

Carbon dioxide digital subtraction angiography as an option for detection of endoleaks in endovascular abdominal aortic aneurysm repair procedure

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Objective: The purpose of this study was to evaluate carbon dioxide digital subtraction angiography (CO₂-DSA) as an option for the detection of endoleaks (ELs) in the endovascular abdominal aortic aneurysm repair (EVAR) procedure.

Methods: Forty patients with abdominal aortic aneurysm who were scheduled to undergo EVAR were enrolled in the study. There were 35 men and five women (mean age, 77.9 years). All patients had both iodinated contrast conventional DSA (C-DSA) and CO₂-DSA immediately after EVAR. The sensitivity and specificity were calculated for the ability of CO₂-DSA to detect ELs. We also correlated with computed tomography findings 6 months after EVAR.

Results: C-DSA showed that 27 of the 40 patients (68%) had 28 ELs (type I, four; type II, 20; type III, three; type IV, one). CO₂-DSA showed that 16 of the 40 patients (40%) had 17 ELs (type I, four; type II, 10; type III, three; type IV, none). For the prediction of direct ELs (type I and type III) with use of C-DSA as the criterion standard, CO₂-DSA has a sensitivity of 1.0 and a specificity of 1.0. For the detection of persistent type II ELs (n = 11) with use of computed tomography findings 6 months from EVAR as the criterion standard, CO₂-DSA has a sensitivity of 0.87 and a specificity of 0.97. C-DSA has a sensitivity of 0.82 and a specificity of 0.64.

Conclusions: CO₂-DSA is reliable for the detection of direct ELs and persistent type II ELs in EVAR. CO₂-DSA can be an option to detect ELs in the EVAR procedure. (*J Vasc Surg* 2015;61:298-303.)

Endovascular aortic aneurysm repair (EVAR) has become one of the treatment modalities for abdominal aortic aneurysm (AAA) with suitable anatomy. The benefits of EVAR include lower short-term morbidity and mortality than with open surgery.¹⁻³ However, the use of iodinated contrast conventional digital subtraction angiography (C-DSA) during EVAR can lead to potential adverse events for patients with known allergy to contrast material or who are at risk for contrast-induced nephropathy.^{4,5} Carbon dioxide is a non-nephrotoxic, nonallergenic gas and is a potential substitute for C-DSA in EVAR. The use of carbon dioxide digital subtraction angiography (CO₂-DSA) has been studied extensively since the development of a safe and efficient delivery system.^{6,7} However, a recent study showed that CO₂-DSA is not a reliable method to detect type II endoleaks (ELs) intraoperatively with use of C-DSA as the criterion standard.⁷ The purpose of

this study was to evaluate CO₂-DSA as an option for the detection of ELs in the EVAR procedure.

METHODS

The research protocol was approved and reviewed by the Institutional Review Board. Informed consent of the patients was obtained.

We performed this prospective study between 2011 and 2013 at our hospital. Forty patients with infrarenal AAA who were scheduled to undergo EVAR were enrolled in the study. They consisted of 35 men and five women between the ages of 75 and 83 years (mean age, 77.9 ± 8.4 years) (Table 1). No patient had renal dysfunction because we eliminated patients with renal dysfunction from this study. All patients underwent both C-DSA and CO₂-DSA immediately after EVAR for infrarenal AAA. Also, all patients were followed up by computed tomography (CT) for more than 6 months after EVAR (mean, 12.5 ± 2.5 months).

All patients underwent infrarenal EVAR with iodinated contrast material (iomeprol, Iomeron 300; Bracco, Milan, Italy). Two commercially available endografts were used: Excluder (W. L. Gore & Associates, Flagstaff, Ariz; n = 24) and Zenith (Cook, Bloomington, Ind; n = 16). The type of endograft used was determined by the physician's preference based on the patient's anatomy. All procedures were performed under general anesthesia in a hybrid endovascular operating room with fixed angiographic

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Table I. Baseline characteristics of 40 patients

Characteristics	Patients (N = 40)
Age, years	77.9 ± 8.4
Female gender	5 (13)
Hypertension	36 (90)
Coronary artery disease	6 (15)
Current smoking	20 (50)
Hyperlipidemia	12 (30)
Diabetes mellitus	9 (23)

Continuous data are presented as mean ± standard deviation and categorical data as number (%).

equipment (Siemens Medical Solutions, Forchheim, Germany) with a CO₂ imaging package.

Our technique for CO₂-DSA was as follows. A sterile bag (Merit Medical, South Jordan, Utah) with attached tubing with a three-way stopcock (Terumo, Tokyo, Japan) was filled with CO₂. The bag was purged and filled with CO₂ three times to remove room air contamination. The stopcock was then closed, cutting off connection to the inflated bag, while connecting to the tubing with a one-way valve to a sidearm (Terumo). The sidearm of the tubing was connected to a 30-mL lock syringe (Terumo).

The lock syringe was filled and purged at least three times before hand injection. These steps create a closed CO₂ system. Hand injection of 30 mL/s with DSA was performed. High frame rates of six frames per second and stacking technology were required to produce adequate images. After undergoing a standard procedure with iodinated contrast material for the proper deployment of an endograft, each patient underwent one anteroposterior view C-DSA and CO₂-DSA.

After EVAR, paired C-DSA and CO₂-DSA were performed immediately. If type I or type III ELs were identified, additional treatment for EL was performed. If additional treatment was performed, only C-DSA was performed after treatment to avoid prolonged procedure time. However, these data were not evaluated. In this study, paired C-DSA and CO₂-DSA studies were evaluated immediately after EVAR.

After completion of EVAR for all patients, the interpreting radiologists were blinded to the patient's identity by replacement of any identifiers on the workstation of the angiograms. All cases with no patient identifiers were reviewed at once by two experienced cardiovascular radiologists (each radiologist with more than 10 years of experience). Final decisions about the DSA findings were reached by consensus.

After EVAR, follow-up CT studies were done at 1 week, 1 month, and 6 months in all patients. CT was obtained by Somatom Definition (Siemens Medical Solutions) before and after EVAR. Axial CT images were evaluated in a contiguous 1-mm-thick section. Unenhanced and contrast-enhanced CT images were obtained from the thoracic inlet to the inguinal level. Coronal and sagittal reformatted images were also evaluated. A total of 100 mL of contrast material (Iomeprol, Iomeron 300;

Bracco) was injected intravenously at a rate of 3 mL/s, followed by a saline chaser with an automated injector. Our standard triple-phase CT protocol was performed in all cases. This protocol consists of unenhanced acquisition, an arterial phase, and a late delayed phase; all were acquired during an inspiratory breath-hold.

CT studies were retrospectively evaluated by two experienced cardiovascular radiologists (each with more than 5 years of experience) who were blinded to the patient's clinical information and previous imaging findings. Axial images as well as multiplanar reconstructions were reviewed on external workstations. Final decisions about the CT findings were reached by consensus.

For each case, the presence of an EL was assessed. An EL was defined as the presence of contrast material within the aneurysm sac beyond the graft on the arterial or delayed phase image and the absence of contrast material in the corresponding location on the unenhanced image, virtual or standard. ELs were classified as previously described⁸: type I, leak caused by incomplete attachment of the proximal or distal portion of the prosthesis due to technical or anatomic problems; type II, leak caused by retrograde flow into the aneurysm sac through aortic collateral arteries; type III, leak caused by graft defect or a graft module disconnection; and type IV, leak caused by the porosity of the prosthesis.

In this study, direct ELs were defined as type I and type III ELs, which have high-risk leaks and high pressure and require urgent management.⁹ Persistent EL was defined as an EL that did not disappear >6 months because previous studies revealed that patients with persistent type II ELs (>6 months) should be considered for more frequent follow-up or a more aggressive approach to reintervention.¹⁰ On CT 6 months after EVAR, any remaining ELs were defined as persistent ELs.¹⁰

Statistical analysis. All values are shown as the mean ± standard deviation. Statistical analysis was done with clinical and morphologic variables by the paired *t*-test or the Mann-Whitney *U* test for continuous variables. In all tests, *P* < .05 was considered significant (release 11.5; SPSS, Chicago, Ill).

The interpretations were compared between radiologist 1 and radiologist 2. The Cohen κ statistic was performed to assess interobserver agreement. The Cohen κ coefficient is accepted as a stringent statistical method for comparing two observers.¹¹ The κ coefficients were calculated for the detection of ELs.

After a consensus was obtained for C-DSA and CO₂-DSA as described before, the final diagnoses were used to calculate statistical measures. The final C-DSA diagnosis was used as the criterion standard. The true positives, true negatives, false positives, and false negatives of CO₂-DSA were calculated for detection of ELs in the EVAR procedure. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CO₂-DSA were calculated. The diagnostic accuracy was compared by the Fisher test.

After a consensus was obtained for CT findings of persistent ELs 6 months after EVAR as described before,

Table II. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CO₂-DSA for the detection of endoleak (EL) immediately after EVAR

EL type	Sensitivity	Specificity	PPV	NPV
All types	0.61	1	1	0.54
Type I	1	1	1	1
Type II	0.5	1	1	0.67
Type III	1	1	1	1
Types I and III	1	1	1	1

CO₂-DSA, Carbon dioxide digital subtraction angiography; EVAR, endovascular aneurysm repair.

the CT diagnoses were used to calculate statistical measures. The CT findings of persistent ELs were used as the criterion standard. The true positives, true negatives, false positives, and false negatives of C-DSA and CO₂-DSA were calculated for detection of persistent ELs. The sensitivity, specificity, PPV, and NPV of C-DSA and CO₂-DSA were calculated.

RESULTS

C-DSA vs CO₂-DSA immediately after EVAR. In all EVAR procedures, the mean iodinated contrast material used was 128 ± 32 mL. The mean fluoroscopy time was 42 ± 23 minutes.

C-DSA showed that 27 of the 40 patients (68%) had 28 ELs (type I, four; type II, 20; type III, three; type IV, one). One patient had two types of ELs (type I and type II). On the other hand, CO₂-DSA showed that 16 of the 40 patients (40%) had 17 ELs (type I, 4; type II, 10; type III, 3; type IV, 0). One patient had two types of ELs (type I and type II). Type II ELs seen on C-DSA but not on CO₂-DSA were supplied by the lumbar artery (n = 5) and inferior mesenteric artery (n = 5) on C-DSA. There was not a significant difference in size of AAA between type II EL groups identified (mean diameter, 5.8 ± 1.5 cm) and not identified (mean diameter, 5.9 ± 1.6 cm) by CO₂-DSA.

The interobserver agreement between radiologist 1 and radiologist 2 for the detection of ELs, with use of C-DSA, was 0.68. The same κ statistic for interpretation with use of CO₂ was 0.65.

Seven direct ELs (type I, four; type III, three) were identified immediately after deployment. Additional treatments for high-flow-type ELs (subsequent balloon angioplasty, six; aortic cuff placement, one) were performed. Finally, all direct ELs disappeared on C-DSA.

For the detection of any ELs with use of C-DSA as the criterion standard, CO₂-DSA has a sensitivity of 0.61 and a specificity of 1.00 (Table II; Figs 1-3). The PPV was 1.00, and the NPV was 0.54. The results were compared among patients grouped by body mass index (BMI) and between patients with a BMI <25 and those with a BMI ≥25. Seventeen patients had a BMI <25, and 23 patients had a BMI ≥25. No statistically significant difference was

seen between the accuracy rates for the diagnosis of ELs (70.6% vs 73.5%, respectively).

For the detection of type I ELs with use of C-DSA as the criterion standard, CO₂-DSA has a sensitivity of 1.00 and a specificity of 1.00 (Table II). The PPV was 1.00, and the NPV was 1.00.

For the detection of type II ELs only with use of C-DSA as the criterion standard, CO₂-DSA has a sensitivity of 0.50 and a specificity of 1.00 (Table II). The PPV was 1.00, and the NPV was 0.67.

For the detection of type III ELs only with use of C-DSA as the criterion standard, CO₂-DSA has a sensitivity of 1.00 and a specificity of 1.00 (Table II). The PPV was 1.00, and the NPV was 1.00.

For the detection of direct ELs including type I and type III ELs with use of C-DSA as the criterion standard, CO₂-DSA has a sensitivity of 1.00 and a specificity of 1.00 (Table II). The PPV was 1.00, and the NPV was 1.00.

Preprocedure and postprocedure serum creatine data were available in all patients. The mean preprocedure and postprocedure values were 0.95 ± 0.34 and 0.96 ± 0.41 mg/dL, respectively. There was no significant difference between them. Otherwise, no patients had any complications due to CO₂-DSA.

C-DSA vs CO₂-DSA 6 months after EVAR. All type I, type III, and type IV ELs in eight patients had disappeared 1 week after EVAR on CT. Six months after EVAR, CT studies did not show any type I, type III, and type IV ELs.

Nine of 20 type II ELs identified by C-DSA (45%) were persistent 6 months after EVAR. The remaining 11 of 20 type II ELs identified by C-DSA (55%) had disappeared 1 week after EVAR on CT. On the other hand, nine of 10 persistent type II ELs identified by CO₂-DSA (90%) were persistent. One remaining type II EL identified by CO₂-DSA had disappeared 1 week after EVAR on CT. Of the 10 type II ELs seen on C-DSA but not on CO₂-DSA, none progressed to persistent type II ELs.

During the follow-up period, four new type II ELs appeared at 1 week (n = 3) and 3 months (n = 1) after EVAR. Two of the four newly identified type II ELs had disappeared 6 months after EVAR, but two of the newly identified type II ELs remained, which were persistent type II ELs. Six months after EVAR, CT studies showed 11 persistent type II ELs. Ten of 11 patients with a persistent type II EL had no increase in size of the AAA. One remaining patient had an increase in size of the AAA (1 mm).

For the detection of persistent type II ELs (n = 11) with use of CT findings 6 months after EVAR as the criterion standard, CO₂-DSA had a sensitivity of 0.87 and a specificity of 0.97. The PPV was 0.90, and the NPV was 0.93. On the other hand, C-DSA had a sensitivity of 0.82 and a specificity of 0.64. The PPV was 0.45, and the NPV was 0.90.

DISCUSSION

The use of CO₂ arteriography was first developed by Hawkins in 1982.¹² Since then, it has been recognized



Fig 1. An 81-year-old man after endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA). **A**, Conventional digital subtraction angiography (C-DSA) image shows type II endoleak (EL) through lumbar arteries (*arrow*). **B**, Carbon dioxide digital subtraction angiography (CO₂-DSA) image also shows type II EL through lumbar arteries (*arrows*).

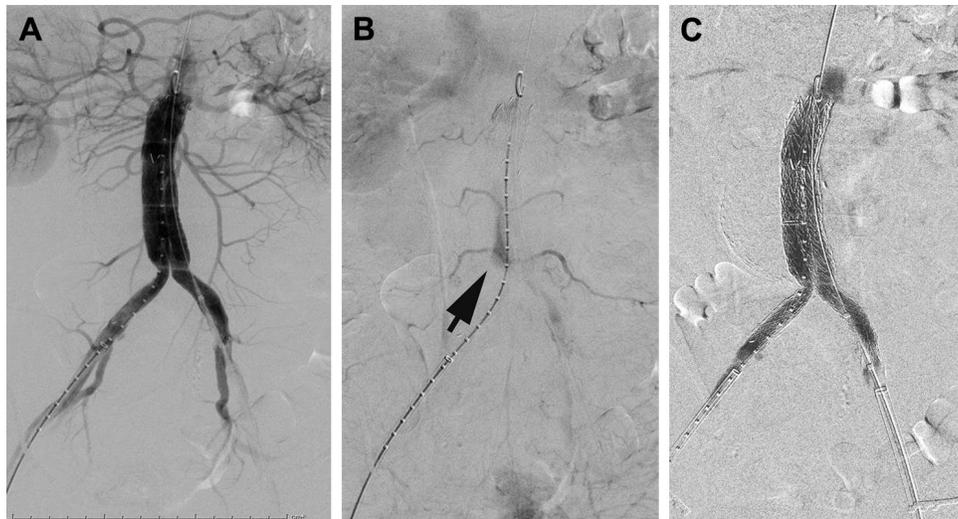


Fig 2. An 83-year-old man after endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA). **A** and **B**, Conventional digital subtraction angiography (C-DSA) images show type II endoleak (EL) through lumbar arteries (*arrow*). **C**, On carbon dioxide digital subtraction angiography (CO₂-DSA) image, type II EL cannot be identified.

that CO₂ has many properties that make it an effective contrast agent for angiography.^{12,13} Two of the most appealing characteristics of CO₂ are that it is non-nephrotoxic and nonallergenic.

In this study, no patients had any complications due to CO₂-DSA. According to previous reports, vapor lock can

occur by trapped CO₂ gas in the vessels. In fact, the volumes of CO₂ injected are too low to cause this complication.^{7,13} Vapor lock of the mesenteric arteries can cause transient intestinal ischemia, but this complication can easily be prevented by aspirating trapped CO₂ through the angiographic catheter.¹⁵ Some authors believe that

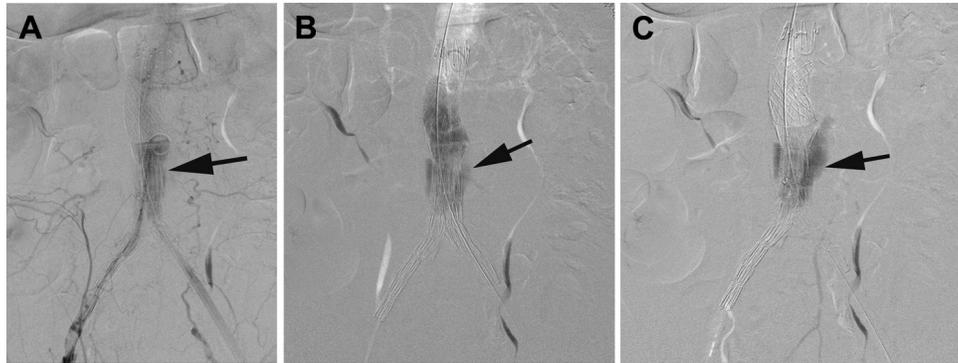


Fig 3. An 80-year-old man after endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA). **A**, Conventional digital subtraction angiography (C-DSA) image shows type III endoleak (EL) (*arrow*). **B** and **C**, Carbon dioxide digital subtraction angiography (CO₂-DSA) images also show type III EL (*arrow*).

vapor lock is of concern only when there is room air contamination because the dissolution of CO₂ begins almost instantaneously after displacement, allowing rapid pulmonary elimination.⁷

Taking advantage of these properties of CO₂ requires an advanced fluoroscopic imaging modality equipped with adequate mobility and digital subtraction to maximize the benefit of its nondependent preference and to capture its rapid disappearance with a higher frame rate.

So far, multiple studies have shown the safety and feasibility of CO₂ angiography in EVAR.^{7,14-18} Also, a few studies have shown the accuracy of CO₂-DSA in detecting ELs.^{16,17,19} Huang et al reported that the sensitivity to detect any EL and both the sensitivity and specificity to detect type I ELs with CO₂-DSA are acceptable.⁷ However, for detection of type II ELs with CO₂-DSA, the sensitivity and PPV are poor.⁷ In this study, both the sensitivity and specificity to detect type I and type III ELs with CO₂-DSA were good. However, for detection of type II ELs with CO₂-DSA, the sensitivity and PPV were poor, which were findings similar to those of previous reports.⁷ According to previous reports, this may be related to the fact that CO₂ is a gas, and to achieve a useful angiogram, the relative position of the area being imaged must be nondependent.¹³ Type II ELs are attributed to back-bleeding from aortic branches. The lumbar branches are posterior in location. With the patient supine, CO₂ is unlikely to distribute posteriorly, thereby not revealing type II ELs on the angiogram. However, our results showed that type II ELs seen on C-DSA but not on CO₂-DSA were supplied by the lumbar artery ($n = 5$) and inferior mesenteric artery ($n = 5$) on C-DSA. We speculate that the volume and speed of blood flow may contribute to visualization of CO₂-DSA more than the location of the artery.¹³ This would also explain why CO₂-DSA-positive type II ELs tend to persist. In this study, for the detection of persistent type II ELs with use of CT findings 6 months after EVAR as the criterion standard, CO₂-DSA had high sensitivity and specificity. In this study, for the detection of direct ELs including type I and type III ELs with use of C-DSA as

the criterion standard, CO₂-DSA had high sensitivity and specificity. In addition, the interobserver agreement for the detection of any ELs by CO₂-DSA was high. These results suggest that CO₂-DSA is reliable to detect direct ELs, including type I and type II ELs.⁹ In fact, type IV ELs are not clinical problems, and many type II ELs disappear during the follow-up period. Only persistent type II ELs can be a clinical problem. According to previous reports, persistent type II ELs increase the incidence of poor outcomes, including aneurysm sac growth, reintervention rate, need for conversion to open repair, and rupture. In patients with persistent type II ELs (>6 months), more frequent follow-up or reintervention should be considered.¹⁰ This study revealed that CO₂-DSA is more reliable than C-DSA for the prediction of persistent type II ELs in EVAR. In addition, CO₂-DSA had high sensitivity and specificity to detect direct ELs. Therefore, CO₂-DSA can be an option to detect ELs during the EVAR procedure. CO₂-DSA during EVAR can reduce the dose of contrast material and the risk for contrast-induced nephropathy in patients with renal dysfunction.

A previous study revealed that the interobserver agreement between observers 1 and 2 for the detection of ELs with use of C-DSA was similar.⁷ However, the same κ statistics for interpretation with use of CO₂-DSA varied widely.⁷ In this study, the interobserver agreement between radiologist 1 and radiologist 2 for the detection of ELs, with use of both C-DSA and CO₂-DSA, was similar. The reason that the difference occurred is unknown. However, there were several differences in the methods between our study and previous studies, and further studies are needed to clarify the interobserver agreement with use of CO₂-DSA.

A few reports have shown that only CO₂-DSA was used during the whole EVAR procedure.^{13-15,20} However, in some cases, C-DSA was needed because of the low quality of CO₂ vascular images.^{12,20} If the operator is well informed about using CO₂, many EVAR procedures could be performed with CO₂-DSA alone.

In this study, the incidence of ELs (68%) on C-DSA was higher than in previous reports because DSAs were

obtained immediately after EVAR.⁷ If type I or type III ELs were identified, additional treatment for EL was performed. If additional treatment was performed, we confirmed disappearance of type I or type III ELs by C-DSA. Therefore, all type I and type III ELs finally disappeared during the EVAR procedure. Many type II ELs disappeared during the follow-up period. Six months after EVAR, the incidence of ELs (28%) on CT was not higher than in previous reports.⁷ During the follow-up period, four new type II ELs appeared from 1 week to 3 months after EVAR. It is difficult to predict new ELs, and follow-up imaging studies are needed.

There were the following limitations in this study. First, the number of patients was small; additional studies involving larger numbers of patients are required. Second, we used two types of stent graft, which may have a potential bias; however, there were no episodes based on the type of stent graft in this study. Third, it is not clear whether our injection method of CO₂ is the best way to depict ELs. It is therefore necessary to perform optimization studies.

CONCLUSIONS

This study limited to 40 patients revealed that CO₂-DSA exhibited only a moderate sensitivity and specificity. However, CO₂-DSA was able to predict persistent type II ELs with a high sensitivity and specificity. Type II ELs missed on CO₂-DSA were not a problem in the short term. Therefore, CO₂-DSA can be an option to detect ELs during the EVAR procedure, and it may reduce the dose of contrast material and the risk for contrast-induced nephropathy in patients with renal dysfunction.

AUTHOR CONTRIBUTIONS

Conception and design: ES, IS
Analysis and interpretation: ES, IS
Data collection: ES, HN
Writing the article: ES, HN, UM
Critical revision of the article: ES, IS
Final approval of the article: ES, HN, IS, UM
Statistical analysis: ES, IS
Obtained funding: ES, HN, IS, UM
Overall responsibility: ES

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