analyzed and compared at different procedure steps: preoperative CO_2-angiography from Pigtail and femoral Introducer-sheath (1^{st}Step), angiographies from Pigtail at 0%, 50% and 100% of main body deployment (2^{nd}Step), contralateral hypogastric artery (CHA) visualization with CO_2 injection from femoral Introducer-sheath (3^{rd}Step) and completion angiogram from Pigtail and femoral Introducer-sheath (4^{th}Step). Intraoperative and postoperative CO_2-related adverse events were also evaluated. Chi-squared and Wilcoxon were used for statistical analysis.

Results

In the considered period, 65 patients undergoing CO_2-EVAR were enrolled, 55/65(84.5%) male with a median age of 75(11.5) years. The median ICM was 20(54) cc; 19/65(29.2%) procedures were performed with 0cc ICM. In the 1st Step the median image quality was significantly higher with CO_2 injected from the femoral introducer [Pigtail 2(3) vs.3(3) Introducer, p=.008]. In the 2nd Step LoRA was more frequently detected at 50% (93%vs.73.2%, p=.002) and 100% (94.1%vs.78.4%, p=.01) of main body deployment compared with first angiography from Pigtail; similarly, image quality was significantly higher at 50% [3(3) vs. 2(3), p=<.001] and 100% [4(3) vs. 2(3), p=.001] of main body deployment. CHA was detected in 93% cases (3rdStep). The mean image quality was significantly higher when final angiogram (4thStep) was performed from introducer (Pigtail 2.6 ± 1.1vs.3.1 ± 0.9 Introducer, p=<.001). The rates of intra- and postoperative adverse events (pain, vomit, diarrhea), all transient and clinically mild, were 7.7% and 12.5% respectively.

Conclusions

Preimplant CO_2-angiography should be performed from femoral Introducer-sheath. Main body steric bulk during its deployment should be used to improve image quality and LoRA visualization with CO_2. CHA can be satisfactorily visualized with CO_2. Completion CO_2-angiogram should be performed from femoral Introducer-sheath. This operative protocol allows to perform CO_2-EVAR with 0cc or minimal ICM, with a low rate of mild temporary complications.

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Chapter 1

Backgroud

Renal Function Worsening in Patients Undergoing EVAR

Acute Kidney Injury (AKI) following the Kidney Disease Improving Global Outcomes (KIDGO) can be defined as an increase of serum creatinine (SCr) ≥0.3 mg/dL within 48 hours or an increase to ≥1.5 times the initial value within 1 week or an urine output ≤0.5 mL/kg/hour for 6 hours[1]. This condition is multifactorial and often related to iodinated contrast medium (ICM) administration in the so-called contrast-induced nephropathy (CIN).

The incidence of CIN after computer tomography using intravenous ICM injection higher than 5%[2]. The intra-arterial injection of ICM during angiographies is associated with a higher CIN occurrence[3]. CIN, therefore, is a critical consideration during the performance of diagnostic and interventional radiological procedures in patients with renal impairment, occurring in 10 to 30% of such patients.

Endovascular aortic repair (EVAR) is presently the treatment of choice for abdominal aortic aneurysms (AAA), in patients with anatomical feasibility; the best results in comparison with open repair are related to lower mortality in the postoperative and in the mid-term follow-up[4]. EVAR in patients with renal dysfunction or severe contrast allergy can be very dangerous, due to the ICM used during these interventions, possibly leading to end-stage renal disease and hemodialysis. As reported by Greenberg R et al[5], the cause of renal dysfunction after endovascular repair is probably multifactorial, it occurs in a small number of patients, and the effect appears to be transient in most cases.

The incidence of AKI after EVAR procedures has been ranged between 5-18% in literature[6]. Minimizing the use of ICM is therefore of paramount importance in EVAR procedures in patients with severe renal insufficiency.

Gallitto et al[7] described a mini-invasive approach during planning, execution and follow-up of EVAR procedures, using bone landmarks, doppler ultrasound and contrast-enhanced ultrasound

(CEUS), with the aim to minimize the exposure of patients to ICM and the subsequent risk of renal function worsening. Similarly, Bush et al[8] reported the imaging modalities that do not use ICM, such as gadolinium-enhanced magnetic resonance angiography (MRA), non-contrast computed tomography (CT), CO_2 or gadolinium aortography, and intravascular ultrasound (IVUS), concluding that EVAR can be performed safely in patients with renal dysfunction or severe contrast allergy utilizing non-iodinated contrast-based imaging modalities[8].

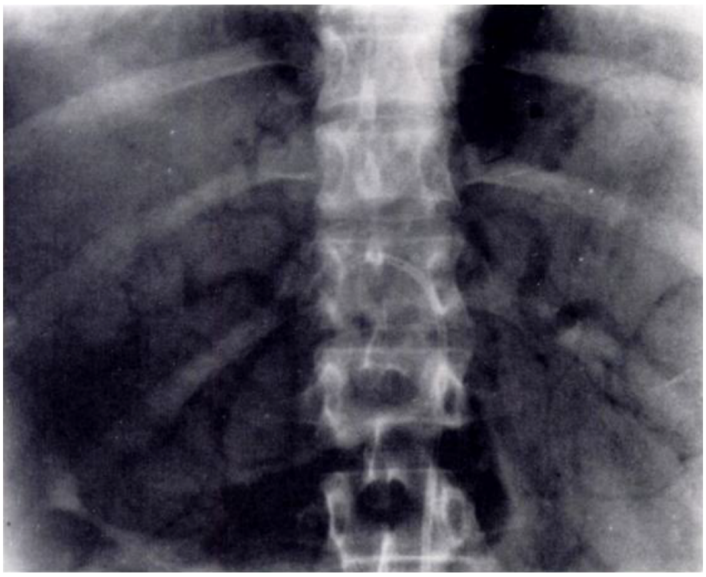
The History of CO_2 as an Intra-arterial Contrast Agent

CO_2 (Carbon Dioxide) is a non-nephrotoxic and non-allergic gas, which was first injected retroperitoneally in 1914, to outline the abdominal structures radiographically[9]. In 1956 Oppenheimer MJ et al[10] reported the use of CO_2 as a contrast medium in radiologic procedures with safe injections of carbon dioxide into the right atrium, in order to detect pericardial effusion and consequently diagnose diseases of pericardium[11,12,13,14,].

Lately, digital subtraction arteriography (DSA) for intravenous angiocardiography and arteriography allowed to improve the imaging of contrast media of very low concentration[15]. This radically improved the technique using less contrast medium and obtaining, therefore, higher quality images.

Hawkins IF[16] reported for the first time in 1981 the use of CO_2 as contrast media during digital subtraction angiographies, in order to reduce the amount of iodinated contrast medium (ICM), which was nephrotoxic for patients. In that paper, Hawkins recounted that in 1971 he injected inadvertently 70 cm^3 of CO_2 into a celiac artery with unexpected good images of the arterial tree (figure 1) and surprisingly without side effects.

Figure 1. Inadvertent room CO_2 injection (70 cm^3) in celiac artery with good visualization of major arteries. From *Hawkins IF. Carbon dioxide digital subtraction arteriography. AJR Am J Roentgenol. 1982 Jul;139(1):19-24.*



Hawkins IF described the technique (manual CO_2 injections) in detail and reported his first experience with 20 patients, which was safe and effective in terms of quality of images[16]. In 1984, Coffey R et al[17] reported the first experience of CO_2 injection in the cerebrovascular district in albino rats, with the occurrence of multifocal ischemic infarctions and disruption of the blood-brain barrier to macromolecular tracers. The authors recommended caution in the use of CO_2-DSA in super-aortic trunks, in order to avoid embolization of the central nervous system[17]. In contrast to these data Shifrin EG et al[18] described the use of CO_2 for cerebral angiography in 14 dogs, with no electroencephalographic or neurological side effects.

In 1991, Weaver FA et al[19] published the experience of 40 angiographies with CO_2-DSA in patients, who had contraindications for the use of ICM. The injections of CO_2 were performed in peripheral arteries of lower limbs using a syringe connected to a 5F catheter. The technique was safe, except from a postoperative nonfatal myocardial infarct after a popliteal percutaneous transluminal angioplasty (PTA) in one patient, transient tachypnea and tachycardia during a carbon dioxide/digital subtraction arteriography study in another patient[19].

After the first experience, the team of surgeons and radiologists of the university of Florida in 1993[20] published again a reviewed case series of 128 angiographies performed with CO_2 with an additional analysis of the quality of images. The authors concluded that CO_2 angiographies provided good quality of images with minimal risk. The technique was performed using a pre-procedural administration of intravenous glucagon in order to reduce bowel gas motion; the CO_2 was injected through a 4F catheter connected to a dedicated CO_2 gas arterial injector, developed at the university of Florida[20]. Carbon Dioxide related complications were seen in only two patients, one had postoperative diarrhea without sequelae and the other suffered a respiratory arrest 30 minutes after an emergency mesenteric CO_2 arteriogram; he was severely ill at the time of the arteriogram and subsequently died[20].

Moreover, Hawkins IF et al in 1994[21,22] reported a case series of 800 patients undergone angiography with CO_2. The images obtained were of equivalent diagnostic quality compared with those using conventional ICM. In the University of Florida, carbon dioxide became the radiologic contrast agent of choice in patients with renal insufficiency, especially in those with diabetes mellitus or pre-existing allergy to ICM[21].

In 1997 the 26-years-long experience of the university of Florida with CO_2 angiography was reported[23]. In 1998, Eschelman DJ et al[24] reported their experience with carbon dioxide manually injected through a 60 ml-syringe in 26 vascular interventional procedures (21 arterial, 5 venous). The only CO_2 was inadequate in 7/26 procedures, which required a minimal amount of ICM to be accomplished. In particular, procedures performed in the iliac and infrainguinal arteries required a minimal supplemental iodinated contrast material[24]. The authors concluded that carbon dioxide failed to provide satisfactory guidance in half of the intraabdominal procedures[24].

As underlined by Hawkins et al[25], the hand delivery of CO_2 was fraught with several potential dangers, such as delivery of unknown and possibly excessive volumes, explosive delivery and air contamination; the University of Florida invented a carbon dioxide dedicated injector, which was not approved by the United States Food and Drug Administration. For that reason, a plastic bag delivery system was introduced, which applied the principles learned during the development of the dedicated injector[25]. This system was then improved with the introduction of an O-ring fitting connection of CO_2, which decreased the possibility of inadvertent air aspiration and consequent less chance of operator error[26].

Bees NR et al reported in 1999 the first experience with an automated carbon dioxide injector[27], which allowed to increase the practicability and safety of using CO_2 routinely. The automated injector allowed to perform successfully carbon dioxide interventional arterial procedures with a diffusion of the technique in many centers around the world.

The first interventional approach was limited to peripheral arteriography and percutaneous transluminal angioplastiy (PTA)[28,29] in patients with peripheral artery disease (PAD); thereafter, the improvement of technical knowledge about CO_2 allowed to use it successfully also in the great vessels like the aorta in order to embrace the aneurysmal disease.

In 2007, Chao A et al[30] reported the first experience with endovascular aortic aneurysm repair (EVAR) performed using carbon dioxide angiography in 16 patients.

In 2020, Gallitto et al[31] described the first case series of juxtarenal and pararenal abdominal aneurysms treated with fenestrated endovascular aortic repair (FEVAR) performed using CO_2 and fusion imaging in order to reduce the ICM amount in these procedures.

Chapter 2

The Use of CO_2 in Standard Endovascular Aortic Aneurysm Repair

The first case series of endovascular aortic repair (EVAR) for unruptured abdominal aortic aneurysm (AAA) using CO_2 was published by Chao et al in 2007[30]. Sixteen patients underwent EVAR with CO_2 angiography with similar outcome compared with patients treated with ICM, except from longer fluoroscopy and operating room times and increased radiation exposure in the CO_2 group. However, in 13/16 of patients treated with CO_2 an adjunctive injection of ICM was necessary. In this first experience, an Angio Flush 3 fluid collection bag (Angiodynamics), with attached tubing and a stopcock inflated with CO_2 was used.

The first experience reported by Criado E et al in 2008[32] included the treatment 18 patients with EVAR performed using CO_2, which was delivered again using the Angio Flush delivery system. There was no postoperative CO_2-related complication.

Lee AD et al in 2010[33] published the successful experience with CO_2 EVAR using Angioset delivery system and introduced, for the first time, the problem of renal arteries visualization with CO_2, which was only 53% in that case series.

In 2012, Criado et al[34] again reported their updated experience with EVAR using CO_2 guidance and Angio flush delivery system, which is still the largest available in literature with 114 cases. The authors described a method of CO_2 administration through the sidearm of the aortic endograft delivery sheath, a method termed “catheter-less” angiography. Although other options exist for EVAR without the use of ICM, such as intravascular ultrasound guidance, the benefits of conventional fluoroscopic guidance and the high expense of intravascular ultrasound imaging should be taken into consideration in those instances.

The CO_2 EVAR case series published by Fujihara M et al[35] on 98 patients with chronic kidney disease (CKD) reported the first complications in literature related with CO_2 injections in EVAR procedures. Ten patients had transient leg pain and 4 complained of abdominal pain during the procedure. Furthermore, major adverse events occurred in 2 patients, who had intractable abdominal pain and were diagnosed with severe non-occlusive mesenteric ischemia (NOMI); in spite of intensive treatment, both patients resulted in death within 2 days. In this experience carbon dioxide was, in fact, delivered by manual injection; medical grade CO_2 gas cylinder with a regulator was connected to a sterile plastic tube with a bacteria-removal filter and a 50-ml delivery syringe. The complications occurred may be possibly related with the manual injection of CO_2, which is not safe particularly in the abdominal vessels.

In 2017, De Angelis C et al[36] had similar problems in 13 patients with CKD treated with EVAR and CO_2 angiography; the manual injection of CO_2 was related with 2 cases of abdominal pain and 1 case of renal function worsening. In the same year, De Almeida Mendes C et al[37] reported their case series of 16 patients treated with EVAR and CO_2, which was injected manually with no adverse events in the postoperative period; however, 10 of the 16 cases required ICM supplementation, which was performed because the image produced with CO 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 one internal iliac artery. Takeuchi Y et al[38] also reported the experience with 30 patients with CKD treated with EVAR and CO_2, which was successfully delivered with hand injection using digital subtraction imaging; there was one case of postoperative intestinal necrosis not related with CO_2 but potentially due to cholesterol embolism.

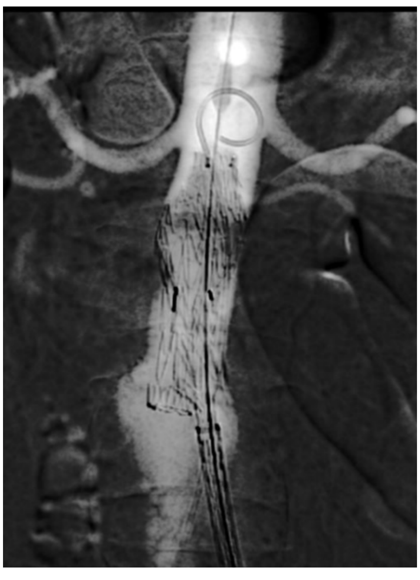
The first experience of CO_2 EVAR performed with an automated injector was published in 2018 by Mascoli C et al[39]. Thirty-one patients were treated with a technical success of 100% and an excellent visualization of hypogastric arteries (100% of cases); however, the juxtarenal landing zone was correctly identified with CO_2 angiography only in 19/31 cases (61%). There were no postoperative major adverse events, but 3 patients had nausea and hypotension after the procedure, which regressed spontaneously[39].

The three years' experience of the same group with 72 CO_2-EVAR procedures performed with automated injector was published in 2021 by Vacirca et al[40]. The authors reported the safety of the technique, which allowed to use a lower amount of ICM if compared with ICM-EVAR, with a consequent significant benefit on postoperative renal function. However, they found that the radiation dose is however significantly higher in CO_2-EVAR.

The Technique

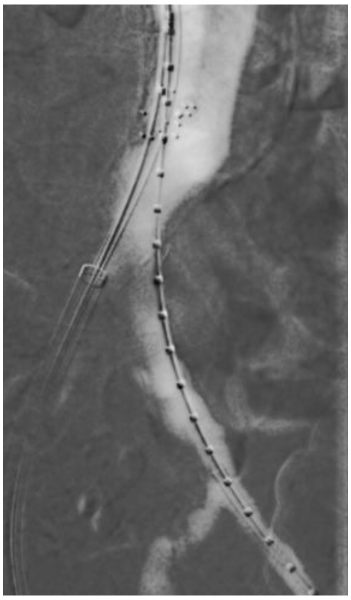
To adequately prepare patients to carbon dioxide injection in order to have better quality of images, activated carbon and poor slag diet should be administrated the two days before the intervention. After femoral arteries are exposed through bilateral incisions caudal to the inguinal ligaments, floppy guidewires are advanced into the suprarenal aorta under fluoroscopic guidance from both femoral sides and short 9-10 F sheaths are placed over the wire. The patient is given heparin. A floppy guidewire is then exchanged for a Lunderquist Extra Stiff Guidewire (Cook Medical Inc) or similar wire, and its tip placed in the proximal descending thoracic aorta from the side selected for main body deployment. The endograft main body is then advanced over the extra-stiff guidewire. Now it is possible to perform CO_2 injections in order to visualize the lowest renal artery. Sometimes the injections are performed from a short sheath but in most cases, CO_2 is injected through a diagnostic catheter 4-5 F (Pigtail or similar), which is advanced into the pararenal aorta (Figure 2).

Figure 2. CO_2 Angiography through 5F Pigtail catheter with correct visualization of renal arteries.



After the first angiographies, the main body is deployed according with the position of the lowest renal artery. Carbon dioxide injector is then connected to the contralateral sheath in order to visualize the contralateral hypogastric artery and consequently deploy the contralateral leg over another extra-stiff wire (Figure 3).

Figure 3. Hypogastric artery visualization with CO_2.



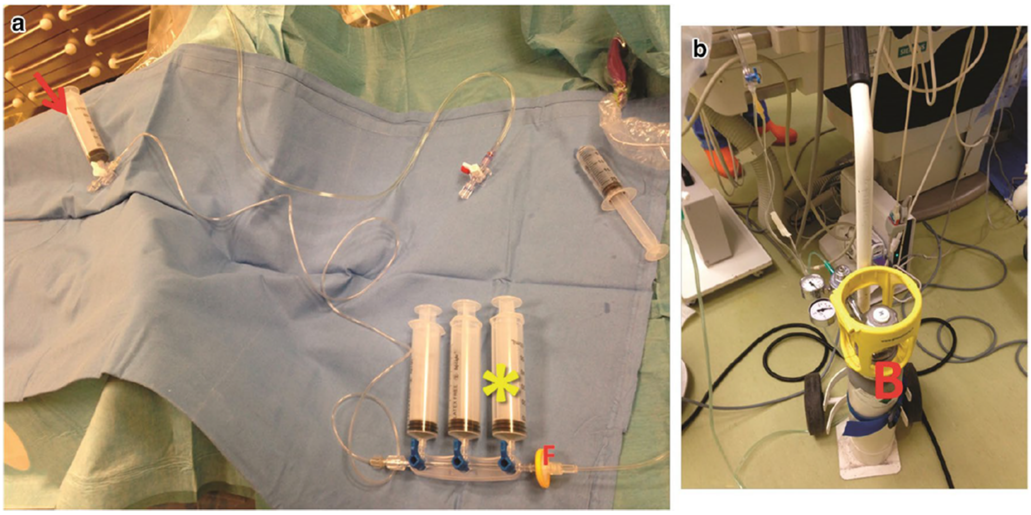
Then the CO_2 injector is connected to the ipsilateral sheath in order to detect the origin the ipsilateral hypogastric artery and deploy the ipsilateral leg. The final angiogram can be performed connecting CO_2 line to a short sheath or through a 5 F catheter (Figure 4).

Figure 4. Final Angiogram with CO_2.

The real technical variation between one center and another is the system used to deliver CO_2.

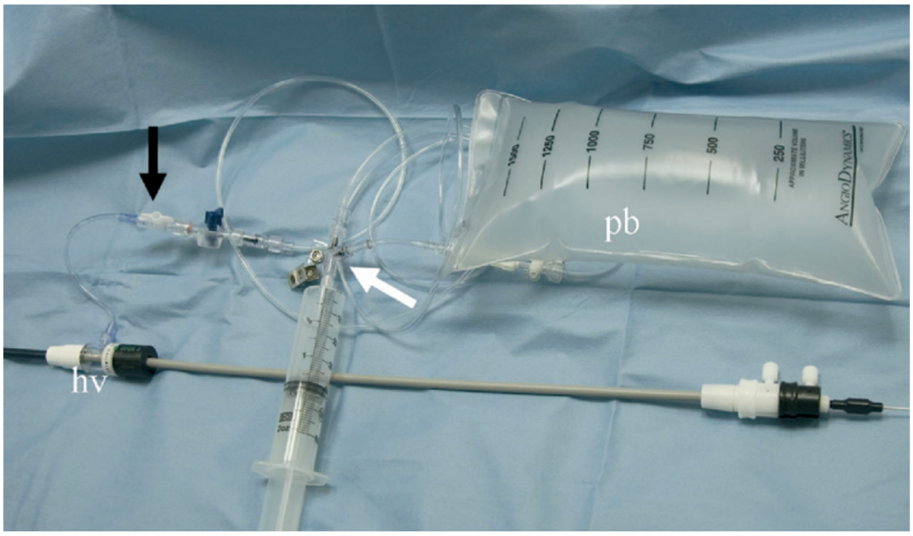
- Manual Injection: the manual injection system is normally "home-made" and composed by three Luer-lock syringes linked together forming a "reservoir", connected to another 20-ml syringe for diagnostic injection and to a disposable gas cylinder filled with 99% laboratory-grade CO_2 through a filter (Figure 5)[36]. The CO_2 canister (cylinder) is medical grade. The filter (0.2 µm) was necessary was specific to hold big particles (such as air) and purify the injected CO_2. Moreover, the filter prevented CO_2 emission into the room, that could be toxic and undetectable by the operators[9].

Figure 5. Manual CO_2 injection system in standard EVAR. From: *De Angelis C, Sardanelli F, Perego M, Alì M, Casilli F, Inglese L, Mauri G. Carbon dioxide (CO_2) angiography as an option for endovascular abdominal aortic aneurysm repair (EVAR) in patients with chronic kidney disease (CKD). Int J Cardiovasc Imaging. 2017 Nov;33(11):1655-1662.*



- Angioflush (AngioDynamics) delivery system: this system is connected to the side port of the endograft. About 20-milliliters of CO_2 are injected with a 60-milliliter syringe holding pressure in the plunger until the gas is heard and seen bubbling as it exits between the sheath and the grey dilator (Figure 6)[34]. At this point, a marked reduction in resistance is felt in the plunger and the delivery sheath is immediately advanced into the artery. This indicates that the fluid contained in the delivery sheath has been displaced by the CO_2 gas bubble which now occupies most of its lumen. This purging maneuver facilitates smooth, non-explosive CO_2 delivery during intravascular angiographic injection, and prevents air contamination of the delivery sheath while it remains outside the vascular lumen.

Figure 6. The Angioflush delivery system. From: *Criado E, Upchurch GR Jr, Young K, Rectenwald JE, Coleman DM, Eliason JL, Escobar GA. Endovascular aortic aneurysm repair with carbon dioxide-guided angiography in patients with renal insufficiency. J Vasc Surg. 2012 Jun;55(6):1570-5.*



- <u>Automated CO_2 Injector (Angiodroid):</u> the injection can be performed from the short sheath or through a diagnostic catheter. Each injection volume is 50-100 mL of CO_2, and the injection pressure can vary between 300-600 mm Hg (Figures 7 and 8)[39].

Figure 7. CO_2 infusion line connected to the sidearm of 10F/11 mm length sheet (yellow arrow) and ICM infusion line connected to pig tail catheter (white arrow). From: *Mascoli C, Faggioli G, Gallitto E, Vento V, Pini R, Vacirca A, Indelicato G, Gargiulo M, Stella A. Standardization of a Carbon Dioxide Automated System for Endovascular Aortic Aneurysm Repair. Ann Vasc Surg. 2018 Aug;51:160-169.*

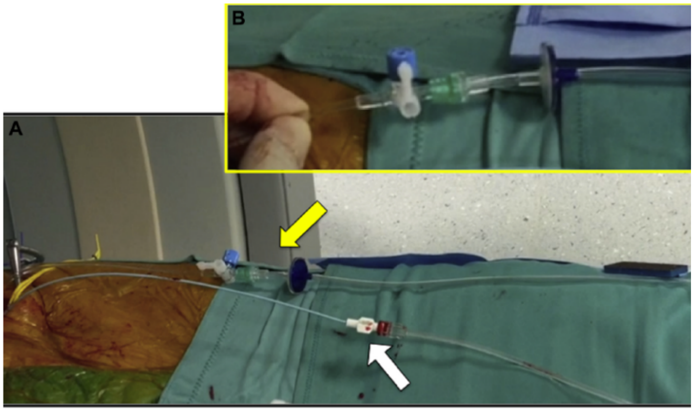
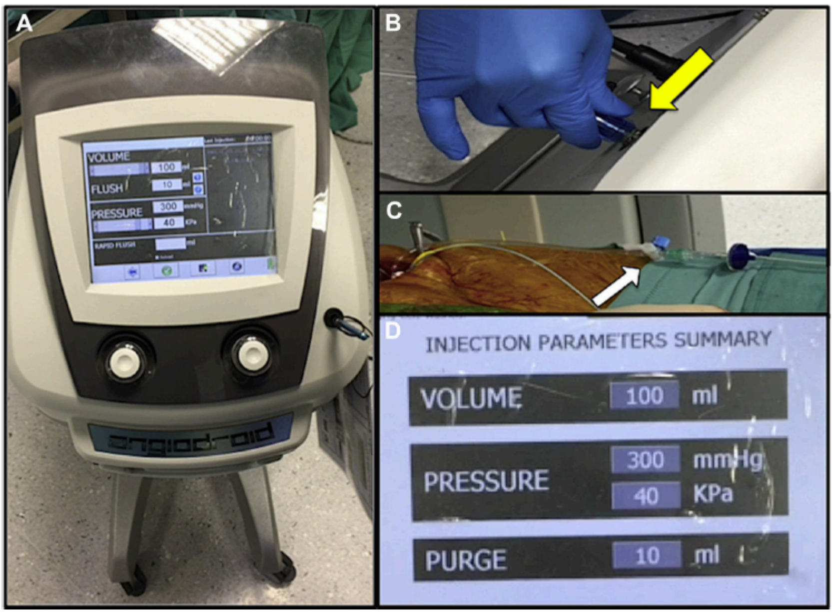


Figure 8. Tubing connection between automated injection system (yellow arrow) and the sidearm of 10F/11mm length sheet (white arrow). The display shows CO_2 injection volume and pressure. From: *Mascoli C, Faggioli G, Gallitto E, Vento V, Pini R, Vacirca A, Indelicato G, Gargiulo M, Stella A. Standardization of a Carbon Dioxide Automated System for Endovascular Aortic Aneurysm Repair. Ann Vasc Surg. 2018 Aug;51:160-169.*



Renal Arteries Visualization

As published by Lee AD et al[33],Mascoli C et al[39] and Vacirca et al[40] one of the main limitations about EVAR with CO_2 is the visualization of the lowest renal artery, which is crucial for the deployment of the endograft main body and consequently for the success of the endovascular implant. Lee AD et al[33] reported that carbon dioxide angiography successfully demonstrated the renal artery anatomy in 9/17 (53%) cases, in Mascoli et al[39] experience in 19/31 (61.3%) cases and in Vacirca et al[40] in 50/72 (69.4%) of CO_2-EVAR procedures.

The difficulty in the visualization of the lowest renal artery was possibly due to the presence of a wide AAA true lumen, significantly greater to that of patients in whom the lowest renal artery was properly visualized (96 [IQR: 25] mm^3 vs. 57 [IQR: 10] mm^3, $p=0.03$)[39]. This seemed to be confirmed by the fact that the lowest renal artery was correctly showed in 100% of the cases at completion CO_2 angiography, when the aortic lumen volume is reduced by the endograft and CO_2 has less dispersion. Furthermore, the difficulty to visualize renal artery may be probably related with the buoyancy property of carbon dioxide gas, which distribute in the anterior part of great vessels like the aorta; when the lowest renal artery originates posteriorly, CO_2 cannot opacify the vessel.

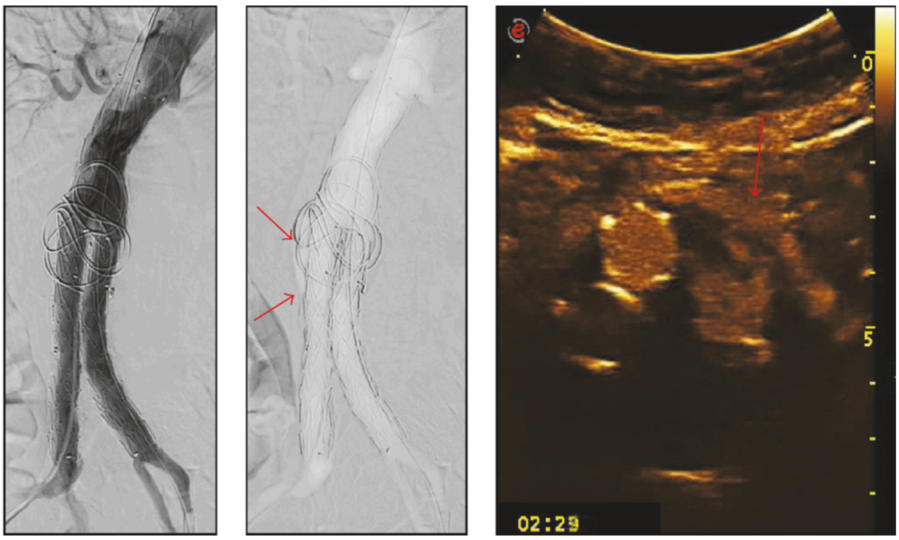
Type II Endoleak Detection

At final angiogram, CO_2 can be used also to detect the presence of possible endoleaks in EVAR procedures.

Huang SG et al[41] analyzed this aspect for the first time, comparing endoleak detection using ICM and CO_2 angiography. The authors concluded that interobserver agreement for the detection of endoleaks is superior with ICM compared to CO_2-DSA; however, the sensitivity for detecting any endoleak and both the sensitivity and specificity for detecting type I endoleaks using CO_2-DSA were acceptable. For detecting type II endoleaks using CO_2-DSA, the sensitivity and positive predictive value were poor. The evaluation performed by Sueyoshi E et al[42] reported that CO_2-DSA is reliable for the detection of persistent type II endoleaks in EVAR, with a higher sensitivity and specificity if compared with ICM (CO2-DSA: sensitivity 0.87, specificity 0.97; ICM-DSA: sensitivity 0.82, specificity 0.64).

The experience published by Mascoli C et al[43] about type II endoleak detection with carbon dioxide angiography with automated injector showed that CO_2 angiography is a safe and effective method for type II endoleak detection in EVAR, with a significantly higher agreement with CEUS if compared with angiography with ICM. Particularly, the only type II endoleak detected by ICM angiography was also detected by CO_2 angiography and CEUS (Figure 9); three type II endoleak detected by CO_2 angiography were not detected by CEUS. No cases of type II endoleak undetected by CO_2 angiography were visualized by CEUS.

Figure 9. Final angiogram with CO_2 and ICM angiographies in EVAR. The CO_2 angiography shows a type II endoleak, which is not visible with ICM; CEUS confirms the presence of type II endoleak. From: *Mascoli C, Faggioli G, Gallitto E, Vento V, Indelicato G, Pini R, Vacirca A, Stella A, Gargiulo. The Assessment of Carbon Dioxide Automated Angiography in Type II Endoleaks Detection: Comparison with Contrast-Enhanced Ultrasound. Contrast Media Mol Imaging. 2018 Mar 26;2018:7647165.*



Adverse Events

- Mesenteric Ischemia: As mentioned above, Fujihara M et al[35] reported 2 cases of non-occlusive mesenteric ischemia (NOMI) occurred in the postoperative period, which led patients to death. This is the only major adverse event related with CO_2 reported in literature up to now, analyzing all case series available in literature; however, the consequentiality between CO_2 angiography and mesenteric ischemia was not demonstrated and should be further investigated. Nevertheless, CO_2 manual injection is not always safe due to the high risk of air contamination and no precise control on injection pressure and should be avoided in angiographies of the abdominal arteries and in EVAR procedures.
- Leg pain: This adverse event was reported exclusively in the experience of Fujihara M et al[35] in 10/98 (10%) patients treated with EVAR and CO_2-DSA. The symptoms were transient and lasted very shortly. However, leg pain after CO_2 angiography is reported in literature in many patients with PAOD and can be overcome using lower pressure of the gas during the injection. Again, manual injection with possible air contamination and no precise control on injection pressure can be related with leg pain.
- Abdominal pain: Transient abdominal pain was reported by Fujihara M et al[3527] in 4/98 (4%) patients and by De Angelis C et al[36] in 2/13 (15%) patients. Carbon dioxide might cause a transient pain due to blood flow blockage into anterior vessels, such as superior and inferior mesenteric artery. Simply rotating the patient or applying a gentle pressure on the abdomen might be enough to fully restore the blood flow, and to resolve the symptoms. However, caution has to be made and at least few minutes should be waited in between one CO_2 administration and the other[36].
- Nausea and Hypotension: Mascoli et al[39] and Vacirca et al[40] reported 3 cases of postoperative severe hypotension, which regressed spontaneously. Carbon dioxide and in general hypercapnia, by its very nature, can lead to arterial hypotension, as reported in other experiences[30]. This symptom is generally transient and not dangerous for patients.

- Longer procedure time and higher radiation exposure: In the first experience with EVAR and CO_2, Chao A et al[30] reported a longer procedure and fluoroscopy time and higher radiation exposure. This result is strictly related with the low familiarity of vascular surgeons with the technique, which required more images and higher x-ray exposure. Vacirca et al[40] reported similar results, with a significantly higher mean radiation dose (total DAP) compared with ICM-EVAR. Therefore, after the initial learning curve, it is very important to reduce as much as possible the radiation dose for patient and surgeon security.

Chapter 3

Three Years' Experience with CO_2 in Standard EVAR Procedures

Objectives

Contrast induced nephropathy occurs in up to 7.5% of cases in endovascular aortic repair (EVAR). Carbon Dioxide (CO_2) has been proposed as an alternative agent to iodinated contrast medium (ICM); however, specific protocols are not universally adopted, and the visualization of the renal arteries may be suboptimal in some cases. The aim of this study was to analyze our CO_2-EVAR experience with automatic injections, in order to identify the anatomical characteristics associated with the best visualization of all the aortic vessels, with particular attention to the lowest renal artery (LoRA).

Methods

From 2016 to 2019, all EVAR performed with either CO_2 or ICM were analyzed and compared. CO_2-EVAR was performed using an automated injector (600 mmHg pressure; 100 cc volume); a small amount of ICM was injected in case of difficulty in LoRA visualization or doubts at the completion angiogram. Clinical and CT-Scan preoperative characteristics were considered. The study endpoints were technical success, amount of ICM and radiation dose, postoperative renal function and possible CO_2-related adverse events. Statistical analysis was by Fisher's exact, t-Student, Mann-Whitney tests and ROC curve.

Results

In the considered period, 321 EVAR procedures, 72 (22.4%) with CO_2 and 249 (77.6%) with ICM, were performed. The two groups were similar for clinical characteristics and preoperative renal function. ICM was injected in a significantly lower amount in the CO_2-EVAR group (52.8 ± 6.1 vs. 88.1 ± 9.2 cc, $p<0.001$), which received a significantly higher mean radiation dose (Total DAP: 500550.8 ± 377394.6 mGy/cm^2 CO_2-EVAR vs. 332301.8 ± 230139.3 mGy/cm^2 ICM-EVAR, p=0.001). Postoperative eGFR decreased significantly less in the CO_2-EVAR (2.3 $\pm$ 1.1 ml/min) compared with the ICM-EVAR group (10.6 $\pm$ 5.3 ml/min), p<0.001.

LoRA was correctly visualized in 50/72 (69.4%) cases of CO_2-EVAR, which had a significantly longer proximal neck [Median (IQR): 30 (14) vs. 18 (15) mm, p=0.001]. At ROC curve, a proximal neck length >24.5 mm was predictive of LoRA visualization (72.1% sensitivity, 73.8% specificity). Three CO_2-EVAR cases had intraoperative transient hypotension with no consequences. Sixteen/72 (22.2%) CO_2-EVAR procedures were performed using 0 cc of ICM.

Conclusions

CO_2-EVAR by automated injections is safe and requires a lower amount of ICM if compared with ICM-EVAR, with a consequent significant benefit on postoperative renal function. If specific anatomical situations are present, ICM may be completely unnecessary. The radiation dose is however significantly higher, therefore procedural protocols need further refinements.

Keywords

Aneurysm, abdominal aortic, iodinated contrast medium, carbon dioxide, renal function.

Introduction

Endovascular aortic repair (EVAR) is currently considered one of the first line treatments of abdominal aortic aneurysms (AAA), and it may be preferable over open repair due to its lower invasiveness. However, EVAR procedures are not devoid of postoperative complications, including renal function worsening, which is associated with decreased long-term survival[44].

The cause of renal dysfunction after EVAR is possibly multifactorial, with a transient effect in most cases[5]. One of the main cause for this could be the intraoperative administration of iodinated contrast medium (ICM), which may lead to contrast induced nephropathy (ICM) in up to 7.5% cases of EVAR[45]. From this perspective, EVAR procedures in patients with renal dysfunction can be particularly harmful, possibly leading to end-stage renal disease and hemodialysis; in these cases, minimizing the amount of ICM is important [7].

Carbon Dioxide (CO_2) - a non-allergic and non-nephrotoxic gas - has been proposed as an alternative to ICM for interventional procedures and its use during endovascular aortic repair (CO_2-EVAR) has increased in the last ten years[30,32,33,34,35,36,37,38] , particularly after the diffusion of automated injectors, able to ensure precise volumes and pressures of CO_2 delivery[39].

Despite these premises, standardized technical protocols are lacking, and the predictors of an optimal visualization of the important landmarks for a successful EVAR are largely unknown. Specifically, some authors reported a correct visualization of the lowest renal artery (LoRA) in only 50-60% of cases[33,39], which is clearly insufficient to warrant a precise deployment of the endograft main body. With this study we aimed to analyze the experience of a single center in CO_2-EVAR procedures, in order to define a precise technical protocol and the possible advantages of this procedure compared with EVAR performed with ICM (ICM-EVAR).

Methods

From September 2016 to September 2019 all EVAR procedures performed with CO_2 and ICM in a single center were retrospectively analyzed and compared.

EVAR procedure was performed following the current guidelines about abdominal aortic aneurysm (AAA) treatment in terms of aneurysm diameter and adequate patients' clinical and anatomical characteristics[46].

Only EVAR standard procedures, defined as aorto-bi-common-iliac procedures inside the manufacturer instructions for use, were considered. Ruptured AAA were excluded from data collection; however, symptomatic AAA urgently treated with EVAR were included. Aorto-uniliac implants with femoro-femoral bypass, iliac branch devices, or external iliac landing with hypogastric artery embolization were all excluded from the study.

Either infra-renal (Gore Excluder C3 - W.L.Gore & Associates, Flagstaff, Arizona, USA; Vascutek Anaconda - Vascutek, Terumo , Inchinnan, Scotland, UK) or supra-renal fixation endografts (Cook Zenith Flex/Cook Zenith Alpha -Cook Medical, Bloomington, Indiana, USA; and Medtronic Endurant Medtronic, Minneapolis, Minnesota, USA) were used in the study period.

Patients were treated by either CO_2-EVAR or ICM-EVAR outside a specific randomization plan. The study was approved by our Institutional Review Board. Every patient signed a specific consent form of acceptance to be included in the study. All data were entered into a dedicated database.

Preoperative characteristics

All patients' preoperative characteristics, such as age, gender, cardiovascular risk factors - chronic hypertension (blood pressure ≥140/90 mmHg), dyslipidemia (total cholesterol >200 mg/dl or low density lipoprotein >120 mg/dl), diabetes mellitus (≥126 mg/dl at fasting plasma glucose), current smoking habit, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), peripheral artery disease (≥3 stage of Rutherford classification[47]), atrial fibrillation, anticoagulant therapy, cerebrovascular insufficiency (carotid stenosis >50%), preoperative Creatinine (mg/dl), estimated glomerular filtration rate (eGFR ml/min), chronic kidney disease requiring hemodialysis and the American Society of Anesthesiologists (ASA) score were included in the database and stratified in CO_2-EVAR and ICM-EVAR groups. All patients were evaluated by computed tomography angiography (angio-CT) before treatment, in order to define all the anatomical characteristics. The angio-CT was performed several months before the procedure, except for urgent cases, in which the CT was done less than 72 hours before EVAR. The center lumen line and volume rendering were assessed for the planning of each case, using a dedicated software for vessels analysis (3mensio, Vascular Imaging, Bilthoeven, The Netherlands). Maximum diameter of the AAA, length and diameter, as well as severe tortuosity (angle <120°), calcification (>50% of vessel lumen), thrombosis (>50% of vessel lumen) of the aneurysmal proximal neck, were all defined following the Chaikof classification[48]. Following the clock position, renal arteries were defined anterior in case of ostium originating between 9.30 and 2.30 (hh.mm). The diameter of the LoRA was also considered. The number of accessory renal arteries, which were all covered during the procedure, was compared between CO_2-EVAR and ICM-EVAR groups.

Procedural Outcome

The two CO_2-EVAR and ICM-EVAR populations were compared in terms of procedural outcome, including the number of urgent cases, the mean ICM amount injected in cc, and the radiation dose, which was measured in mGy/cm^2 using fluoroscopy, digital subtraction angiography (DSA) and total dose-area product (DAP). All DSA angiographies, in both CO_2-EVAR and ICM-EVAR procedures, were performed using the same frame rate, which was 6 frames per second (fps). Also type of anesthesia, whether general, spinal or local, were analyzed and compared in the 2 groups.

Postoperative Outcome

Thirty-day mortality and postoperative Creatinine (mg/dl) and eGFR (ml/min) of CO_2-EVAR and ICM-EVAR groups were analyzed. Patients' of both populations – CO_2- and ICM-EVAR – underwent postoperative intravenous fluid therapy with 1000-1500 cc for the first 24 hours, independently of the preoperative renal function. The mean increase of serum Creatinine (mg/dl) and the mean decrease of eGFR (ml/min) in the postoperative period (second postoperative day), as well as postoperative renal function worsening requiring hemodialysis were used as indices of renal impairment.

The length of hospitalization was also analyzed.

CO_2-EVAR Operative Technique

Patients were submitted to a slag-free diet the day before the intervention and activated carbon was administered the same day (Simethicone 2 tablets, 3 times a day), in order to minimize bowel gas disturbance of intraoperative images. Carbon dioxide injections were performed using the Angiodroid (Angiodroid Srl, San Lazzaro di Savena, Bologna, Italy) automated delivery system, which is specific for CO_2 arteriography. This is the only automated CO_2 injector currently available in the market, which allows to inject the gas at a preset volume and pressure; other systems, such as CO_2-Angioset (Optimed, Ettlingen, Germany) or Co2mmander (Angioadvancements, Florida, USA) are carbon dioxide reduction valves connected to a gas cylinder and a syringe, with higher probability of gas dispersion.

All the procedures were performed in a new-generation Philips hybrid room (Philips Healthcare, Best, The Netherlands).

The CO_2 automated injector was connected together with the ICM injector to a three-way stopcock, which was in its turn connected to a 5 F diagnostic Pig-tail catheter. Before the first injection, it is necessary to flush the automated injector; thereafter it is possible to perform successive CO_2 injections with no additional latency time.

The volume of each carbon dioxide injection was between 50 and 100 mL, and the injection pressure varied between 300-600 mmHg, according to the injector's instructions for use.

Floppy guidewires were inserted either percutaneously or after surgical cut down in both the femoral arteries and advanced into the suprarenal aorta under fluoroscopic guidance over (11 cm long) 10 F sheaths. Systemic heparinization was given at 50-70 UI/kg, in order to achieve and maintain an activated clotting time (ACT) between 200 and 300 seconds. One of the floppy guidewires was then exchanged for a Lunderquist Extra Stiff Guidewire (Cook Medical Inc), and its tip placed in the proximal descending thoracic aorta from the side selected for the main body deployment. The endograft main body was then advanced over the extra-stiff guidewire. CO_2 injections were performed at this point through a 5 F Pig-tail catheter connected to the three-way stopcock, which was advanced into the pararenal aorta from the contralateral access in order to visualize the LoRA.

After the first CO_2 angiography, the main body was deployed according with the position of the LoRA. If the LoRA was not correctly visualized, a small amount of 10 cc of ICM was then injected. Carbon dioxide injector was then connected to the contralateral sheath in order to visualize the contralateral hypogastric artery and consequently deploy the contralateral leg over another extra-stiff wire. The CO_2 injector was then connected to the ipsilateral sheath in order to detect the origin the ipsilateral hypogastric artery and deploy the ipsilateral leg. The final angiogram was performed connecting the CO_2 line either to a short 10F sheath or through a 5 F Pig-tail catheter.

CO_2-EVAR Group Analysis

The technical success was defined as the accomplishment of an aorto-bi-iliac implant using CO_2 with patency of renal and hypogastric arteries, absence of type I/III endoleaks, and no conversion to open repair or 24-hour mortality. The endoleaks were stratified according to White and May et classification[49]. The total number of CO_2 injections was analyzed, as well as the visualization of the LoRA and the hypogastric arteries. The mean amount of ICM (ml) used during the procedure was calculated and cases with zero iodinated contrast injections were identified. Fluoroscopy, digital subtraction angiography (DSA) and total dose-area product (DAP) were reported as measure of radiation during the procedure (mGy/cm^2). Iodinated contrast medium and radiation dose were compared in procedures performed in the first year of learning curve (LC-CO_2-EVAR) and in those accomplished afterwards by experienced operators (EX-CO_2-EVAR).

The possible intraoperative side-effects or adverse events related with carbon dioxide angiographies, were reported. The Endoleak detection at final angiogram with CO_2 or ICM was confirmed using doppler ultrasound (DUS) or contrast-enhanced ultrasound (CEUS) with SonoVue contrast before patients' discharge.

The possible postoperative side-effects or adverse events possibly related with carbon dioxide angiography were recorded.

Lowest renal artery visualization in CO_2-EVAR

All the anatomical characteristics of the proximal aneurysm neck (length, diameter, tortuosity, valcification/thrombosis), of the LoRA (diameter and anterior clock position between 9.30 and 2.30) and of the aneurysm sac (diameter) were analyzed in order to identify the possible predictors of LoRA visualization with CO_2 angiography.

Statistical Analysis

Categorical variables were expressed as frequency and compared using Fisher's exact test. Continuous variables were reported as mean ± standard deviation and median and interquartile range (IQR) for smaller groups and compared using Student's t-test and Mann-Whitney tests. ROC curve by the Youden *J* statistic (J = sensitivity + specificity − 1) was used to test sensitivity and specificity and to identify every possible cut-off of significant results in continuous variables. All the statistical tests were two-sided and p values of 0.05 or less were considered statistically significant. Statistical analysis was performed by SPSS 23.0 for Apple (SPSS Inc, Chicago, Illinois, USA).

Results

From September 2016 to September 2019, 321 EVAR procedures were performed, 72/321 (22.4%) with CO_2 and 249/321 (77.6%) with ICM. Patients had a mean age of 76.9 ± 7.8 years and 290/321 (90.3%) of them were male.

Preoperative characteristics

Patients' clinical preoperative characteristics are reported in Table I. As shown, CO_2-EVAR and ICM-EVAR populations were similar in terms of clinical characteristics and preoperative renal function. The overall number of accessory renal arteries, which were all covered during endografting, was similar between the 2 groups (n° accessory renal arteries: CO_2-EVAR 5/72 (7%) vs. 19/249 (7.6%) ICM-EVAR, p=0.94).

Table I. Clinical preoperative characteristics.

	Tot N=321 *N (percent) or Mean ± SD*	CO_2-EVAR=72 *N (percent) or Mean ± SD*	ICM-EVAR=249 *N (percent) or Mean ± SD*	P value
Age	77.1 ± 7.7	76.7 ± 8.2	77.2 ± 7.5	0.66
Male sex	290 (90.3%)	67 (93.1%)	223 (89.5%)	0.49
Hypertension	277 (86.2%)	60 (83.3%)	217 (87.1%)	0.42
Active Smoker	77 (23.9%)	19 (26.4%)	58 (23.2%)	0.35
Dyslipidemia	232 (72.2%)	56 (77.8%)	176 (70.6%)	0.28
Diabetes	57 (17.7%)	16 (22.2%)	41 (16.4%)	0.28
Coronary Artery Disease (CAD)	98 (30.5%)	20 (27.8%)	78 (31.3%)	0.55
Chronic Obstructive Pulmonary Disease (COPD)	138 (43%)	32 (44.4%)	106 (42.5%)	0.78
Peripheral Artery Occlusive Disease (PAOD)	23 (7.1%)	2 (2.8%)	21 (8.4%)	0.10
Atrial Fibrillation	53 (16.5%)	11 (15.3%)	42 (16.8%)	0.78
Oral Anticoagulant Therapy	54 (16.8%)	11 (15.3%)	43 (17.2%)	0.85
Cerebrovascular Insufficiency	53 (16.5%)	14 (19.4%)	39 (15.6%)	0.46
Hemodialysis	3 (0.9%)	1 (1.4%)	2 (0.8%)	1
Preoperative Creatinine (mg/dl)	1.1 ± 0.7	1.2 ± 0.8	1.0 ± 0.6	0.09
Preoperative eGFR (ml/min)	70.9 ± 15.8	66.4 ± 14.4	71.5 ± 16.2	0.08
ASA score 3/4	303 (94.4%)	68 (94.4%)	235 (94.3%)	0.12

Procedural Outcome

Procedural results about the overall population, as well as those about CO_2-EVAR and ICM-EVAR subgroups are reported in Table II. The mean ICM amount was significantly lower in CO_2-EVAR group compared with ICM-EVAR population (52.8 ± 6.1 cc CO_2-EVAR vs. 88.1 ± 9.2 cc

ICM-EVAR, $p<0.001$); the DSA radiation dose DAP (366901.1 $\pm$ 307701.3 mGy/cm^2 CO_2-EVAR vs. 175862.6 $\pm$ 126061.3 mGy/cm^2 ICM-EVAR, $p<0.001$) and total radiation dose DAP (500550.8 $\pm$ 377394.6 mGy/cm^2 CO_2-EVAR vs. 332301.8 $\pm$ 230139.3 mGy/cm^2 ICM-EVAR, $p=0.001$) were significantly higher in CO_2-EVAR population compared with ICM-EVAR group.

Table II. Procedural outcome.

	Tot N=321 *N (percent) or Mean $\pm$ SD*	CO_2-EVAR=72 *N (percent) or Mean $\pm$ SD*	ICM-EVAR=249 *N (percent) or Mean $\pm$ SD*	P value
Urgent Cases	25 (7.7%)	4 (5.5%)	21 (8.4%)	0.42
Suprarenal Fixation Graft	175 (54.5%)	41 (57%)	134 (53.8%)	.9
ICM amount (ml)	80.9 $\pm$ 8.5	52.8 $\pm$ 6.1	88.1 $\pm$ 9.2	<0.001*
Fluoroscopy Radiation Dose DAP (mGy/cm^2)	150159.2 $\pm$ 129219.1	142109.5 $\pm$ 113534.4	156439.2 $\pm$ 132303.8	0.33
DSA Radiation Dose DAP (mGy/cm^2)	265270.9 $\pm$ 247845.7	366901.1 $\pm$ 307701.3	175862.6 $\pm$ 126061.3	<0.001*
Total Radiation Dose DAP (mGy/cm^2)	414635.3 $\pm$ 320944.8	500550.8 $\pm$ 377394.6	332301.8 $\pm$ 230139.3	0.001*
Anesthesia Type: General Spinal Local	 135 (42.3%) 181 (56.7%) 3 (0.9%)	 28 (38.9%) 44 (61.1%) 0	 107 (43.3%) 137 (55.5%) 3 (1.2%)	0.48

*p < 0.05 significant

Postoperative Outcome

The postoperative outcome of, CO_2-EVAR and ICM-EVAR populations is reported in Table III. The mean postoperative Creatinine increase was significantly lower in CO_2-EVAR population compared with ICM-EVAR group (0.08 $\pm$ 0.04 mg/dl CO_2-EVAR vs. 0.17 $\pm$ 0.09 mg/dl ICM-EVAR, $p=0.01$) and the mean postoperative eGFR decrease was significantly higher (2.3 $\pm$ 1.1 ml/min CO_2-EVAR vs. 10.6 $\pm$ 5.3 ml/min ICM-EVAR, $p<0.001$).

Table III. Postoperative outcome of CO_2-EVAR and ICM-EVAR populations.

	Tot N=321 *N (percent) or Mean ± SD*	CO_2-EVAR=72 *N (percent) or Mean ± SD*	ICM-EVAR=249 *N (percent) or Mean ± SD*	P value
Death	4 (1.2%)	0	4 (1.6%)	0.93
Postoperative Creatinine (mg/dl)	1.16 ± 0.7	1.2 ± 0.9	1.15 ± 0.6	0.53
Postoperative eGFR (ml/min)	67.8 ± 7.1	69.2 ± 7.8	67.2 ± 6.7	0.47
Creatinine Increase (mg/dl)	0.15 ± 0.08	0.08 ± 0.04	0.17 ± 0.09	0.01*
eGFR Decrease (ml/min)	8.8 ± 4.9	2.3 ± 1.1	10.6 ± 5.3	<0.001*
Renal Function Worsening Requiring Hemodialysis	2 (0.6%)	0	2 (0.8%)	1
Post-OP Hospital Stay (days)	4.8 ± 3.1	4 ± 2.3	5 ± 3.5	0.27

*p < 0.05 significant

CO_2-EVAR group Analysis

The anatomical characteristics of patients submitted to CO_2-EVAR are reported in Table IV.

As shown in Table V, the technical success was achieved in 100% of cases. The mean number of CO_2 injections performed was 7.8 ± 3.4 per procedure and the mean amount of ICM used in the procedures was 52.8 ± 6.1 ml. The LoRA was correctly visualized in 50/72 (69.4%) cases, whereas the hypogastric arteries were detected in 100% of cases.

Table IV. Anatomical characteristics of CO_2-EVAR patients.

	CO_2-EVAR=72 *N (percent) or Mean ± SD*
Aneurysm Maximum Diameter (mm)	56.4 ± 12
Proximal Neck Length (mm)	28.5 ± 7.2
Proximal Neck Diameter (mm)	23 ± 3.6
Proximal Neck Severe Angulation (<120°)	3/72 (4.1%)
Proximal Neck Severe Calcification (>50%)	2/72 (2.7%)
Proximal Neck Severe Thrombosis (>50%)	8/72 (11.1%)
Lowest Renal Anterior Origin (clock position 9.30-2.30)	40/72 (55.5%)
Lowest Renal Diameter (mm)	5.7 ± 1.2

In 16/72 (22.2%) cases of CO_2-EVAR the procedure was accomplished with no iodinated contrast medium at all.

In procedures performed during operators' learning curve LC-CO_2-EVAR the median amount of ICM used [Median ICM cc: LC-CO_2-EVAR 88 (22) vs 30 (11) EX-CO_2-EVAR $p<0.001$] and total radiation dose [Total DAP mGy/cm^2: LC-CO_2-EVAR 471354 (42361) vs 246555 (15367) EX-CO_2-EVAR $p<0.001$] were significantly higher compared with those performed by experienced operators EX-CO_2-EVAR.

Three patients developed a transient significant hypotension during the procedure, which resolved spontaneously. Two of them, under locoregional anesthesia, experienced nausea before becoming hypotensive, then had systolic blood pressure <100 mmHg for about 10 minutes with no necessity of pharmacologic intervention. The other patient, under general anesthesia, developed only severe hypotension, with systolic blood pressure below 60 mmHg for about 5 minutes, which resolved spontaneously. All the three patients underwent angio-CT immediately after the intervention with no evidence of any unexpected feature; the ICM used for the angioCT was included in the amount of ICM used for the EVAR procedure in these patients in order to not distort the results. The procedural details are reported in Table V.

Table V. Procedural details of CO_2-EVAR.

	CO_2-EVAR=72 *N (percent) or Mean ± SD*
Technical Success	72 (100%)
N° of CO_2 Injections	7.8 ± 3.4
Lowest Renal Artery Visualization with CO_2	50 (69.4%)
Hypogastric Arteries Visualization with CO_2	72 (100%)
ICM amount (ml)	52.8 ± 6.1
Zero Contrast	16 (22.2%)
Anesthesia Type: General Spinal Local	 28 (38.9%) 44 (61.1%) 0
Intraoperative Adverse Events CO_2-related	3 (4.1%)

At final angiogram, no type I or type III endoleaks were detected by CO_2 angiography; these data were confirmed by postoperative DUS/CEUS. A type II endoleak was identified in 10 (13.8%) cases; however, at DUS/CEUS performed before discharge in 8 (11.1%) cases type II endoleak was detected.

There were no cases (0/72 patients) of post-operative adverse events related to CO_2 injection.

The Lowest Renal Artery Visualization in CO_2-EVAR

As reported above, the LoRA was correctly visualized in 50/72 (69.4%) CO_2-EVAR cases. The only anatomical characteristic significantly related with the LoRA visualization was the median proximal neck length. Particularly, the proximal neck was significantly longer in cases where LoRA was correctly visualized [LoRA visualized 30 (IQR:14) vs LoRA not visualized 18 (IQR:15) mm, p=0.001], as reported in Table VI.

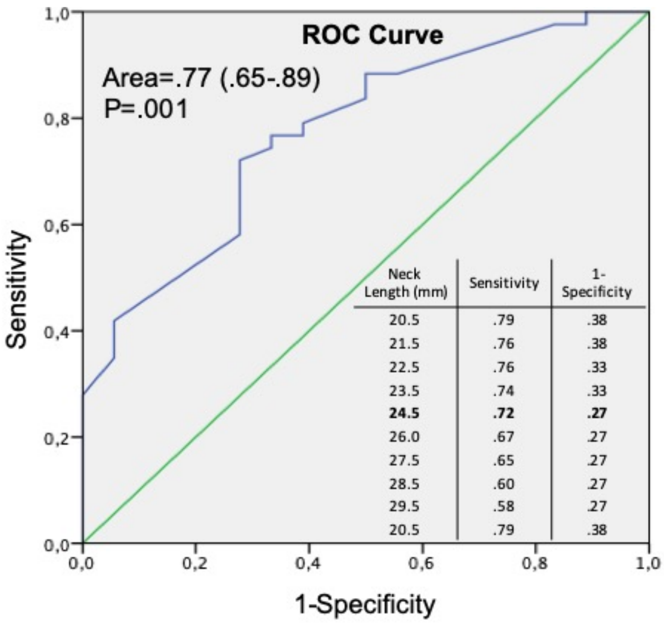
Table VI. The impact of anatomic characteristics on lowest renal artery visualization.

	CO_2-EVAR=72		
	LoRA Visualization *N (percent) or Median (IQR)*		P value
	Yes	No	
Proximal Neck Length (mm)	30 (14)	18 (15)	0.001*
Proximal Neck Diameter (mm)	22 (4)	25.5 (8)	0.34
Proximal Neck Severe Angulation	2 (2.7%)	1 (1.3%)	0.22
Proximal Neck Severe Calcification	1 (1.3%)	1 (1.3%)	0.16
Proximal Neck Severe Thrombosis	5 (7%)	3 (4.1%)	0.2
Lowest renal anterior origin	30 (41.6%)	10 (13.8%)	0.25
Lowest renal diameter (mm)	6 (2)	5.5 (2)	0.46
Aneurysm Maximum Diameter (mm)	56 (13)	53 (11)	0.12

*p < 0.05 significant

The ROC curve was then used to identify a cut-off value of proximal neck length. A proximal neck longer than 24.5 mm was predictive of LoRA visualization with 72.1% sensitivity and 73.8% specificity, as shown in Figure 10.

Figure 10. ROC curve evaluation for the sensitivity and specificity of proximal neck length (in mm) as a predictor for lowest renal artery visualization. By the Youden J statistica, the best cut-off value was 24.5 mm. Area [95% confidence interval (CI)].



Discussion

In this 3-year experience, 72 EVAR procedures were accomplished with CO_2 angiography, with 0% mortality and a significant lower impact on renal function compared with usual ICM. To the best of our knowledge, this is the largest series of EVAR with the use of an automated carbon dioxide injector. As a matter of fact, several papers described EVAR with CO_2, however none of them was performed with an automated injector, therefore their procedural protocols are difficult to be compared. In 2012, Criado E et al[34] reported the largest experience with CO_2-EVAR so far, including 114 cases treated with Angio flush delivery system. One year later, Huang SG et al[41] analyzed 76

CO_2-EVAR procedures, focusing on endoleak detection. Other 98 cases of CO_2-EVAR performed with manual injections were reported by Fujihara M et al[35] in 2015.

In the present series, the technical success of CO_2-EVAR was 100% and the hypogastric arteries were correctly visualized in all cases. This aspect should not be ignored; as reported in our preliminary experience [39], the distal sealing zone in CO_2-EVAR procedures performed with automated injectors is always well detectable, particularly when the injection is performed through the 10F-11cm long sheath.

Ten type II endoleaks were detected with CO_2 at completion angiogram in this series, but only 8 of them were visible at pre-discharge DUS and/or CEUS. This finding is consistent with previous reports by our group (Mascoli C et al[43]) and by Huang SG et al[41], where CO_2 angiography showed higher sensitivity and specificity in type II endoleak detection compared with standard ICM angiogram and CEUS .

As already reported in our preliminary experience[39] , intraoperative adverse events related with carbon dioxide angiography are negligible, since only 3 patients (4.1%), developed a transient intra-procedural severe hypotension with spontaneous regression and no postoperative consequences .

With our device, the mean amount of ICM used to accomplish CO_2-EVAR procedures was 52.8 $\pm$ 6.1 ml, greater than the amount used by Criado E et al (37 ml)[34] and Fujihara M et al (15.0 $\pm$ 18.1 ml)[35]. This difference, not impacting on postoperative renal function, can be explained with the learning curve of the technique, which initially required more ICM in order to achieve a similar image quality of standard angiographies.

Of most importance, the mean ICM amount was significantly lower in CO_2-EVAR group compared with ICM-EVAR population (52.8 $\pm$ 6.1 cc CO_2-EVAR vs. 88.1 $\pm$ 9.2 cc ICM-EVAR, $p<0.001$). De Almeida Mendes et al[37] had a median of 5.5 cc of ICM in the CO_2-EVAR and 35.5 in the iodine group; in Chao et al[30] case series, the mean iodinated contrast use was 27 cc for carbon dioxide group and 148 cc in control group ($p <.0005$). Similarly, Criado et al[34] showed a lower ICM mean amount in CO_2-EVAR (37 vs 106 cc; $p <.001$), the same as Takeuchi et al[38] (18 vs. 55 cc, p

<0.0001). Therefore, our study is consistent with the literature in demonstrating the advantage of CO_2-EVAR procedures in terms of amount of ICM used.

The procedural outcome, however, showed a significantly higher DSA radiation dose DAP (366901.1 $\pm$ 307701.3 mGy/cm^2 CO_2-EVAR vs. 175862.6 $\pm$ 126061.3 mGy/cm^2 ICM-EVAR, $p<0.001$) and total radiation dose DAP (500550.8 $\pm$ 377394.6 mGy/cm^2 CO_2-EVAR vs. 332301.8 $\pm$ 230139.3 mGy/cm^2 ICM-EVAR, $p=0.001$) in the CO_2-EVAR population compared with the ICM-EVAR group. The literature shows inconsistencies in this regard, since Chao et al[30] had similar results, whereas Takeuchi et al[38] found no difference in the 2 populations and Criado et al[34] found longer radiation dose in the ICM-EVAR population. In our experience, the higher radiation exposure in CO_2 patients could be explained with the initial learning curve needed to refine the technique for both surgeons and radiology technicians. Furthermore, the automated injector needs to be better synchronized with the c-arm, in order to reduce x-ray dose exposure during DSA.

The eventual scope of our study is to evaluate the possible benefit on postoperative renal function which can be obtained by decreasing the amount of ICM through CO_2 in EVAR procedures. In this experience, the mean postoperative Creatinine increase was significantly lower in the CO_2-EVAR population compared with the ICM-EVAR group (0.08 $\pm$ 0.04 mg/dl CO_2-EVAR vs. 0.17 $\pm$ 0.09 mg/dl ICM-EVAR, $p=0.01$), with a significant difference in the mean postoperative eGFR decrease (2.3 $\pm$ 1.1 ml/min CO_2-EVAR vs. 10.6 $\pm$ 5.3 ml/min ICM-EVAR, $p<0.001$). Similarly, Criado et al[34] showed a greater eGFR decrease (12.7%) in EVAR performed with ICM rather than CO_2 ($p=0.004$). Recently, similar results were found also in fenestrated endovascular repairs (FEVAR); CO_2-FEVAR required a lower overall amount of procedural ICM, with consequent benefits on perioperative renal function [31].

Abdominal or legs pain or mesenteric ischemia were reported by Fujihara et al[35] , but were not observed in our series; this occurrence may be therefore related with the manual injection of CO_2. Our data show that CO_2-EVAR can be considered safe using an automated injector also at high volume (100 cc) and pressure (600 mmHg) of gas injection.

The visualization of the lowest renal artery is however still suboptimal in some CO_2-EVAR procedures. Lee et al[33] reported that carbon dioxide angiography successfully showed the renal artery anatomy in 9/17 (53%) cases, and the same occurred in 19/31 cases (61.3%) of our preliminary experience [39]. A difficult visualization of the lowest renal artery can be determined by the presence of a wide AAA true lumen; this hypothesis is supported by the great enhancement of its visualization with the reduction of the volume of the aortic lumen obtained with the insertion of the endograft main body, which reduces the CO_2 dispersion. Furthermore, one should consider the buoyancy property of the carbon dioxide gas, which tend to distribute in the anterior part of the great vessels like the aorta; when the lowest renal artery originates posteriorly, the CO_2 buoyancy impedes the opacification of this vessel. This is not the only reason to explain the difficulty in renal artery visualization, however. By increasing the expertise with CO_2 injection, the lowest renal artery was correctly visualized in 50/72 (69.4%) cases. Surprisingly, a more efficient LoRA detection was not directly related with the anterior origin of the lowest renal (clock position between 9.30 and 2.30) but with the length of the proximal neck, with a threshold value of 24.5 mm at ROC curve. This aspect has not been analyzed before in the literature and should be further investigated; however, it can be hypothesized that a longer proximal neck provides a lower dispersion of the gas in the aneurysm sac, a preferential distribution of carbon dioxide in the para visceral aorta and a consequent better visualization of the renal arteries. By ameliorating the knowledge of these mechanisms, we were able to perform as many as 16 cases (22.2%) with no ICM injection, obtaining therefore an ICM free EVAR procedure. Furthermore, it should be taken in account that the lowest renal artery can also been visualized using other methods of landmark for main body deployment, such as IVUS or placement of a catheter in the lowest renal artery itself. The combination of these techniques with CO_2-angiography allows to complete an EVAR implant without ICM injection. CO_2-EVAR procedures with zero iodinated contrast can be of primary usefulness in all the patients with AAA and in particular in those allergic to ICM or with chronic kidney disease.

The present study has some important limitations. Both data collection and analysis were performed retrospectively. Despite being one of the largest case series about this topic, the sample of CO_2-EVAR analyzed is small (72 patients), with consequent lack of statistical power; our results should be therefore validated with a larger population of patients. Furthermore, the analysis is affected by our learning curve in performing EVAR with this new method.

Conclusions

According with our three years' experience, CO_2-EVAR using automated injection is safe and effective and allows to use a significantly lower amount of ICM when compared with ICM-EVAR, with a consequent benefit on postoperative renal function. However, CO_2-EVAR required significantly higher radiation doses in this series; technical refinements of the procedural protocols are therefore necessary.

The CO_2 visualization of the lowest renal artery, which is obviously crucial in EVAR, allows to perform successful ICM-free implants, and is facilitated by specific anatomic condition, such as a long proximal neck.

Chapter 4

STUDY PROTOCOL

Final Version 09/07/2018

CO2-EVAR

An innovative approach to Automated Carbon Dioxide Angiography during Endovascular Abdominal Aortic Aneurysm repair – (Proof of concept study)

Sponsor	DIMES – Università di Bologna
Center Leader	Prof. Dr. Mauro Gargiulo Department of Specialized, Diagnostic and Experimental Medicine S.Orsola-Malpighi Hospital Bologna, Italy E-mail: mauro.gargiulo2@unibo.it Phone: +39 051 2144252
Study Title	An innovative approach to Automated Carbon Dioxide (CO_2) Angiography during Endovascular Abdominal Aortic Aneurysm repair (EVAR)
Acronym	*CO2-EVAR*
Study Design	Study type: *interventional, non-pharmacological, prospective* Allocation: non-randomized Endpoint-classification: *safety, reliability and image quality*
Study Objective	Carbon Dioxide (CO_2)-based angiography is a digital subtraction angiography, where CO_2 is used as an intra-arterial contrast agent. This practice started in 1970s and it is commonly used for patients who have an impaired renal function, allergy to iodinated contrast media or that could have a contrast-induced nephropathy risk (CIN risk). Carbon dioxide is in fact an effective and low-risk alternative to iodinated contrast agent, which is nowadays used in endovascular procedures, thanks to its unique properties, such as no risk for nephrotoxicity or allergic reaction. For many years, the two most important restrictions for this technique consisted of: 1) the absence of a delivery system that could minimize the risk of air contamination during the CO2 angiography and allow controlled injection (in terms of pressure and volume of injection) of the carbon dioxide and 2) customized imaging protocol for a better visualization of CO_2 during DSA acquisition. Now, with the availability a reliable automated CO_2 injector system (Angiodroid Srl, Italy) and the improvement in DSA protocols, CO_2 angiography is increasingly utilized for vascular imaging and endovascular procedures. The literature on CO_2 angiography still lacks on studies regarding the systematic use of the technique in EVAR procedures by taking the advantage of the partial release of the stent-graft below the renal arteries. Hereby, the partially opened

	stent-graft leads to an improved visualization of the aortic district and to the accurate detection of the renal ostia. Our study will specifically examine the image quality and safety of carbon dioxide gas as intra-arterial contrast agent using the Angiodroid automated CO2-injection system during EVAR procedures. We will focus on studying image quality during the different steps of stent graft deployment and implantation and on defining a guideline for the detection of the renal ostia, the hypogastric arteries and relevant endoleaks during EVAR procedures. Our hypothesis is that the CO_2-angiography through the dedicated CO_2-injector could provide the same angiographic information and image quality with iodinated contrast agent, which is nowadays used in endovascular procedures.
Endpoint	*Primary endpoint:* - Technical success to assess the renal ostia and the hypogastric arteries (defined as 100% accuracy correlated to the iodinated contrast agent angiography or IVUS/FUSION techniques) *Secondary endpoints:* - Image quality for guiding the procedure defined as good for stent-graft implantation or low not allowing stent-graft implantation - Type I-IV endoleak detection - Amount of CO2 at each deployment step (renal arteries, right/left hypogastric artery, final angiography) - Aneurysm exclusion without type I or III endoleaks at the CT scan at discharge Safety endpoints - Any adverse event within 24 hours
Inclusion Criteria	• Age > 18 years • Male, female • Patients with indication for AAA • Informed consent achievement
Patient-Exclusion Criteria	• Severe COPD (Chronic Obstructive Pulmonary Disease) • Known atrium- or ventricular septal defect with right-left-shunt • Severe renal arteries atherosclerosis • Ruptured AAA • Current partecipation in other interventional studies
Number of patients	100 patients
Investigation	In the context of this study, we will examine DSA images of patients undergoing endovascular repair of infrarenal abdominal aortic aneurysms Dynamic acquisition and post-processed final image will be both evaluated.
Medical Products	

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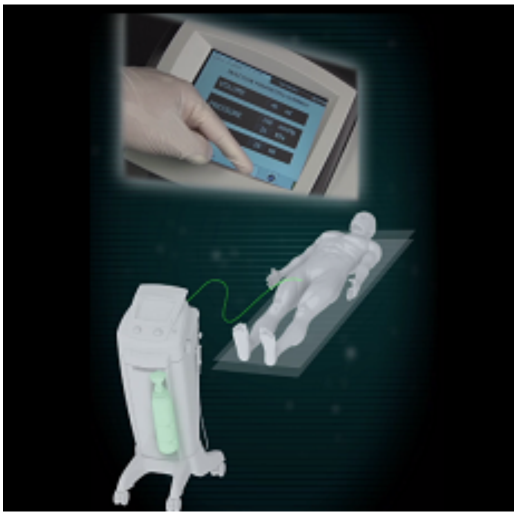
CO2 and Angiodroid CO2 Injector.
The device is an innovative carbon dioxide injector for peripheral interventional angiography below the diaphragm.

Safety and accuracy of this medical device are guaranteed by the following technical features:

No air contamination risk: internal pneumatic circuit it is always kept at positive pressure
Setting the gas quantity referring to the atmospheric pressure
Setting the injection pressure based on systolic pressure and hydraulic angiographic catheter resistance

EVAR endograft:
The study will include all endograft devices that allows partial release of the prosthesis during the intervention; in order not to introduce a bias a proper system will be chosen.

</td>
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<tr>
<td>Treatment Plan</td>
<td>
Recruitment of patients with indication for AAA ≥18 years
↓
Informed consent
↓
Patient preparation and set up with preoperative analysis of the AAA volume
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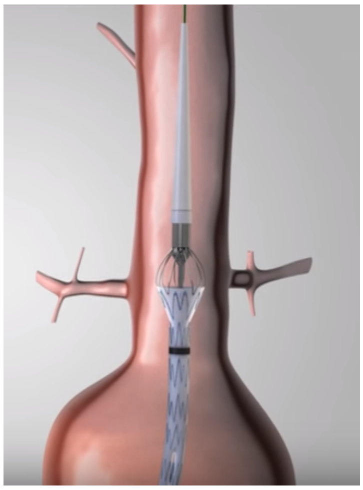
	↓ AAA angiography with CO2 (Angiodroid injector) through pig tail catheter above the renal arteries during the release process of the Stent Graft: images will be taken in different steps of the endograft deployment. ↓ Evaluation of CO2- contrast-enhanced angiography
Application	Usually CO2 is only applied in case of a contraindication to iodinated contrast media, which is nowadays used in endovascular procedures, i.e. for renal failure patients or patients who have allergic reaction to iodine. Using the new automated CO2-injector of Angiodroid, it should be examined if it is possible to replace contrast media containing iodine during EVAR procedures. The low-risk procedure of using CO2 during angiography to patients with AAA is especially for patient with reduced renal function the best option. During the EVAR procedures the amount of iodine contrast is large: the use of CO2 with an automatic injector reduces iodine doses and standardizes the procedure.
Study Assessment	Even though CO2 is used as an alternative contrast media for patients with reduced renal function since many years, there is no existing prospective study on using CO2 in EVAR procedure during the partial release of the endoprothesis and the use of CO2 in this vascular territory remains still not standardized. Encouraging results have been highlighted but there are no guidelines for its use and its benefits have not yet been clearly outlined. Due to the buoyancy of the CO2 gas, if the position of the renal arteries ostia is posterior in the transverse plane, it is difficult to visualize them adequately, even by injecting high volumes of CO2. Besides, if the aneurysmatic sack is large, the gas could be trapped in, providing a poor angiographic image. In our study, during EVAR procedures, the obstruction generated by the Stent Graft System at the "proximal neck level" of the aneurysm makes it easier to fill the renal arteries with the CO2.  In case of positive results, there is the possibility to significantly reduce the use of contrast media containing iodine and blood analysis to assess blood parameters (TSH, T3, T4, Creatinine, eGFR) before angiography could not be necessary anymore. In addition, since medical CO2 is not relevant to the budget, it would be a considerable cost saving measure. Besides, the possibility to drastically reduce the use of ICM (iodinated contrast media, which is nowadays used in endovascular procedures, at least 50%) can avoid or reduce patient premedication and postmedication (in case excessive amount of iodine has been injected).
Practical benefit	The practical benefit is the possible significant reduce of using contrast media containing iodine, primarily in patients with thyroid, renal disease, secondly in any patient, in order to avoid contrast-induced nephropathy (CIN) risk.

Risk assessment	Side effects and safety profiles have to be considered in using CO2 during angiography. In the arterial system, CO2 is only allowed in vessel-sections below the diaphragm. To avoid an accidental distribution supra-aortal with the risk of pulmonary embolism, the patients are positioned head down (Trendelenburg). Furthermore, aneurysmal accumulation of CO2 (Vapor Lock to aneurysmata) is also known as possible, but still rare. This adverse event can easily be avoided by changing the position of the patient (lateral decubitus) or by massaging the painful area. In using an automated injection as a closed system with constant lower pressure compared to the conventional systems, it is nearly impossible to inject accidentally air in the vascular system and trigger an air embolism or cause intimal arterial injuries.
Monitoring	During angiography, vital parameters of patients are continuously detected and visible on the monitors. All general requirements for safety during interventional radiology will be applied. Blood parameters (TSH, T3, T4, Creatinine, eGFR) will be monitored 24 hours after the intervention as follow up.
Planned experimental layout	Patient with the indication to AAA will be subjected to a preliminary examination for the measurement of the planned diagnostic and interventional values. After the verification, the angiography procedure will be planned. At least 24 hours before angiography, a physician will check the indication again and conduct an informed consent discussion about possible complications and risks during and after intervention. He will then inform the patient about the ongoing study. If the patient agrees to participate, he needs to sign the additional informed consent regarding the study participation. This declaration is revocable at any time. The 2 days before the procedure, the patient will be adequately prepared through a specific low-residue diet to reduce intestinal gas. Food to avoid will be fried food, salad, legume, potatoes, fresh fruit, dried fruit, fat meat, milk, sweets and carbonated soft drinks. Food allowed will be rice, pasta, soups, grilled meat and fish, hard cheese, biscuits and crackers without fiber, toasts, filtered juices, tea, coffee, infusions and not carbonated soft drinks. The day of the procedure and day before the patient should take activated carbon (Simeticarbon), 2 tablets 3 times a day. Eventually, it will be possible to give an appropriate drug (e.g. Buscopan, Glucagone) just before the procedure starts to reduce peristalsis. Intraprocedural angiographies should be performed with patient in apnea. The day after the procedure, patient can eat white meat and/or white fish with rice and potatoes. Avoid vegetables at dinner. Aneurysm graduation and dimensions will be measured after diagnostic angiography and before intervention. CO2 gas Volume and Pressure will be settled based on hydraulic resistance of the catheter, the aorta diameter and blood flow measured through echo. Preoperative analysis of the AAA free volume from thrombus (important variable for adequate visualization of renal osteo) will be performed before the intervention. Nitrous oxide should be avoided during anesthesia. If not, more attention to CO2 volumes should be made, not exceeding the volumes recommended by the literature. Indicative injection parameters of the ACDA will be as follows: pressure [500 – 750] mmHg, and volume [40 -100] ml. The parameters can be set according to the clinical judgment directly by the automatic Angiodroid injector. During

	injections, systolic pressure will be monitored to determine injection pressure according to injection protocols. The injection and stent-graft deployment will be performed in 6 steps, that are traditionally performed with the iodine contrast agent during EVAR: 1. Control angiography of the aneurysm 2. Placement of the endograft (still inside the sheath) at the right position (below the lowest renal artery 3. Partial opening of the stent graft – Correction of the position 4. Angiographic demonstration of the contralateral hypogastric artery 5. Angiographic demonstration of the ipsilateral hypogastric artery 6. Control angiography of the aneurysm and exclusion of endoleaks Besides, the procedure will be performed using iodine also as a contrast medium after some CO2 injections in order to validate the quality of CO2 angiography. In case of any complications or difficulties any repeat angiopgraphies except of the aforementioned should be reported. The calculated values through the software-quantification-tool will be compared and statistically analyzed. Injection parameters (Pressure/Volume) will be recorded and statistically analyzed, relating to degree of partial release of the stent graft system, and a general protocol for EVAR procedure will be draw up.

Planned operative protocol	**STEP1: Detection of Renal Arteries (RAs) with no endograft deployed.**
	- Common Femoral Artery (CFA) access and contralateral limb access performed (CFA)
	- Insertion of both introducer-sheaths for inserting the endograft main body and the contralateral limb: in this way the total or partial occlusion of both the CFAs would increase the chances of CO2 to flow more proximal to the renal arteries as it will hardly flow into the lower limbs.
	- Pigtail insertion through introducer-sheath, placing the pigtail tip between the RAs and Superior Mesenteric Artery (SMA): place the catheter right above the RAs but below SMA in order to optimize the CO2 flow into the RAs reducing the amount of gas into the SMA.
	- Suggested injection parameter: Volume = 100; Pressure = 600 mmHg.
	- 1st CO_2 Injection from Pigtail.
	- 2nd CO_2 Injection from Introducer-sheath (10F, 11cm long).
	
	If RAs not detected, operator can choose the following solutions:
	  - 3rd CO_2 Injection from Pigtail/introducer-sheath using a “double-injection”: one CO_2 injection (suggested Volume = 50 cc; Pressure = 250 mmHg) without DSA/Fluoroscopy in order to fill the aorta with CO_2 and then another CO_2 injection very close to the previous (suggested Volume = 100 cc; Pressure = 600 mmHg) with DSA.
	  - 4th CO_2 Injection with patient in Trendelenburg (5°) position (suggested Volume = 100 cc; Pressure = 600 mmHg).
	  - 5th CO_2 Injection CO_2 through the lumen of the Aorta Occlusive balloon normally used for expanding the Endograft to the internal wall of the aorta (suggested Volume = 100 cc; Pressure = 600 mmHg). Place the tip of the balloon right below the RAs. Inflate the balloon partially and not totally to perform an “artificial stenosis” which obstructs the passage of the gas to distal regions providing a better gas flow into the renal arteries.
	  - Inject a small amount of Iodine (10 cc) or alternative contrast media or method (e.g. IVUS/FUSION techniques), performing the Complementary Approach between CO2 and other contrast media.
	  - Perform a CO2 selective injection (suggested Volume = 50 cc, Pressure = 250 mmHg).
	
	STEP2: Renal Arteries (RAs) Detection with endograft partially deployed

	- Place the endograft main body into the aorta and partially deploy it (0%, 50%, 100%) - Perform CO_2 injections from the pigtail at different deployment stages: more is the deployment, more important will be the “artificial stenosis” provided by the endograft and easier the CO_2 will flow into the renal arteries. Suggested injection parameters: Volume = 100 cc; Pressure = 600 mmHg. **STEP3: Detection of Hypogastric Arteries (HAs) after endograft total deployment** - Maintain the Trendelenburg (5°) - Inject CO_2 counter flow through the introducer-sheath. - Suggested injection parameters: Volume = 100 cc; Pressure = 600 mmHg **STEP 4: Final check after Endograft contralateral limb deployment** - Suggested injection parameters: Volume = 100; Pressure = 600 mmHg. - 1st CO_2 Injection from Pigtail. - 2nd CO_2 Injection from Introducer-sheath. Injecting counter flow through the introducer-sheath will provide better imaging of the aorta and renal arteries. Counter flow injections require higher pressure than injecting CO2 on the same direction of blood.
Statistical analysis	*Primary endpoint:* Verification of conformity of the method according Cohens Kappa (Kappa-Coefficient in 95% confidence interval) *Secondary endpoint:* Image quality: - Verification of conformity methods according Fleiss‘ Kappa (Kappa-Coefficient in 95% confidence interval) Safety: - Descriptive statistics (absolute and relative frequencies of safety parameters)
Safety (documentation of adverse events and serious adverse events)	Possible general AE: - bleedings after incorrect punctions - nerve injuries - secondary haemorrhage - haematoma at injection point - pain Possible AE to iodine contrast media: - allergic reaction - acute renal failure - acidosis - sickness - vomit - diarrhea Possible serious AE: - vapor lock - clinically relevant air embolism - livedo reticularis
Literature	1. Rolland Y, Duvauferrier R, Lucas A et al. Lower limb angiography: a prospective study comparing carbon dioxide with iodinated contrast material in 30 patients. AJR 1998; 171: 333–7. 2. Palena LM, Diaz-Sandoval LJ, Candeo A, Brigato C, Sultato E, Manzi M. Automated Carbon Dioxide Angiography for the Evaluation and Endovascular Treatment of Diabetic Patients With Critical Limb Ischemia. J Endovasc Ther. 2016; Feb;23(1):40-8 3. Scalise F, Novelli E, Auguadro C, Casali V, Manfredi M, Zannoli R. Automated

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Notes	

CO_2-EVAR

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Versione 03/05/2019

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Chapter 5

CO_2-EVAR Study - Results

Background

Endovascular aortic repair (EVAR) represents nowadays the mainstay in the treatment of abdominal aortic aneurysms (AAA), due to the lower rate of postoperative mortality and morbidity compared with open repair[50]. However, one of the most common complications related to EVAR is acute kidney injury, which can occur in up to 18% of patients and is mostly related to iodinated contrast medium injection (ICM)[6]. For that reason, carbon dioxide (CO_2) was proposed as an alternative to iodine in patients with AAA and chronic kidney disease or allergy to ICM[30].

The first case series about CO_2-EVAR showed good results in terms of renal outcome of patients, but the technique is presently still defective. In fact, some issues regarding the visualization of the lowest renal artery (LoRA) or the best quality image in angiographies performed from pigtail or introducer-sheath, are still unsolved even using automated CO_2 injector[39,40].

The aim of this European multicentric study was to analyze CO_2-EVAR procedures' steps in terms of LoRA and hypogastric artery (HA) visualization as well as image quality in order to create an operative protocol to standardize the procedure.

Methods

This is a European multicentric interventional non-randomized study. Patients undergoing standard CO_2-EVAR procedures were prospectively enrolled in the different European centers between 2018 and 2021. The 5 European centers involved were Vascular Surgery, Department of Experimental, Diagnostic and Specialty Medicine, S.Orsola-Malpighi Hospital of Bologna (Italy), Vascular Center, Skåne University, Hospital of Malmö (Sweden), Clinic for Vascular Surgery, St. Franziskus Hospital of Münster (Germany), Vascular Surgery, University Hospital of Münster (Germany) and Vascular Surgery, Athens Medical Group, Kifisia Athens (Greece).

Standard EVAR was defined as aorto-bi-common-iliac implant following the endoprosthesis' manufacturer instructions for use.

The inclusion criteria were age > 18 years, patients with indication for standard endovascular treatment of AAA (diameter ≥5.5 cm for males and ≥5 for females), and informed consent achievement. The exclusion criteria were severe chronic obstructive pulmonary disease, known atrium- or ventricular septal defect with right-left shunt, severe renal arteries atherosclerosis and ruptured AAA.

The study protocol and all the accompanying documentation was approved by our local ethical committee with the protocol code "CO2-EVAR". Every patient signed a dedicated consent form to be recruited in the study. Moreover, the study was registered in ClinicalTrials.gov with the Protocol ID "CO2-EVAR".

Patients' data were collected and inserted in a dedicated database.

Preoperative Characteristics

All preoperative clinical characteristics were evaluated such as age and sex. Hypertension was diagnosed in case of blood pressure ≥140/90 mmHg, only active smokers were considered in smoke as preoperative risk factor, dyslipidemia was defined as blood cholesterol ≥240 mg/dl, diabetes mellitus was defined as ≥126 mg/dl at blood glucose test. Anemia was defined in case of hemoglobin <13 g/dl in male and <11 g/dl in female patients. Congestive heart failure was diagnosed in case of ≥ Stage C following the New York Heart Association Classification. Coronary artery disease was defined in case of history of acute coronary syndrome. Chronic obstructive pulmonary disease was diagnosed for stage 1 or 2 following the GOLD classification (as reported above, patients with stages ≥3 were excluded from enrollment).

Peripheral artery disease was defined in case of Rutherford category ≥3. Cerebrovascular Insufficiency was diagnosed in case of history of ischemic stroke or transient ischemic attack. Preoperative renal function was assessed evaluating chronic kidney disease in hemodialytic treatment, eGFR (ml/min) and Creatininemia (mg/dl). Moreover, pCO_2 (mmHg) and tCO_2 (mEq/l) at hemogasanalysis were evaluated. The anesthesiologic risk was stratified using the American Society of Anesthesiology (ASA 1,2,3 and 4) classification.

Anatomical Characteristics and Endograft Used

The proximal neck of the AAA was evaluated with preoperative Angio Computed Tomography (CT-Scan) in terms of diameter (mm) and length (mm). The ostium of the LoRA artery was judged anterior if it was between 9.01 and 2.59 at clock position.

The type of endograft used was with suprarenal (Cook, Medtronic, Jotec, Endologix) or infrarenal (Gore) fixation depending on anatomy and on center experience and habit.

Patients Preparation

In order to avoid air in the bowel and consequently improve image quality during CO_2 injections, the protocol provided the preparation of the patient with low-residue diet and activated Carbon administrated the day before the procedure. The type of anesthesia used, whether general, spinal or local was also reported.

The Technique and Procedure Steps

CO_2-EVAR was performed using the Angiodroid (San Lazzaro, Bologna, Italy) automated CO_2 injector, which was preoperatively connected to the diagnostic Pig-tail together with the ICM injector. After bilateral femoral puncture, a 8 or 10F short introducer sheath was bilaterally inserted and a Lunderquist guidewire was bilaterally advanced in the thoracic aorta. The 5F diagnostic Pigtail connected to CO_2 and ICM was positioned between the renal arteries and the superior mesenteric artery (following the bone landmarks preoperative evaluation at CT-Scan) in order to perform the preimplant aortography, useful to detect the LoRA position.

- STEP 1: Detection of LoRA and image quality assessment with no endograft deployed. The first CO_2 injection (suggested Volume = 100 cc; Pressure = 600 mmHg) was performed from the Pigtail and the second injection (suggested Volume = 100 cc; Pressure = 600 mmHg) from the 8 or 10F introducer-sheath in order to compare different image qualities. In case the LoRA was not detected with the first two angiographies, a double-injection technique was used, one CO_2 injection (suggested Volume = 50 cc; Pressure = 250 mmHg) without DSA/Fluoroscopy in order to fill the aorta with CO_2 and then another CO_2 injection very close to the previous (suggested Volume = 100 cc; Pressure = 600 mmHg) with DSA. In case the LoRA was not visualized, other techniques could be used, such injection with patient in Trendelenburg (5°) position (suggested Volume = 100 cc; Pressure = 600 mmHg), CO_2 injection through the lumen of the aorta occlusive balloon normally used for expanding the Endograft to the internal wall of the aorta (suggested Volume = 100 cc; Pressure = 600 mmHg), selective small CO_2 injection after LoRA cannulation with an angulated catheter, small ICM injection (10 cc) or alternative contrast media or method (e.g. IVUS/FUSION techniques).
- STEP 2: Detection of LoRA and image quality assessment at different steps (0%, 50% or 100%) of main body deployment with CO_2 angiography performed from Pigtail (Volume = 100 cc; Pressure = 600 mmHg).
- STEP 3: Detection of HA contralateral to main body deployment side in order to deploy contralateral leg and image quality evaluation with CO_2 injection performed from contralateral 10F introducer-sheath (suggested Volume = 100 cc; Pressure = 600 mmHg).
- STEP 4: Final angiogram after aorto-bis-iliac complete implant in order to assess the presence of endoleak, the number of renal and hypogastric arteries visualized. The first injection was performed from Pigtail (suggested Volume = 100 cc; Pressure = 600 mmHg) and the second from 8 or 10F introducer-sheath (suggested Volume = 100 cc; Pressure = 600 mmHg) in order to compare the results.

The intraoperative image quality with CO_2 were judged by the operators as 1=low, 2=sufficient, 3=good and 4=excellent.

Additional Procedure Details

Other procedure details evaluated were the overall number of CO_2 injections and the overall volume of CO_2 (cc), the overall number of ICM injections and overall ICM volume (cc), as well as the number of procedures accomplished with 0 cc of ICM (0-iodine). The total radiation dose area product (DAP) in mGy/cm^2, the fluoroscopy DAP and DSA DAP were also recorded.

The intraprocedural adverse events possibly related to CO_2 injections were also reported, such as severe hypotension (>50 mmHg systolic blood pressure), pain, vomit and diarrhea.

Postoperative Outcome

Postoperative mortality was evaluated together with the presence of Endoleak at duplex (DUS) or contrast-enhanced (CEUS) ultrasound or CT-Scan and the postoperative eGFR (ml/min) and Creatinine (mg/dl) and possible decrease of eGFR or increase of Creatinine compared to the preoperative values. The renal function worsening requiring postoperative hemodialysis was also reported as well as the postoperative pCO_2(mmHg) and tCO_2 (mEq/l) at hemogasanalysis.

Possible postoperative CO_2-related adverse events were also evaluated, like severe hypotension (>50 mmHg systolic blood pressure), pain, vomit and diarrhea.

Endoleak Detection

The endoleak detection at final angiogram with CO_2 was compared with the postoperative endoleaks detected with duplex or contrast-enhanced ultrasound or CT-Scan in order to verify the sensibility of CO_2 angiographies on endoleak diagnosis.

Safety Assessment

Possible risk factors for intraprocedural or postoperative adverse events related to CO_2 injection were also evaluated.

0-iodine Procedure Analysis

Anatomical and procedural predictors for the accomplishment of a 0-iodine procedure were analyzed.

Statistical Analysis

Categorical variables were expressed with N (%), whereas the continuous variables were expressed with median and interquartile range (IQR) or mean ± standard deviation (SD). Statistical significance was reached for p value <0.05. Chi-squared analysis was performed to compare categorical variables, Wilcoxon median test and t Student test to compare continuous variables. Cox binary regression was used for multivariate analysis (95% confidence interval) for those variables with p<0.10 at univariate. The statistical analysis was performed with SPSS 23.0 for Apple (SPSS Inc, Chicago, Illinois, USA).

Results

In the considered period (2018-2021), 65 patients were enrolled for the CO_2-EVAR multicentric study. Two patients (3.1%) were recruited by the Vascular Surgery of Athens, 22 (33.8%) by the Vascular Surgery of Bologna, 25 (38.5%) by the Vascular Surgery of Malmö, 2 (3.1%) by the Vascular Surgery of St. Franziskus Hospital Münster and 14 (21.5%) by the Vascular Surgery of the University Hospital Münster.

Preoperative Characteristics

Patients' clinical characteristics are reported in Table VII.

Table VII. Patients' preoperative characteristics

	Tot N=65 *N (percent) or Median (IQR)*
Age	75 (11)
Male sex	55 (84.5%)
Hypertension	43 (66.2%)
Active Smoker	15 (23.1%)
Dyslipidemia	34 (52.3%)
Diabetes	11 (17%)
Anemia	4 (6.2%)
Congestive Heart Failure (CHF)	4 (6.2%)
Coronary Artery Disease (CAD)	23 (35.4%)
Chronic Obstructive Pulmonary Disease (COPD)	11 (17%)
Peripheral Artery Occlusive Disease (PAOD)	8 (12.3%)
Iodine Allergy	4 (6.2%)
Cerebrovascular Insufficiency (Stroke – TIA)	8 (12.3%)
Hemodialysis	0
Preoperative Creatinine (mg/dl)	1.05 (0.5)
Preoperative eGFR (ml/min)	65 (30)
Preoperative pCO_2 (mmHg)	31 (7)
Preoperative tCO_2 (mEq/l)	27 (5)
ASA score	3 (1)

Anatomical Characteristics and Endograft Used

The anatomical characteristics of proximal neck and LoRA ostium are reported in Table VIII together with the Endograft used for CO_2-EVAR implant.

Table VIII. Anatomical characteristics and endograft used

	Tot N=65 *N (percent) or Median (IQR)*
Aorta diameter at the renal ostia (mm)	22 (4)
Proximal Neck Length (mm)	25 (10)
Anterior Lowest Renal Artery (9.01-2.59 Clock Position)	30 (46.2%)
Type of Endograft Used Cook Gore Medtronic Endologix Jotec	 32 (49.2%) 16 24.6%) 12 18.5%) 3 (4.6%) 2 (3%)

Patients Preparation

Twenty/65 (30.8%) patients were prepared for CO_2-EVAR with low-residue diet and 17/65 (26.2%) received activated carbon the day before the procedure. The procedure was performed in general anesthesia in 55/65 (84.6%) cases, in spinal in 9/65 (13.8%) cases and in local anesthesia in 1/65 (1.5%) case.

Procedural steps analysis

The step 1 (first preimplant CO_2 injection) of the procedure showed a significantly better image quality if the angiography was performed from femoral introducer compared with injection from pigtail [Median image quality: Pigtail 2(3) vs 3(3) Introducer, p=0.008]. These data are reported in Table IX.

Table IX. Step 1 (first preimplant CO_2 injection): comparison between pigtail and introducer injections.

	Pigtail Injection *N (percent) or Median (IQR)*	Introducer Injection *N (percent) or Median (IQR)*	P Value
Injection Pressure (mmHg)	600 (150)	600 (150)	.31
Injection Volume (cc)	100 (1)	100 (1)	.31
LoRA Detection	49 (75.3%)	47 (72.3%)	.47
Image quality	2 (3)	3 (3)	.008*

*p<0.05

In step 2 (CO_2 angiographies in different main body deployment phases), image quality (p=<.001) and LoRA detection (p=<.001) were significantly higher at 50% and 100% of main body deployment compared with 0% as shown in Table X.

Table X. Step 2: comparison between injections at 0%, 50% and 100% of main body deployment.

	0% MB Deployment *N (percent) or Median (IQR)*	50% MB Deployment *N (percent) or Median (IQR)*	Tot MB Deployment *N (percent) or Median (IQR)*	P Value
Injection Pressure (mmHg)	600 (150)	600 (150)	600 (150)	1
Injection Volume (cc)	100 (1)	100 (20)	100 (1)	1
LoRA Detection	78.4%	92.3%	93.8%	<.001*
Image quality	3 (3)	3 (3)	4 (3)	<.001*

*p<0.05

Furthermore, the LoRA visualization was significantly higher at 50% (LoRA visualization: Step 1 75.3% vs 92.3% at 50% MB deployment step 2, p=.002) and at 100% (LoRA visualization: Step 1 75.3% vs 93.8% at 100% MB deployment step 2, p=.01) of main body deployment compared with first angiography from pigtail in Step 1. Similarly, also the image quality was significantly higher at 50% [Median image quality: 1st Step 2(3) vs 3(3) at 50% MB deployment step 2, p=<.001] and at 100% [Median image quality: 1st Step 2(3) vs 4(3) at 100% MB deployment step 2, p=.001] of main body deployment compared with first angiography from pigtail in Step 1.

In step 3, CO_2 injection performed from contralateral femoral introducer-sheath, which was performed with a median pressure of 600 (150) mmHg and a median volume of 100 (1) cc,

the contralateral hypogastric artery was correctly visualized in 61/65 (93.8%) cases. The median quality image was 3 (1).

In step 4, CO_2 final angiogram performed from pigtail and from introducer-sheath, image quality was significantly higher from femoral introducer compared with injection from pigtail [Mean image quality: Pigtail 2.6 ± 1.1 vs 3.1 ± 0.9 Introducer, p=<.001], as reported in Table XI.

Table XI. Step 4.

	Pigtail Injection *N (percent) or Mean ± SD*	Introducer Injection *N (percent) or Mean ± SD*	P Value
Injection Pressure (mmHg)	654 ± 76.3	659 ± 74.1	.31
Injection Volume (cc)	100 ± 7.2	100 ± 8	.31

Renal Arteries Detection	1.4 ± 0.7	1.6 ± 0.6	.13
HA Detection	1.9 ± 0.2	1.9 ± 0.3	.31
Image Quality	2.6 ± 1.1	3.1 ± 0.9	<.001*
Endoleak Detection	18 (27.7%)	17 (26.2%)	.32

*$p<0.05$

Additional Procedure Details

Table XII shows the procedural data with the amount of CO_2 and ICM [17 (51) cc] injections, the radiation dose and the intraoperative CO_2-related adverse events, which occurred in 5/65 (7.7%) patients. One patient had a transient abdominal pain procedure possibly due to CO_2 injection, 2 patients experienced abdominal pain and vomit and 2 patients reported nausea and vomit. All these CO_2-related events had no intraoperative or postoperative consequences on patients.

Table XII. Procedure details.

	Tot N=65 *N (percent) or Median (IQR)*
N° of CO_2 Injections	9 (4)
Volume of CO_2 Injected	990 (481)
N° of ICM Injections	1 (3)
Volume of ICM Injected	17 (51)
N° of 0-Iodine EVAR	19 (29.2%)
Fluoroscopy Radiation Dose DAP (mGy/cm^2)	40895 (109682)
DSA Radiation Dose DAP (mGy/cm^2)	203148 (385018)
Total Radiation Dose DAP (mGy/cm^2)	247983 (517397)
Intraoperative Severe Hypotension	0
Intraoperative Pain	3 (4.6%)
Intraoperative Vomit	4 (6.2%)
Intraoperative Diarrhea	0
Intraoperative Adverse Events	5 (7.7%)

Postoperative Outcome

Patients' postoperative mortality rate was 0% with 0 (.08) mg/dl of median Creatinine increase and 0 (6.5) ml/min of median eGFR decrease. No patient had a significant renal function worsening requiring hemodialysis. There were 8/65 (12.3%) cases of postoperative possibly CO_2-related adverse events. Three patients had pain, 3 had vomit and 3 had diarrhea. There were no other consequence of this symptoms, which were all temporary during the hospitalization. All postoperative data are reported in Table XIII:

Table XIII. Postoperative outcome.

	Tot N=65 *N (percent) or Median (IQR)*
Death	0
Endoleak at DUS/CEUS/CT Scan	10 (15.4%)
Postoperative Creatinine (mg/dl)	1.02 (0.5)
Postoperative eGFR (ml/min)	66 (32.5)
Creatinine Increase (mg/dl)	0 (.08)
eGFR Decrease (ml/min)	0 (6.5)
Renal Function Worsening Requiring Hemodialysis	0
Postoperative pCO_2	41 (7)
Postoperative tCO_2	26 (4)
Postoperative Severe Hypotension	0
Postoperative Pain	3 (4.6%)
Postoperative Vomit	3 (4.6%)
Postoperative Diarrhea	2 (3.1%)
Postoperative Adverse Events	8 (12.3%)

Endoleak Detection

The analysis of different endoleaks was performed between CO_2 injections at final angiogram (Step 4) from pigtail and from introducer and compared with postoperative endoleak at DUS, CEUS or CT-Scan, as reported in Tables XIV, XV and XVI.

The overall endoleaks [Endoleak: final pigtail angiogram 18/65 (27.7%) vs 10 (15.4%) postoperative, p=.04] and in particular type II endoleak [Type II endoleak: final pigtail angiogram 15 (23%) vs 7 (10.8%) postoperative, p=.04] was detected significantly more in the final angiogram with CO_2 injected from pigtail compared with the postoperative imaging.

Table XIV. Endoleak analysis: final CO_2 angiogram from pigtail vs postoperative DUS/CEUS/CT-Scan.

	Final Angiogram Pigtail *N (percent)*	Postoperative *N (percent)*	P Value
Type I	2 (3.1%)	2 (3.1%)	1
Type II	15 (23%)	7 (10.8%)	.04*
Type III	1 (1.5%)	1 (1.5%)	1
Endoleak	18 (27.7%)	10 (15.4%)	.04*

*p<0.05

Table XV. Endoleak analysis: final CO_2 angiogram from introducer vs postoperative DUS/CEUS/CT-Scan.

	Final Angiogram Introducer *N (percent)*	Postoperative *N (percent)*	P Value
Type I	2 (3.1%)	2 (3.1%)	1
Type II	14 (21.5%)	7 (10.8%)	.09
Type III	1 (1.5%)	1 (1.5%)	1
Endoleak	17 (26.2%)	10 (15.4%)	.09

Table XVI. Endoleak analysis: final CO_2 angiogram from introducer vs from introducer.

	Final Angiogram Pigtail *N (percent)*	Final Angiogram Introducer *N (percent)*	P Value
Type I	2 (3.1%)	2 (3.1%)	1
Type II	15 (23%)	14 (21.5%)	1
Type III	1 (1.5%)	1 (1.5%)	1
Endoleak	18 (27.7%)	17 (26.2%)	1

Safety Assessment

In table XVII are reported factors related to intraoperative CO_2 adverse events at univariate. The only significant risk factor was a spinal/local anesthesia ($p=<.001$). The multivariate was not performed due to the smallness of events (N=5).

Table XVII. Risk factors for intraoperative CO_2-related adverse events

	No Intraoperative AE N=60 *N (percent) or Median (IQR)*	Intraoperative AE N=5 *N (percent) or Median (IQR)*	P Value
Age	73 (13)	75 (15)	.80
Active smoker	29 (48.3%)	5 (100%)	.07
Dyslipidemia	12 (20%)	3 (60%)	.06
Preoperative pCO_2 (mmHg)	41 (6)	44 (10)	.92
Preoperative tCO_2 (mEq/l)	27.1 (5)	25 (7)	1
Not General Anesthesia	5 (8.3%)	5 (100%)	<.001*
CO_2 Volume	1300 (650)	500 (650)	.4
N° CO_2 Injections	13 (6)	5 (6)	.41
0-Contrast	18 (30%)	1 (20%)	1

*p<0.05

Moreover, Table XVIII shows predictors for postoperative CO_2-related adverse events at univariate. The only significant risk factor was preoperative diabetes mellitus ($p=.02$). At multivariate analysis (Table XIX), diabetes mellitus was confirmed as an independent risk factor for postoperative adverse events [6 (0.9-37.7), p=.04], whereas the CO_2 volume was protective for postoperative adverse events occurrence [0.99 (0.98-1), p=.03].

Table XVIII. Risk factors for postoperative CO_2-related adverse events

	No Postoperative AE N=57 *N (percent) or Median (IQR)*	Postoperative AE N=8 *N (percent) or Median (IQR)*	P Value
Male	50 (87.7%)	5 (62.5%)	.09
Age	75 (13)	69 (10)	.41
Diabetes Mellitus	4 (12.3%)	4 (50%)	.02*
Preoperative pCO_2 (mmHg)	41 (7)	38 (10)	.74

Preoperative tCO_2 (mEq/l)	27 (5)	27 (10)	1
CO_2 Volume	1300 (650)	340 (100)	.05
N° CO_2 Injections	13 (6)	4 (1)	.14
Postoperative pCO_2 (mmHg)	41 (8)	39 (7)	.7
Postoperative tCO_2 (mEq/l)	26 (3)	29 (5)	1
0-Contrast	18 (31.6%)	1 (12.5%)	.42

*p<0.05

Table XIX. Multivariate analysis of risk factors for postoperative CO_2-related adverse events.

	Postoperative AE *OR (C.I.)*	P Value
Male	0.09 (0.01-0.8)	.07
Diabetes Mellitus	6 (0.9-37.7)	.04*
CO_2 Volume	0.99 (0.98-1)	.02*

*p<0.05

Finally, a comparison between pCO_2 and tCO_2 before and after the procedure was performed in order to assess the possible consequences of CO_2 injections on hemogasanlysis. The median preoperative and postoperative pCO_2 were not statistically different [Median (IQR) preoperative pCO_2 40 (8) mmHg vs 40 (5) mmHg postoperative pCO_2, p=.41], as well as the tCO_2 [Median (IQR) preoperative tCO_2 27.2 (4.6) mEq/l vs 26.1 (4) mEq/l postoperative tCO_2, p=.6].

0-iodine Procedure Analysis

Nineteen/65 (29.2%) of procedures were performed with 0-iodine at all as reported in Table XII. In Table XX are reported factors related to the possibility to achieve a 0-iodine procedure at univariate, which were LoRA detection with the preimplant angiography from Pigtail in step 1 (p=.02), LoRA detection with the preimplant angiography from introducer in step 1 (p=.001) and also its image quality (p=.03).

Table XX. Predictors of 0-Iodine CO_2-EVAR at univariate

	No-0-Iodine EVAR *N (percent) or Median (IQR)*	0-Iodine EVAR *N (percent) or Median (IQR)*	P Value
Proximal Neck Diameter	23 (5)	20 (3)	.08
Proximal Neck Length	25 (11.5)	25 (11)	.81
Anterior LoRA	21 (45.7%)	9 (47.4%)	1
LoRA Detection 1st STEP Pigtail	30 (66.7%)	18 (94.7%)	.02*
Image Quality 1st STEP Pigtail	2 (2)	3 (2)	.45
LoRA Detection 1st STEP Introducer	23 (59%)	19 (100%)	.001*
Image Quality 1st STEP Introducer	3 (2)	4 (1)	.03*
LoRA Detection 0% 2nd STEP	25 (71.4%)	17 (94.4%)	.07
Image Quality 0% 2nd STEP	2 (2)	3 (1)	.17
LoRA Detection 50% 2nd STEP	34 (89.5%)	18 (100%)	.29
Image Quality 50% 2nd STEP	3 (1.5)	4 (1)	.12
LoRA Detection 100% 2nd STEP	30 (90.9%)	18 (100%)	.54
Image Quality 100% 2nd STEP	3.5 (1.8)	4 (1)	1
HA Visualization 3rd STEP	32 (92.5%)	17 (94.4%)	1
RA Detection 4th STEP Pigtail	2 (1)	2 (1)	.83
HA Detection 4th STEP Pigtail	2 (0.1)	2 (0.1)	.52
Image Quality 4th STEP Pigtail	2.5 (3)	3 (1.5)	.05
RA Detection 4th STEP Introducer	2 (1)	2 (0.1)	.11
HA Detection 4th STEP Introducer	2 (0.1)	2 (0.1)	.23
Image Quality 4th STEP Introducer	4 (1)	4 (1)	.17

*$p<0.05$

At multivariate analysis, as shown in Table XXI, the 2 independent predictors of 0-iodine CO_2-EVAR were the LoRA Detection with the preimplant angiography performed from Introducer [0.52 (0.11-1), p=.01] and the image quality in the step 4 with angiography performed from Pigtail [0.35 (0.004-0.29), p=.04].

Table XXI. Predictors of 0-Iodine CO_2-EVAR at multivariate

	0-Iodine EVAR *OR (C.I.)*	P Value
Proximal Neck Diameter	0.23 (0.02-0.37)	.87
LoRA Detection 1st STEP Pigtail	0.09 (0.04-.62)	.66
LoRA Detection 1st STEP Introducer	0.52 (0.11-1)	.01*
Image Quality 1st STEP Introducer	0.20 (0.03-0.30)	.42
LoRA Detection 0% 2nd STEP	0.20 (0.02-0.70)	.30
Image Quality 4th STEP Pigtail	0.35 (0.004-0.29)	.04*

*p<0.05

Discussion

The present study represents the first European multicentric experience with CO_2-EVAR procedures. The population of 65 patients is one of the most numerous case series on the literature after the one of Criado et al[34], Fujihara et al[35], Huang et al[41] and Vacirca et al[40].

In step 1 analysis, the LoRA, which is crucial for main body deployment, was similarly detected by operators in the preimplant CO_2 angiogram from pigtail and from femoral introducer, however, it was found that the injection from femoral introducer-sheath provides best images [Median image quality: Pigtail 2(3) vs 3(3) Introducer, p=0.008]. One possible bias of this analysis could be that the injection from introducer was performed after the one from pigtail and this could maybe improve the image quality, due to the presence of the gas in aorto-iliac axis. There is no similar analysis in the literature.

In step 2, there were significantly better results in terms of LoRA visualization and image quality during the 50% and 100% of main body deployment compared with the first CO_2 angiogram and with the 0% of main body deployment. These data confirm the initial hypothesis about carbon dioxide distribution during the procedure; if the main body endoprosthesis is in the infrarenal aorta, it creates a steric bulk, which impedes the flow of the gas to the legs during the angiographies from pigtail and unlike facilitates the flow to the renal arteries, which is crucial for LoRA visualization. This aspect has never been investigated so far.

In step 3, the visualization of the contralateral hypogastric artery was 93% with a median good image quality, following the results. In the previous experiences published by our group[39,40], the contralateral hypogastric artery was visualized in all cases. Nevertheless, the present results are still satisfactory and allow to confirm that contralateral hypogastric artery can be correctly visualized with CO_2 without the needing of iodine injections.

In step 4, the completion CO_2 angiogram provided better images when the injection was performed from femoral introducer-sheath. Again, this result could be misread, because the CO_2 from the introducer was injected after the pigtail injection; the gas still present in the aorta could possibly improve image quality.

The CO_2-EVAR procedures were accomplished with a minimal median amount of iodine injection [17 (51) cc], significantly lower compared with the other case series. Vacirca et al[40] reported about 50 cc, but similar to the case series of Fujihara et al[35] who reported a mean consumption of 15 cc of ICM.

The postoperative outcome in terms of mortality (0%) and renal function [0 (.08) mg/dl of median Creatinine increase and 0 (6.5) ml/min of median eGFR decrease] was excellent. As reported by Vacirca et al[40] and Fujihara et al[35] in other experiences, CO_2-EVAR with restrictive use of iodine can guarantee an almost zero impact on patients' renal function. Consequently, it could be used in all patients and particularly in those with chronic kidney disease.

Moreover, the endoleak analysis reported that the final angiogram with CO_2 has a high sensitivity for endoleaks [Endoleak: final pigtail angiogram 18/65 (27.7%) vs 10 (15.4%) postoperative, p=.04] and in particular type 2 endoleak [Type II endoleak: final pigtail angiogram 15 (23%) vs 7 (10.8%) postoperative, p=.04]. Mascoli et al[43] reported similar results in their experiences with three type II endoleak detected by CO_2 angiography and not detected by CEUS, whereas Huang et al[41] concluded in their experience that for the detection of endoleaks ICM is superior to CO_2-DSA, but the sensitivity for detecting any endoleak and both the sensitivity and specificity for detecting type I endoleaks using CO_2-DSA were acceptable.

The rates of intraoperative and postoperative CO_2-related adverse events were 7.7% and 12.3% respectively. These complications, which were abdominal pain, vomit and diarrhea were all transient with no consequences for patients. These good results, despite the high pressure and volume of CO_2 injections, are probably related to the automated injector, which significantly reduces any air contamination. As reported by Fujihara et al[35] and De Angelis et al[36], who had smilar events, carbon dioxide might cause a transient pain due to blood flow blockage into anterior vessels, such as superior and inferior mesenteric artery.

Furthermore, the only significant risk factor for intraoperative adverse events was a spinal/local anesthesia (p=<.001); the problem could be solved using general anesthesia as much as possible, if not contraindicated in patients undergoing CO_2-EVAR in order to reduce the discomfort. Diabetes mellitus was confirmed as an independent risk factor for postoperative adverse events [6 (0.9-37.7), p=.04]; this aspect has never been reported so far. Moreover, The CO_2 volume was surprisingly protective for postoperative adverse events occurrence [0.99 (0.98-1), p=.03]; also this aspect has been never investigated in literature, but it strengthen the concept that high volumes of CO_2 injected in the aorta are not dangerous for patients using the automated CO_2 injector.

Finally, the 0-iodine analysis reported that independent predictors of 0-iodine CO_2-EVAR were the LoRA detection at preimplant angiography performed from Introducer [0.52 (0.11-1), p=.01] and the image quality in the step 4 with angiography performed from Pigtail [0.35 (0.004-0.29), p=.04]. These aspects underline the importance of this CO_2-EVAR protocol, which allows to reduce ICM amount. The standard CO_2-EVAR procedure protocol with automated injector could be summarized like in Table XXII following the results.

Table XXII. Standard protocol for CO_2-EVAR

STEP 1	CO_2-Aortography from femoral introducer-sheath before main body endograft insertion, in order to check the LoRA correct position	Injection Parameters: Volume: 100 cc Pressure: 600 mmHg

STEP 2	Insertion and deployment of the main body. CO_2-Aortographies to be performed from Pigtail, when the main body is deployed at 50% and 100%, in order to double-check the LoRA position	Injection Parameters: Volume: 100 cc Pressure: 600 mmHg
STEP 3	CO_2 injection from contralateral femoral introducer in order to detect CHA and consequently deploy the contralateral leg	Injection Parameters: Volume: 100 cc Pressure: 600 mmHg
STEP 4	Once aorto-bi-iliac implant completed, final CO_2-Angiogram from femoral introducer. Optional: extra CO_2-Angiogram from pigtail (more sensitive for Endoleak detection)	Injection Parameters: Volume: 100 cc Pressure: 600 mmHg

The study has several limitations. The population of 65 patients is quite small and this reduces the statistical power of the results. The image quality was evaluated by the different operators with no unique standard of measure. The gas injection parameters were suggested by the Angiodroid company, but not corroborated by dedicated clinical trials. The present results should be strengthened by other studies with larger populations.

CO_2-EVAR Study - Conclusions

In CO_2-EVAR procedure, the best image quality at preimplant aortography is obtained when the gas is injected from femoral introducer-sheath.

During the different phases of main body deployment, the endoprosthesis creates a steric bulk, which improves the image quality and the possibility of LoRA detection with CO_2-angiography performed from pigtail.

The CO_2 angiography performed from contralateral femoral introducer-sheath provides good results in terms of image quality and detection of the contralateral hypogastric artery.

The completion CO_2 angiography shows higher image quality if the gas is injected from the introducer-sheath, but the injection from pigtail produces higher sensitivity for endoleak detection, particularly type 2 endoleak.

This operative protocol allows to perform CO_2-EVAR with automated injector with zero-iodine or very small amount of iodinated contrast medium.

CO_2-EVAR is generally safe and all intra- and postoperative adverse events, abdominal pain, vomit or diarrhea, are temporary and benign. Intraoperative adverse events can be overcome using general anesthesia, whenever possible.

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PhD Academic Activities

Relazione sull'attività svolta nel I° anno di Dottorato

- Durante il I° anno sono stati ultimati i documenti necessari all'approvazione dello studio da parte del comitato etico.
- In data 12/12/2018 il Comitato Etico dell'Area Vasta Emilia Centro (AVEC) ha approvato lo studio sperimentale.
- Durante la Round Table presso il Relais Bellaria Hotel di Bologna del 21/06/2019 sono stati discussi con i responsabili dei centri europei partecipanti, Prof. Mauro Gargiulo, Prof Theodosios Bisdas, Prof Giovanni Torsello, Prof Nuno Dias, i punti salienti del protocollo operativo.
- È stato stilato il protocollo operativo definitivo, unitamente ad un form accessibile online da parte dei centri partecipanti per l'inserimento dei dati dei pazienti arruolati nello studio.
- Sono stati arruolati i primi 5 pazienti nel centro della Chirurgia Vascolare dell'Università di Bologna.

Relazione sull'attività svolta nel II° anno di Dottorato e programma delle attività dell'anno successivo

- E' stata stipulata una polizza assicurativa per i pazienti arruolati nello studio
- Sono stati arruolati ulteriori 5 pazienti presso il centro promotore dello studio, Chirurgia Vascolare dell'Università di Bologna (Totale 10 pazienti)
- Sono stati arruolati 3 pazienti presso l'Università di Muenster, 3 pazienti presso l'Università di Malmo e 2 pazienti presso l'Università di Atene
- I dati ricevuti hanno permesso di eseguire alcune analisi statistiche preliminari

Relazione sull'attività svolta nel III° anno di Dottorato e programma delle attività dell'anno successivo

- E' stato completato l'arruolamento di pazienti presso l'Università di Bologna
- E' stato completato l'arruolamento di pazienti presso l'Università di Malmo
- E' stato raggiunto l'arruolamento di 65 pazienti arruolati
- E' stata effettuata l'analisi definitiva dei dati a disposizione

1) *Abstract congressuali ed altre pubblicazioni inerenti il progetto*

"The use of CO2-Angiography and Vessel Navigator Technology decreases Iodinated Contrast Medium amount during FEVAR" *Abstract presentato dal Dott. Andrea Vacirca al LINC 2019, Leipzig, Gennaio 2019.*

"The benefit of combined CO2 automated angiography and fusion imaging in preserving perioperative renal function in fenestrated endografting" *Abstract presentato dal Dott. Rodolfo Pini al Vascular Annual Meeting SVS (Society of Vascular Surgery) 2019, Washington DC, Giugno 2019.*

"Carbon Dioxide Angiography Allows Endovascular Aneurysm Repair to Be Performed With Zero Iodinated Contrast Medium Under Specific Anatomic Conditions" *Abstract presentato dal Dott. Andrea Vacirca al Vascular Annual Meeting, SVS (Society of Vascular Surgery) 2020, Toronto, Giugno 2020.*

“The Impact of Proximal Neck Characteristics on Lowest Renal Artery Visualization in EVAR Procedures with CO_2 Angiography” *Abstract presentato dal Dott. Andrea Vacirca al LINC 2019, Leipzig, Gennaio 2020.*

“The use of CO2-Angiography and Vessel Navigator Technology decreases Iodinated Contrast Medium amount during FEVAR” *Abstract presentato dal Dott. Andrea Vacirca al LINC 2019, Leipzig, Gennaio 2019.*

“The benefit of combined CO2 automated angiography and fusion imaging in preserving perioperative renal function in fenestrated endografting” *Abstract presentato dal Dott. Rodolfo Pini al Vascular Annual Meeting SVS (Society of Vascular Surgery) 2019, Washington DC, Giugno 2019.*

“ACUTE KIDNEY INJURY PREDICTS EARLY AND LATE MORTALITY AFTER ENDOVASCULAR AORTIC REPAIR” *Abstract presentato dal Dott. Andrea Vacirca al Congresso della Società Europea di Chirurgia Vascolare ESVS 2021, Settembre 2021.*

“Carbon Dioxide Angiography Allows Endovascular Aneurysm Repair to Be Performed With Zero Iodinated Contrast Medium Under Specific Anatomic Conditions” *Abstract presentato dal Dott. Andrea Vacirca al Vascular Annual Meeting, SVS (Society of Vascular Surgery) 2020, Toronto, Giugno 2020.*

“The Impact of Proximal Neck Characteristics on Lowest Renal Artery Visualization in EVAR Procedures with CO_2 Angiography” *Abstract presentato dal Dott. Andrea Vacirca al LINC 2019, Leipzig, Gennaio 2020.*

“The use of CO2-Angiography and Vessel Navigator Technology decreases Iodinated Contrast Medium amount during FEVAR” *Abstract presentato dal Dott. Andrea Vacirca al LINC 2019, Leipzig, Gennaio 2019.*

“The benefit of combined CO2 automated angiography and fusion imaging in preserving perioperative renal function in fenestrated endografting” *Abstract presentato dal Dott. Rodolfo Pini al Vascular Annual Meeting SVS (Society of Vascular Surgery) 2019, Washington DC, Giugno 2019.*

2) *Abstract congressuali ed altre pubblicazioni non direttamente inerenti al progetto*

“Predittori di mortalità e recidive nei pazienti con stroke non sottoposti a rivascolarizzazione carotidea.” *Abstract presentato dal Dott. Andrea Vacirca al Congresso SICVE 2018, Napoli, Ottobre 2018.*

“Predittori di sopravvivenza nei tumori aortici.” *Abstract presentato dal Dott. Andrea Vacirca al Congresso SICVE 2018, Napoli, Ottobre 2018.*

“Early and long-term impact of postoperative cerebrovascular complications after carotid endarterectomy” *Poster presentato dal Dott. Andrea Vacirca al Congresso della Società Europea di Chirurgia Vascolare ESVS 2019, Hamburg, Settembre 2019.*

“Revascularization of Critical Limb Ischemia in Patients with No Pedal Arteries Leads to Satisfactory Long-term Limb Salvage” *Poster presentato dal Dott. Andrea Vacirca al Congresso della Società Europea di Chirurgia Vascolare ESVS 2020, Settembre 2020.*

"Il Beneficio dell'Angiografia con CO2 e Fusion Imaging nel Preservare la Funzione Renale nei Pazienti sottoposti a FEVAR" *Abstract presentato dal Dott. Andrea Vacirca al Congresso SICVE 2019, Firenze, Ottobre 2019.*

"Early and long-term impact of postoperative cerebrovascular complications after carotid endarterectomy" *Poster presentato dal Dott. Andrea Vacirca al Congresso della Società Europea di Chirurgia Vascolare ESVS 2019, Hamburg, Settembre 2019.*

"Predittori di mortalità e recidive nei pazienti con stroke non sottoposti a rivascolarizzazione carotidea." *Abstract presentato dal Dott. Andrea Vacirca al Congresso SICVE 2018, Napoli, Ottobre 2018.*

"Predittori di sopravvivenza nei tumori aortici." *Abstract presentato dal Dott. Andrea Vacirca al Congresso SICVE 2018, Napoli, Ottobre 2018.*

"The Role of Vascular Surgeon in a Spine Surgery Program for Oncologic and Degenerative Disease" *Poster presentato dal Dott. Andrea Vacirca al Congresso della Società Europea di Chirurgia Vascolare ESVS 2021, Settembre 2021.*

"Revascularization of Critical Limb Ischemia in Patients with No Pedal Arteries Leads to Satisfactory Long-term Limb Salvage" *Poster presentato dal Dott. Andrea Vacirca al Congresso della Società Europea di Chirurgia Vascolare ESVS 2020, Settembre 2020.*

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"Predittori di sopravvivenza nei tumori aortici." *Abstract presentato dal Dott. Andrea Vacirca al Congresso SICVE 2018, Napoli, Ottobre 2018.*

Partecipazione a Congressi, Seminari e Master aa.aa. 2018/2021

"Congresso Nazionale Società italiana di Chirurgia Vascolare ed Endovascolare" *SICVE 2018, Napoli, Ottobre 2018.*

"Corso Teorico – Pratico sulle tecniche di rivascolarizzazione degli Arti Inferiori" *Humanitas, Rozzano (MI), Ottobre 2018.*

"The use of CO2-Angiography and Vessel Navigator Technology decreases Iodinated Contrast Medium amount during FEVAR" *LINC 2019, Leipzig, Gennaio 2019.*

"A. Vacirca: Introduction to CO2-EVAR study protocol" *Round Table CO2 Angiography, Hotel Relais Bellaria Bologna, Bologna, Giugno 2019.*

"A. Vacirca: CAS in Italia: una realtà consolidata o in divenire? " *Roadsaver Day, Padova, Giugno 2019.*

"Summer School di Chirurgia Vascolare Università di Bologna" *Tutor e membro della faculty, Bologna, Giugno 2019.*

"Congresso Nazionale Società italiana di Chirurgia Vascolare ed Endovascolare" *SICVE 2019, Firenze, Ottobre 2019.*

"Leipzig Interventional Course" *LINC 2020, Leipzig, Gennaio 2020.*

"Vascular Annual Meeting" *Society of Vascular Surgery (SVS) 2020, Toronto, Giugno 2020.*

"European Society of Vascular Surgery Meeting" *ESVS 2020, Krakow, Settembre 2020*

"European Society of Vascular Surgery Meeting" *ESVS 2021, Rotterdam, Settembre 2021*

"Congresso Nazionale Società italiana di Chirurgia Vascolare ed Endovascolare" *SICVE 2021, Cagliari, Ottobre 2021.*

"Leipzig Interventional Course" *LINC 2021, Leipzig, Gennaio 2021*

PhD Publications

Lavori in extenso inerenti il progetto di ricerca di Dottorato

3) **Vacirca A**, Faggioli G, Mascoli C, Gallitto E, Pini R, Spath P, Logiacco A, Palermo S, Gargiulo M. CO_2 automated angiography in endovascular aortic repair preserves renal function to a greater extent compared with iodinated contrast medium. Analysis of technical and anatomical details. Ann Vasc Surg. 2021 Nov 13:S0890-5096(21)00873-6. doi: 10.1016/j.avsg.2021.10.039.
4) **Vacirca A**, Faggioli G, Pini R, Spath P, Gallitto E, Mascoli C, Abualhin M, Gargiulo M. The Efficacy of a Protocol of Iliac Artery and Limb Treatment During EVAR in Minimising Early and Late Iliac Occlusion. Eur J Vasc Surg. *In press*. https://doi.org/10.1016/j.ejvs.2020.07.066
5) Gallitto E, Faggioli G, **Vacirca A**, Pini R, Mascoli C, Fenelli C, Logiacco A, Abualhin M, Gargiulo M. The benefit of combined CO2 automated angiography and fusion imaging in preserving perioperative renal function in fenestrated endografting. J Vasc Surg. 2020 Apr 7. pii: S0741-5214(20)30481-X. doi: 10.1016/j.jvs.2020.02.051.
6) Pini R, Gallitto E, Faggioli G, Mascoli C, **Vacirca A**, Fenelli C, Gargiulo M, Stella A. Predictors of perioperative and late survival in octogenarians undergoing elective endovascular abdominal aortic repair. J Vasc Surg. 2018 Nov 23. pii: S0741-5214(18)32095-0. doi: 10.1016/j.jvs.2018.07.059.
7) **Vacirca A**, Faggioli G, Pini R, Gallitto E, Mascoli C, Cacioppa LM, Gargiulo M, Stella A. The Outcome of Technical Intraoperative Complications Occurring in Standard Aortic Endovascular Repair. Ann Vasc Surg. 2018 Nov 23. pii: S0890-5096(18)30860-4. doi: 10.1016/j.avsg.2018.08.092.
8) Mascoli C, Faggioli G, Gallitto E, Vento V, Indelicato G, Pini R, **Vacirca A**, Stella A, Gargiulo M. The Assessment of Carbon Dioxide Automated Angiography in Type II Endoleaks Detection: Comparison with Contrast-Enhanced Ultrasound. Contrast Media Mol Imaging. 2018 Mar 26;2018:7647165. doi: 10.1155/2018/7647165.
9) Mascoli C, Faggioli GL, Gallitto E, Vento V, Pini R, **Vacirca A**, Indelicato G, Gargiulo M, Stella A. Standardization of a carbon dioxide automated system for endovascular aortic aneurysm repair. Ann Vasc Surg. 2018 Mar 6. pii: S0890-5096(18)30224-3. doi: 10.1016/j.avsg.2018.01.099.

Lavori in extenso non direttamente inerenti il progetto

1) Pini R, Faggioli G, Palermo S, Fronterrè S, Alaidroos M, **Vacirca A**, Gallitto E, Gargiulo M. Clamped Carotid Dissection Can Reduce Postoperative Stroke After Carotid Endarterectomy. Vasc Endovascular Surg. 2021 Oct 18:15385744211052218. doi: 10.1177/15385744211052218.
2) Halliday A, Bulbulia R, Bonati LH, Chester J, Cradduck-Bamford A, Peto R, Pan H; ACST-2 Collaborative Group. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. Lancet. 2021 Sep 18;398(10305):1065-1073. doi: 10.1016/S0140-6736(21)01910-3. Epub 2021 Aug 29.
3) Pini R, Faggioli G, Muscari A, Rocchi C, Palermo S, **Vacirca A**, Gallitto E, Gargiulo M. Carotid Endarterectomy is often not Possible after an Unheralded Stroke: Unheralded Stroke in Carotid Artery Stenosis. J Stroke Cerebrovasc Dis. 2021 Mar;30(3):105594. doi: 10.1016/j.jstrokecerebrovasdis.2020.105594.
4) Pini R, **Vacirca A**, Palermo S, Gallitto E, Mascoli C, Gargiulo M, Faggioli G. Impact of cerebral ischemic lesions on the outcome of carotid endarterectomy. Ann Transl Med. 2020 Oct;8(19):1264. doi: 10.21037/atm-20-1098.
5) Pini R, Faggioli G, Indelicato G, Palermo S, **Vacirca A**, Gallitto E, Mascoli C, Gargiulo M. Predictors and Consequences of Silent Brain Infarction in Patients with Asymptomatic Carotid

Stenosis. J Stroke Cerebrovasc Dis. 2020 Oct;29(10):105108. doi: 10.1016/j.jstrokecerebrovasdis.2020.105108.

6) Pini R, Faggioli G, **Vacirca A**, Gallitto E, Mascoli C, Attard L, Viale P, Gargiulo M. Is it Possible to Safely Maintain a Regular Vascular Practice During the COVID-19 Pandemic? Eur J Vasc Endovasc Surg. 2020 Jul;60(1):127-134. doi: 10.1016/j.ejvs.2020.05.024. Epub 2020 May 19. PMID: 32499169; PMCID: PMC7236703.

7) Collura S, Morsiani C, **Vacirca A,** Fronterrè S, Ciavarella C, Vasuri F, D'Errico A, Franceschi C, Pasquinelli G, Gargiulo M, Capri M. The carotid plaque as paradigmatic case of site-specific acceleration of aging process: The microRNAs and the inflammaging contribution. Ageing Res Rev. 2020 Aug;61:101090. doi: 10.1016/j.arr.2020.101090. Epub 2020 May 28. PMID: 32474155.

8) **Vacirca A**, Faggioli G, Pini R, Teutonico P, Pilato A, Gargiulo M. Unheralded Lower limb threatening ischemia in a COVID-19 patient. *Int J Infect Dis*. 2020;96:590-592. doi:10.1016/j.ijid.2020.05.060

9) Pini R, Faggioli G, **Vacirca A**, Dieng M, Goretti M, Gallitto E, Mascoli C, Ricco JB, Gargiulo M. The benefit of deferred carotid revascularization in patients with moderate-severe disabling cerebral ischemic stroke. J Vasc Surg. 2020 Apr 26:S0741-5214(20)30597-8. doi: 10.1016/j.jvs.2020.03.043. Epub ahead of print. PMID: 32348801.

10) Pini R, Faggioli G, Gallitto E, Mascoli C, Fenelli C, **Vacirca A**, Gargiulo M. Predictors of Survival in Patients Over 80 Years Old Treated with Fenestrated and Branched Endograft. Ann Vasc Surg. 2020 Mar 28:S0890-5096(20)30271-5. doi: 10.1016/j.avsg.2020.03.034. Epub ahead of print. PMID: 32234393.

11) Pini R, Ciavarella C, Faggioli G, Gallitto E, Indelicato G, Fenelli C, Mascoli C, **Vacirca A,** Gargiulo M, Pasquinelli G. Different Drugs Effect on Mesenchymal Stem Cells Isolated From Abdominal Aortic Aneurysm. Ann Vasc Surg. 2020 Mar 12:S0890-5096(20)30194-1. doi: 10.1016/j.avsg.2020.03.001. Epub ahead of print. PMID: 32173476.

12) **Vacirca A,** Faggioli G, Pini R, Freyrie A, Indelicato G, Fenelli C, Bacchi Reggiani ML, Vasuri F, Pasquinelli G, Stella A, Gargiulo M. Predictors of survival in malignant aortic tumors. J Vasc Surg. 2020 May;71(5):1771-1780. doi: 10.1016/j.jvs.2019.09.030. Epub 2019 Dec 17. PMID: 31862201.

13) Pini R, Faggioli G, Gallitto E, Mascoli C, Fenelli C, Ancetti S, **Vacirca A**, Gargiulo M. The different effect of branches and fenestrations on early and long-term visceral vessel patency in complex aortic endovascular repair. J Vasc Surg. 2020 Apr;71(4):1128-1134. doi: 10.1016/j.jvs.2019.07.076. Epub 2019 Oct 18. PMID: 31635962.

14) Pini R, Faggioli G, **Vacirca A,** Dieng M, Fronterrè S, Gallitto E, Mascoli C, Stella A, Gargiulo M. Is size of infarct or clinical picture that should delay urgent carotid endarterectomy? A meta-analysis. J Cardiovasc Surg (Torino). 2020 Apr;61(2):143-148. doi: 10.23736/S0021-9509.19.11120-2. Epub 2019 Oct 9. PMID: 31603297.

15) Vasuri F, Ciavarella C, Fittipaldi S, Pini R, **Vacirca** A, Gargiulo M, Faggioli G, Pasquinelli G. Different histological types of active intraplaque calcification underlie alternative miRNA-mRNA axes in carotid atherosclerotic disease. Virchows Arch. 2019 Sep 10. doi: 10.1007/s00428-019-02659-w.

16) Pini R, Faggioli G, Gargiulo M, Gallitto E, Cacioppa LM, **Vacirca A**, Pisano E, Pilato A, Stella A. The different scenarios of urgent carotid revascularization for crescendo and single transient ischemic attack. Vascular. 2019 Feb;27(1):51-59. doi: 10.1177/1708538118799225.

17) Gallitto E, Faggioli G, Mascoli C, Pini R, Ancetti S, **Vacirca A**, Stella A, Gargiulo M. Impact of previous open aortic repair on the outcome of thoracoabdominal fenestrated and branched endografts. J Vasc Surg. 2018 Dec;68(6):1667-1675. doi: 10.1016/j.jvs.2018.02.051.