

Midterm Outcomes of Endovascular Aortic Aneurysm Repair with Carbon Dioxide–Guided Angiography

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Background: Although iodinated contrast (IC) agents are commonly used in endovascular aneurysm repair (EVAR), perioperative use in patients with renal dysfunction or IC allergies is avoided. Carbon dioxide (CO₂)-guided angiography is a promising alternative. We aimed to evaluate short-term and midterm outcomes of EVAR using CO₂-guided angiography.

Methods: Three hundred eighty-one patients who underwent EVAR from January 2012 to September 2016 were retrospectively reviewed and divided into an IC-EVAR group ($n = 351$) and CO₂-EVAR group ($n = 30$). Subjects in the CO₂-EVAR group had severe renal dysfunction ($n = 27$) and IC allergy ($n = 4$). Intraoperative, postoperative, and follow-up variables were compared.

Results: Compared with the IC-EVAR group, preoperative serum creatinine level was significantly higher (2.0 vs. 0.92 mg/dL, $P < 0.0001$) and mean IC dose was significantly lower (18 vs. 55 mL, $P < 0.0001$) in the CO₂-EVAR group. The fluoroscopy time, operative time, number of stent grafts placed, and technical success rates of the groups were similar; no type I and/or type III endoleaks were detected on completion angiography. There was no acute kidney injury and one case of intestinal necrosis in the CO₂-EVAR group, potentially due to cholesterol embolism. Postoperative endoleak, enlargement of aneurysms, survival, freedom from secondary intervention, and renal function change up to 3 months, postoperatively, were similar between the groups.

Conclusions: CO₂-EVAR is technically feasible and exhibits prominent renal protection. However, consideration of the aortic lumen status remains an important challenge.

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INTRODUCTION

Endovascular aneurysm repair (EVAR) has lower short-term morbidity and mortality than open surgery.^{1,2} Intra-arterial contrast agents are an important component of successful EVAR as the tool of choice for preoperative evaluation of aortic aneurysm morphology as well as precise sizing and intraoperative visualization of the ostia of the renal and hypogastric arteries for graft replacement. Although iodinated contrast (IC) is overwhelmingly the most common contrast agent, the perioperative use of IC agents is not recommended in patients with renal dysfunction or allergies to IC.^{3,4} Many strategies have been proposed with the aim of reducing IC exposure. Alternatives have been developed, such as the use of intravascular ultrasound,^{5–7} high-

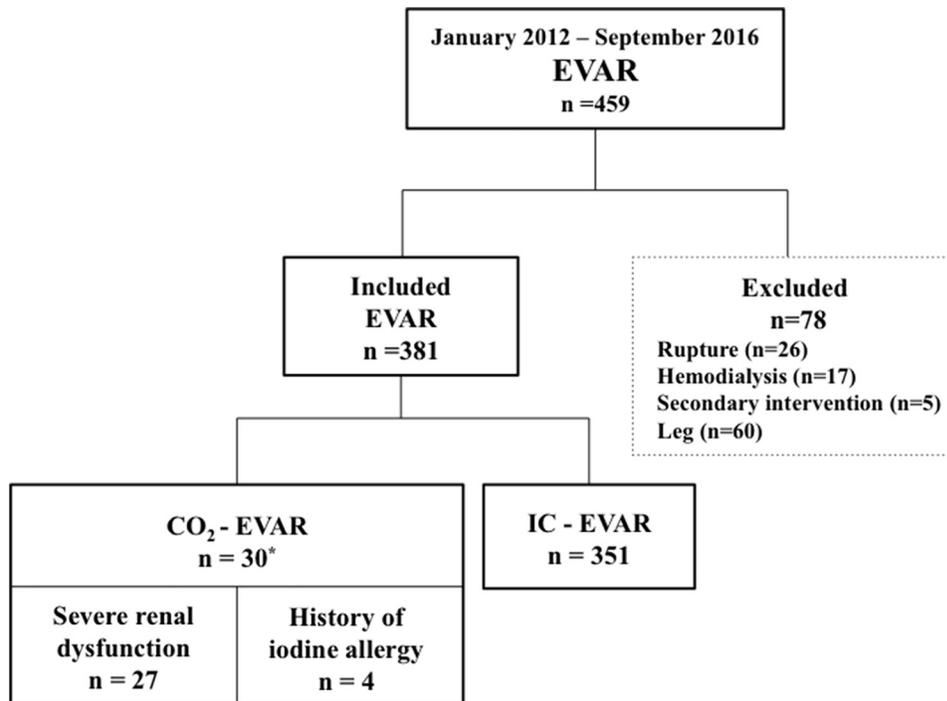


Fig. 1. Flow diagram showing the patients analyzed retrospectively. *One patient had both severe renal dysfunction and history of iodine allergy.

quality 3-dimensional imaging techniques, and fusion of preoperative and intraoperative imaging.⁸ However, despite reports of various methods of renal protection, including the use of perioperative hydration, acetylcysteine, mannitol, dopamine, and fenoldopam, the effects of these methods are controversial.^{9–11}

Carbon dioxide (CO₂)-guided angiography is an alternative contrast approach first described for diagnostic purposes by Hawkins.¹² Although many studies have demonstrated the safety and effectiveness of CO₂-EVAR and its noninferiority to IC-EVAR,^{13–17} the midterm and long-term outcomes of CO₂-EVAR have not been reported to date. The aim of this study was to evaluate the short-term and midterm outcomes of patients who underwent CO₂-EVAR and to compare them with those of patients who underwent conventional IC-EVAR.

METHODS

We retrospectively analyzed data from patients who underwent EVAR at Yamaguchi University (Yamaguchi, Japan) and Saiseikai Shimonoseki General Hospital (Yamaguchi, Japan) from January 2012 to September 2016. Of the 459 patients who

underwent EVAR using commercially available devices, 381 were included in the present study (Fig. 1). The reasons for exclusion of the remaining 78 patients were rupture in 26 patients and hemodialysis in 17 patients because the evaluation of renal function differs quite substantially in these patients from that in elective surgeries and nonhemodialysis patients. In addition, patients undergoing secondary EVAR ($n = 5$) and those in whom only one limb placement was performed ($n = 60$) were also excluded because the operative procedure in these patients tended to be simpler than that in other cases, which may have biased the evaluation of intraoperative variables. More than 40 variables pertaining to patient demographics, comorbidity, medication, anatomy, device used, perioperative outcome, and midterm outcome (including transition of renal function, aneurysm size, types of endoleak, and secondary intervention) were collected.

The Risk/Injury/Failure/Loss/End-stage (RIFLE) classification was used to evaluate the presence of acute kidney injury. The RIFLE classification consists of international criteria to define and stage acute kidney injury within the first 7 postoperative days.¹⁸ Serum creatinine, glomerular filtration rate, and urine volume should be used for this classification; however, we substituted these

parameters with serum creatinine and estimated glomerular filtration rate (eGFR) on postoperative day 1 for convenience. Increases in serum creatinine and decreases in eGFR compared with preoperative findings were classified as follows: ≥ 1.5 times and/or $>25\%$, "risk"; ≥ 2 times and/or $>50\%$, "injury"; and ≥ 3 times and/or $>75\%$, "failure." Furthermore, the need for renal replacement therapy for 4 weeks or more was classified as "loss" and for 3 months or more as "end stage." The following equation was used to calculate eGFR¹⁹: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287} (\times 0.739 \text{ [if female]})$.

Technical success was defined as completion of EVAR without residual type I and/or type III endoleaks, as evaluated by completion angiography. Among midterm outcomes, endoleak was evaluated at the final follow-up point, and enlargement of aneurysms was defined as a size increase of ≥ 5 mm.

The following was our strategy for CO₂-EVAR. Informed consent was obtained from all patients. In general, we did not use IC when performing computed tomography (CT) for preoperative sizing. CO₂, occasionally combined with intravascular ultrasound, was used for intraoperative sizing. IC was injected to dilate the balloon for touch-up of the graft, except in the case of patients with IC allergy, who were injected with a gadolinium contrast agent. IC was also used in completion angiography; however, it was never used for patients with IC allergy. CO₂, gadolinium contrast agent, and transcutaneous echography were used in combination for completion angiography in these patients. Hand injection of CO₂ using digital subtraction imaging was used for angiography. The bolus dose per injection was 20–30 mL in the aorta and 20 mL in the iliac artery at a speed of approximately 10 mL/s. Follow-up CT was performed without IC, and endoleak was evaluated with ultrasonographic pulse echo imaging.

Indications for EVAR included patients with infrarenal abdominal aortic aneurysm of ≥ 5.0 cm or common iliac artery aneurysms of ≥ 3.0 cm with favorable endovascular anatomy. The EVAR procedure consisted of bilateral groin access and initial angiography for localization of the renal and hypogastric arteries and definitive sizing of graft length. The main body of the graft was deployed in the infrarenal position after 1 or 2 angiograms, with magnified views of the perirenal aorta collected. After deployment, placement of the contralateral and ipsilateral limbs was completed by using angiograms to localize the hypogastric arteries. A final angiogram was used to evaluate possible endoleaks and final graft position.

Additional angiographic runs were performed if an endoleak was detected which required additional intervention or placement of additional graft extensions. All type I and III endoleaks were addressed intraoperatively, whereas detected type II endoleaks were only observed.

Statistical analyses were performed with Stata/SE 12.1 (StataCorp, USA). Data are expressed as the mean \pm standard deviation. Continuous variables were compared between 2 groups using Student's *t*-test, and categorical values were compared using χ^2 analysis. A *P* value < 0.05 was considered significant.

RESULTS

Between January 2012 and September 2016, 30 patients underwent CO₂-EVAR, and 351 patients underwent IC-EVAR. We offered CO₂-EVAR to patients with IC allergy ($n = 4$) and all patients with severe renal dysfunction ($n = 27$) who demonstrated chronic kidney disease (CKD) stage IV or V, with the exception of 4 patients with CKD IV. The average patient age was 76 years, and 81% of patients were men. Patients' demographic characteristics, comorbidities, medication use, and anatomy were similar between the 2 groups, with the exception of coronary artery disease. Patients in the CO₂-EVAR group had a mean preoperative serum creatinine level of 2.0 mg/dL and an eGFR of 30 mL/min/1.73 m², whereas IC-EVAR patients had a mean serum creatinine of 0.92 mg/dL and an eGFR of 63 mL/min/1.73 m² ($P < 0.0001$). We used eGFR to assign CKD stages based on the National Kidney Foundation classification for CKD in each group. Although 4 patients underwent IC-EVAR despite having CKD stage IV, almost all patients with severe renal function were included in the CO₂-EVAR group (Table I).

The mean IC dose was significantly lower in the CO₂-EVAR group than the IC-EVAR group (18 vs. 55 mL, $P < 0.0001$). The mean CO₂ dose in the CO₂-EVAR group was 115 mL. Fluoroscopy time, operative time, bleeding, and necessity for blood transfusion were not different between the 2 groups. Stent grafts placed included the Excluder (W.L. Gore & Assoc, Flagstaff, AZ, USA), Endurant (Medtronic, Santa Rosa, CA), Zenith (Cook, Bloomington, IN), Aorfix (Lombard Medical, Irvine, CA), AFX (Endologix Inc, Irvine, CA), and TX2 (Cook, Bloomington, IN), and there was no difference in device choice between the 2 groups. In the IC-EVAR group, one patient had to undergo open conversion that resulted in technical failure, but

Table I. Patient characteristics

	IC, <i>n</i> = 351 (%)	CO ₂ , <i>n</i> = 30 (%)	<i>P</i>
Age (years)	76 ± 9.0	76 ± 7.3	0.61
Male	282 (80)	25 (83)	0.69
BMI	24 ± 18	22 ± 4.2	0.48
CVD	67 (20)	8 (27)	0.42
CAD	95 (29)	15 (52)	0.01
Hypertension	279 (81)	27 (93)	0.11
Diabetes	46 (14)	4 (14)	0.97
Dyslipidemia	153 (46)	17 (59)	0.18
COPD	75 (23)	9 (32)	0.29
Smoking	253 (83)	23 (82)	0.94
Current smoking	75 (28)	5 (20)	0.39
Antiplatelet/ anticoagulant therapy	143 (44)	14 (54)	0.35
Statin use	125 (40)	14 (48)	0.37
Aneurysm size (mm)	50 ± 13	53 ± 8.7	0.29
Saccular type	37 (11)	5 (17)	0.31
Serum creatinine (mg/dL)	0.92 ± 0.3	2.0 ± 1.0	<0.0001
eGFR (mL/min/ 1.73 m ²)	63 ± 18	30 ± 15	<0.0001
CKD stage			<0.0001
Stage 1	20 (5.7)	0 (0)	
Stage 2	169 (48)	2 (6.7)	
Stage 3a	106 (30)	1 (3.3)	
Stage 3b	52 (15)	7 (23)	
Stage 4	4 (1.1)	18 (60)	
Stage 5	0 (0)	2 (6.7)	

Categorical data are presented with percentages; continuous variables are presented as mean (SD).

CKD stages as defined by the National Kidney Foundation (www.kidney.org).

BMI, body mass index; CVD, cerebrovascular disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

there were no residual type I and/or type III endoleaks on completion angiography in either group. The occurrence of intraoperative incidents did not differ between the 2 groups (Table II).

There was a significant difference in operative mortality between the 2 groups. One patient in the CO₂-EVAR group died from intestinal necrosis, whereas there was no operative mortality in the IC-EVAR group. Using clinical judgment, we considered the cause of intestinal necrosis to be cholesterol embolism. We hypothesized that a plaque-rich aortic wall was present, which was not evaluated preoperatively because we only performed simple CT, and that intraoperative picking with the guide wire occurred causing shower emboli to enter the intestinal artery. No other complications were observed in the CO₂-EVAR group. In terms of acute

kidney injury, only one patient was classified as “risk” in the CO₂-EVAR group. Similarly, in the IC-EVAR group, no patients were classified as “failure” or worse condition, and the distribution of kidney injury classifications was similar between the 2 groups (Table III).

With the same mean follow-up period (20 months for both the groups), there was no difference in the occurrence of postoperative endoleak or aneurysm enlargement (Table IV). Fluctuation of renal function evaluated by serum creatinine and eGFR at postoperative day 1 and at 3 months demonstrated similar patterns between the 2 groups, with renal function better at postoperative day 1 than at the preoperative measurement and returning to preoperative levels at 3 months, postoperatively, with the exception of eGFR in the IC-EVAR group. Immediate improvement of renal function after operation is considered to be the result of perioperative hydration (Fig. 2). With respect to midterm outcomes, rates of overall survival and freedom from secondary intervention were similar between the 2 groups (Figs. 3 and 4).

DISCUSSION

CO₂ is unique in its buoyancy, rapid solubility in blood, and quick washout. Although liquid contrast agents fill the lumen and mix with the blood to create radiographic contrast, CO₂ gas acts by displacing the blood within the vessel being studied, serving as a negative contrast agent. Because it is not nephrotoxic or allergenic, the use of CO₂ instead of IC for arterial and venous angiography have been reported in many studies.^{20,21} Its safety and reliability as a guiding method for EVAR has been gradually established.¹⁴ Recent studies have demonstrated that the sensitivity and specificity of CO₂-guided angiography for detecting intraoperative endoleaks were acceptable.^{13,17}

Our study identified that CO₂-EVAR is technically feasible as it has intraoperative complications and requires adjunctive procedures at the same frequency as IC-EVAR. Furthermore, among the cases requiring adjunctive procedures, there were no failure cases in proximal additional graft placement or coil embolization in the CO₂-EVAR group. One point to be aware of regarding angiography with CO₂ is the “vapor lock” phenomenon that occurs when CO₂ gas is trapped and obstructs normal blood flow, usually in cases where excessively large volumes are injected or the time between serial injections is insufficient to allow clearance of the CO₂ gas.²² It is likely that a higher total volume can be

Table II. Intraoperative variables

	IC, <i>n</i> = 351 (%)	CO ₂ , <i>n</i> = 30 (%)	<i>P</i>
IC dose (mL)	55 ± 24	18 ± 15	<0.0001
CO ₂ dose (mL)	-	115 ± 84	-
Fluoroscopy time (min)	49 ± 37	43 ± 29	0.57
Operative time (min)	171 ± 86	172 ± 68	0.94
Bleeding (mL)	258 ± 981	148 ± 125	0.56
Blood transfusion	20 (7.4)	5 (18)	0.06
Stent graft			0.81
Excluder	189 (54)	17 (57)	
Endurant	137 (39)	13 (43)	
Zenith	20 (5.7)	0 (0)	
Aorfix	2 (0.57)	0 (0)	
AFX	2 (0.57)	0 (0)	
TX2	1 (0.28)	0 (0)	
Technical success	350 (99.7)	30 (100)	0.77
EL I or III detected	0 (0)	0 (0)	-
Intraoperative accidents	13 (3.7)	1 (3.3)	0.44
IIA cover	2 (0.57)	1 (3.3)	
RA cover	3 (0.85)	0 (0)	
Leg thrombosis	2 (0.57)	0 (0)	
Access route dissection	4 (1.1)	0 (0)	
Access route bleeding	1 (0.28)	0 (0)	
Open conversion	1 (0.28)	0 (0)	

Categorical data are presented with percentages; continuous variables are presented as mean (standard deviation).

IIA, internal iliac artery; RA, renal artery; EL, endoleak.

used as long as individual doses are small, and sufficient time is allotted between serial injections, although a recommended maximum arterial infection volume of 100 mL has been proposed.^{21,23} Transient ischemic colitis and a case of transient mesenteric ischemia have also been reported after CO₂ angiography, secondary to vapor lock phenomenon.^{24,25} We speculated that cholesterol embolism caused intestinal necrosis in this case because we neither evaluated the arterial mural thrombus using preoperative CT with IC, nor did we observe intraoperative gas traversing the vessel. However, vapor lock due to CO₂ angiography does occur and, accordingly, cannot be ruled out in this case. Severe arterial degeneration of the aorta, referred to as a shaggy aorta, was reported as an independent predictor of cholesterol embolism in EVAR.²⁶ Our strategy was to perform only simple CT, preoperatively, for patients with severe renal impairment, in whom we intended to perform CO₂-EVAR; however, we should be aware of evaluating the aortic wall status in the future. Since then, we have attempted

Table III. Postoperative variables

	IC, <i>n</i> = 351 (%)	CO ₂ , <i>n</i> = 30 (%)	<i>P</i>
Operative mortality	0 (0)	1 (3.3)	0.001
Intestinal necrosis	1 (0.28)	1 (3.3)	0.0005
Buttock claudication	1 (0.28)	0 (0)	-
Blue toe syndrome	1 (0.28)	0 (0)	-
Gastric ulcer	1 (0.28)	0 (0)	-
Stroke	2 (0.57)	0 (0)	-
Wound infection	2 (0.57)	0 (0)	-
Acute kidney injury ^a			0.93
Risk	9 (2.6)	1 (3.3)	
Injury	1 (0.29)	0 (0)	
Failure	0 (0)	0 (0)	
Loss	0 (0)	0 (0)	
ESKD	0 (0)	0 (0)	

Increases in serum creatinine and decreases in eGFR compared with the preoperative measurements were classified as follows: ≥1.5 times and/or >25%, “risk”; ≥2 times and/or >50%, “injury”; ≥3 times and/or >75%, “failure”; need for renal replacement therapy for 3 weeks or more, “loss”; need for renal replacement for 3 months or more, “end stage.”

^aAcute kidney injury is evaluated on the basis of the RIFLE classification, except for the case with open conversion.

Table IV. Midterm outcomes

	IC, <i>n</i> = 351 (%)	CO ₂ , <i>n</i> = 30 (%)	<i>P</i>
Follow-up period (month)	20 (0.2–56)	20 (0.2–55)	0.96
Endoleak	80 (24)	5 (19)	0.27
Type Ia	1 (0.29)	1 (3.7)	
Type Ib	2 (0.59)	0 (0)	
Type II	73 (22)	4 (15)	
Type III	3 (0.88)	0 (0)	
Type IV	0 (0)	0 (0)	
Type V	1 (0.29)	0 (0)	
Enlargement of aneurysms ^a	17 (4.8)	2 (6.7)	0.66
Elimination of aneurysms	21 (6.0)	0 (0)	0.17

^aEnlargement of the aneurysm was defined as a size increase of 5 mm.

to perform preoperative CT angiography in all patients, even in those with severe renal impairment, depending on their situation, to determine the exact condition of the intra-arterial wall.

In this study, we used extremely low doses of IC in both the groups, which is a result of dilution of IC by 1.5-fold in all EVAR cases. Nevertheless, the quality of imaging was still acceptable, and the short-term and midterm outcomes were satisfactory. We believe that these efforts, including the

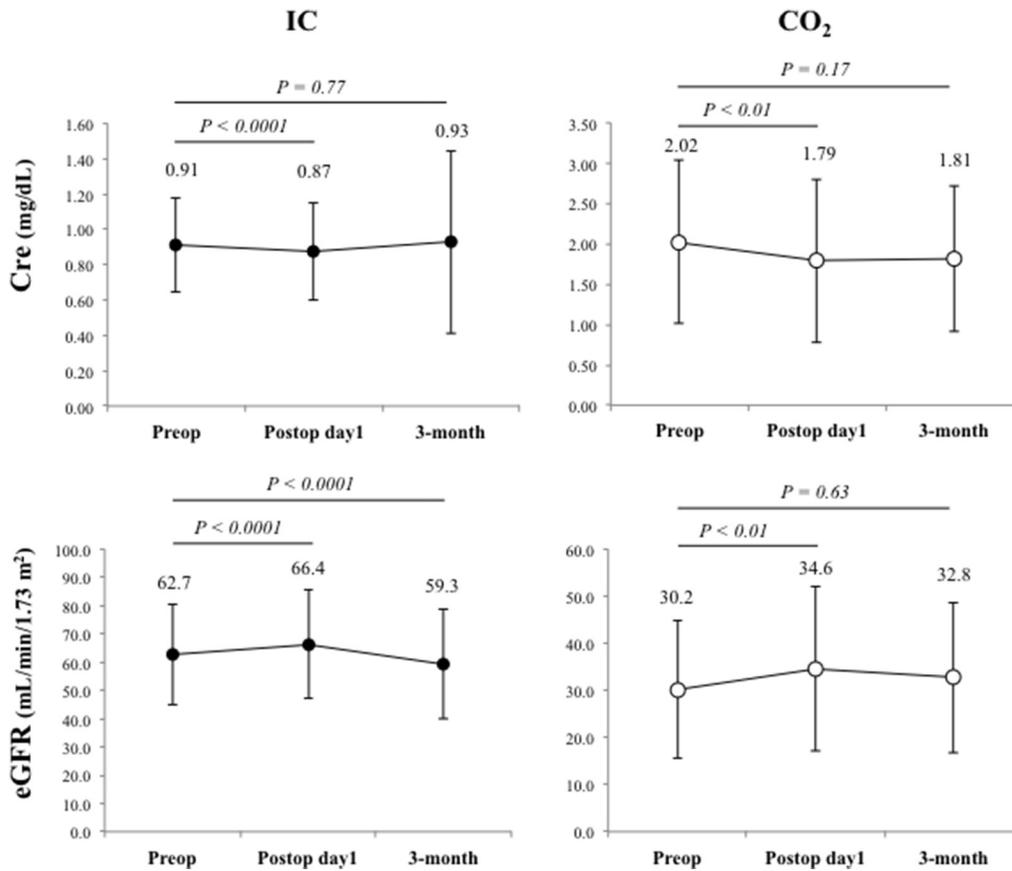


Fig. 2. Fluctuation of mean serum creatinine level and eGFR between patients undergoing IC-EVAR and CO₂-EVAR measured preoperatively on postoperative day 1 and then at 3 months, postoperatively. The data were

compared between preoperative measurement and postoperative day 1 measurement and also between preoperative measurement and measurement at 3 months, postoperatively, by Student's *t*-test.

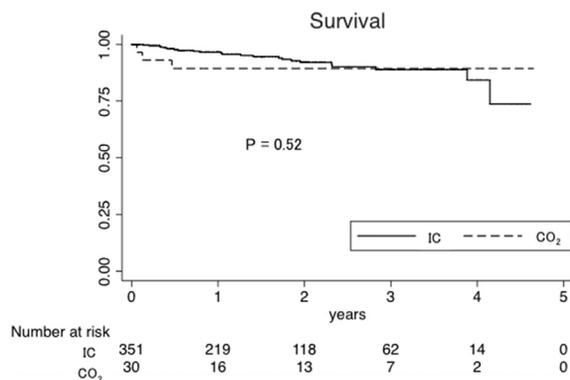


Fig. 3. Kaplan-Meier curve demonstrating overall survival of the IC-EVAR and CO₂-EVAR groups ($P = 0.52$).

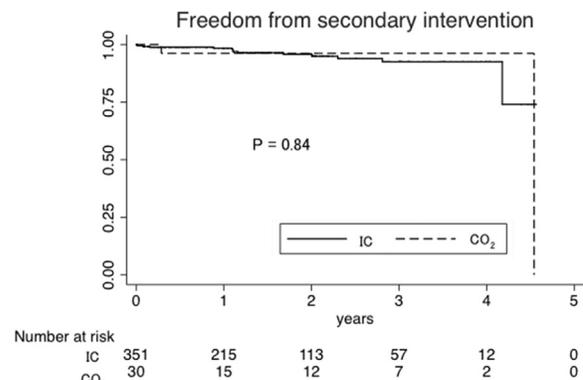


Fig. 4. Kaplan-Meier curve demonstrating freedom from secondary intervention of the IC-EVAR and CO₂-EVAR groups ($P = 0.84$).

CO₂-EVAR strategy, protected renal function throughout the perioperative period, during which no acute kidney injury was observed in the CO₂-EVAR group despite those patients' preexisting severe renal dysfunction. Although several reports

have documented progressively worsening renal function over the long term after EVAR,³ long-term follow-up of renal function may not accurately reflect the influence of EVAR because it is affected

by the normal loss of organ function with aging.²⁷ Therefore, we evaluated renal function only up to 3 months, postoperatively, showing unchanged function in both the groups, except for the eGFR in the IC-EVAR group. This finding suggests a renal protective effect of CO₂-EVAR.

Our study has some limitations including its retrospective and nonrandomized design and enrollment of fewer patients in the CO₂-EVAR group than in the IC-EVAR group. Furthermore, the mean follow-up period was only 20 months. Although our findings are quite valuable for operators performing CO₂-EVAR, these limitations should be addressed in future investigations.

CONCLUSION

CO₂-EVAR is technically feasible and demonstrates a prominent protective effect on renal function. Our findings indicate that CO₂-EVAR is a promising treatment option for patients with severe renal dysfunction or IC allergy. However, it demands careful consideration of the status of the aortic lumen, which cannot be determined by CO₂ angiography and simple CT alone, to avoid severe complications.

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