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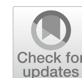

Feasibility and impact of carbon dioxide angiography on acute kidney injury following endovascular interventions in patients with peripheral artery disease and renal impairment

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Abstract

Background Post-contrast acute kidney injury (AKI) is a dreaded complication of endovascular revascularization using iodinated contrast medium in patients with peripheral artery disease and concomitant chronic kidney disease (CKD). This study sought to evaluate the incidence of AKI in patients with peripheral artery disease and CKD undergoing endovascular revascularization and using carbon dioxide (CO_2) as contrast medium.

Methods and Results From 04/2015 to 07/2018, all consecutive peripheral artery disease patients with CKD stage ≥ 3 referred for endovascular revascularization of symptomatic peripheral artery disease were prospectively included. During endovascular revascularization, CO_2 as contrast medium was manually injected and iodinated contrast medium was additionally used when needed. The reference group consisted of 211 cardiovascular risk factor-matched patients undergoing endovascular revascularization with iodinated contrast medium only. CO_2-guided endovascular revascularization was performed in 102 patients, thereof 16 (15.7%) patients exclusively with CO_2. Baseline CKD stage ≥ 4 and iodinated contrast medium volume > 50 ml were disproportionally associated with post-procedural post-contrast AKI. At CKD stage 4 the odds ratio for post-contrast AKI was 13.2 (95% CI 1.489–117.004; $p = 0.02$) for iodinated contrast medium volume 51-100 ml and 37.7 (95% CI 3.927–362.234; $p = 0.002$) for iodinated contrast medium volume > 100 ml. The corresponding values at CKD stage 5 were 23.7 (95% CI 2.666–210.583; $p = 0.005$) and 28.3 (95% CI 3.289–243.252; $p = 0.002$), respectively. Radiation (dose area product) was significantly higher in the CO_2-endovascular revascularization group (6.025 ± 6.926 cGy*cm^2 vs. 4.281 ± 4.722 cGy*cm^2, $p = 0.009$).

Conclusion CO_2 is an applicable and safe alternative to iodinated contrast medium for endovascular revascularization in peripheral artery disease patients with concomitant CKD. Patients with CKD stage 4 or 5, being at highest risk for post-contrast AKI, should primarily be treated by CO_2-guided endovascular revascularization.

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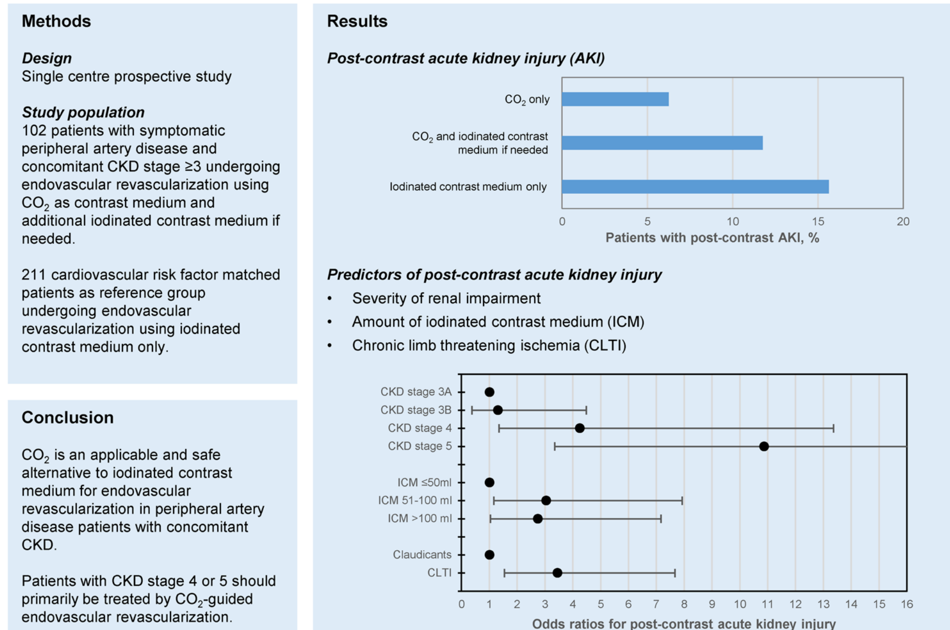
Graphic abstract



Keywords Endovascular revascularization · Chronic kidney disease · Peripheral artery disease · Post-contrast acute kidney injury · Carbon dioxide angiography · Iodinated contrast medium

Introduction

The number of patients suffering from peripheral artery disease is increasing worldwide [1]. Due to the continuous increase in pro-atherosclerotic risk factors such as diabetes mellitus and hypertension alongside an ageing population, the prevalence of peripheral artery disease is expected to rise further in the near future. Particularly, the prevalence of the subset of peripheral artery disease population with the most severe stages of peripheral artery disease, i.e. chronic limb-threatening ischaemia, is rising disproportionately [2]. Revascularization is the pillar of therapeutic management in patients with chronic limb-threatening ischaemia and is increasingly being applied also in patients with limiting claudication not adequately responding to best medical therapy [3, 4]. Due to the high burden of comorbidities resulting in a high perioperative risk, patients with chronic limb-threatening ischaemia are treated preferably and frequently by endovascular revascularization techniques [5, 6].

However, acute kidney injury (AKI) due to the use of iodinated contrast medium during endovascular revascularization is a dreaded complication of iodinated contrast medium as AKI is associated with higher resource utilization costs and adverse short- and long-term outcome [7, 8]. Particularly patients with pre-existent chronic kidney disease (CKD) are at risk for developing post-contrast AKI [9, 10]. In those patients, the risk of post-contrast AKI is directly related to the amount of injected iodinated contrast medium volume [11]. In the literature, the incidence of post-contrast AKI in patients undergoing peripheral angiography or interventions is approximately 10% but differs in various studies and can be as high as 40–50% depending on risk factors and definitions [12–14]. Among patients with manifest atherosclerosis in different vascular territories, the risk of post-contrast AKI is particularly high among those suffering from peripheral artery disease [15]. As the number of patients with concomitant CKD and peripheral artery disease requiring endovascular revascularization increases, the incidence of post-contrast AKI is expected to rise as well. The recognition of the causal relationship between post-contrast AKI and adverse short- and long-term outcome mandate the implementation of novel strategies to minimize the risk of post-contrast AKI.

Carbon dioxide (CO_2) has the potential to serve as an alternative contrast agent for peripheral vascular visualization in patients with renal impairment and hypersensitivity to iodinated contrast medium [16]. In this study, we evaluated the feasibility, safety and impact of CO_2-guided

endovascular revascularization on estimated glomerular filtration rate (eGFR) in patients with symptomatic peripheral artery disease and concomitant CKD and compared the outcome to a risk-profile-matched cohort undergoing endovascular revascularization using standard iodinated contrast medium.

Methods

Study design and patient selection

From April 2015 to July 2018, all consecutive peripheral artery disease patients with concomitant CKD stage ≥ 3 undergoing endovascular revascularization were prospectively included. Inclusion criteria were patients with symptomatic peripheral artery disease of the lower extremities referred for endovascular revascularization with CKD and with an eGFR of < 60 ml/min/1.73 m^2. In these patients, endovascular revascularization was performed by the use of manually injected CO_2. Iodinated contrast medium was additionally used when needed, at the discretion of the operator. The reference group consisted of 211 consecutive peripheral artery disease patients who were matched for age, gender, cardiovascular risk factors and concomitant CKD (eGFR < 60 ml/min/1.73 m^2) undergoing endovascular revascularization using iodinated contrast medium alone. The study protocol was approved by the ethical committee of the Westfälische-Wilhelms-University of Muenster.

CO_2 delivery system

CO_2 was manually injected with CO_2mmander® ELITE (PMDA, LLC.) and AngiAssist® (Robling Medical, Inc.). When performing CO_2 angiography, AngiAssist is connected to the CO_2mmander. CO_2 is provided by a cartridge that is inserted in the device. Gas pressure can be regulated with an adjustment wheel. By pressing the inflating button, CO_2 fills the first of 2 syringes of AngiAssist, which serves as the depot syringe with a maximal volume of 60 ml. Inflow tube (source), depot syringe (60 ml), injection syringe (30 ml) and outflow tube (exit) are connected with a K-valve. The K-valve has 3 possible positions. The first position enables CO_2 flow from the CO_2mmander into the depot syringe, the second position from the depot syringe into the injection syringe and the third position from the injection syringe into the patient through the outflow tube. Two nonreturn valves prevent CO_2/blood reflow and air contamination. It is a self-contained system which leads to high safety of the patient. Moreover, it is comparable to a manually iodinated contrast medium delivery system. AngiAssist is a single-use product, whereas CO_2mmander can be reused.

Clinical and laboratory assessment

All patients had Doppler ultrasound-based ankle-brachial-index measurements before and after revascularization procedures. Laboratory parameters and eGFR were assessed the day before, and 1 and 2 days after endovascular revascularization. Creatinine was measured in the patients' blood serum by spectrometry. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI). Patients were classified into four stages of CKD as follows: stage 3A: eGFR 45–59 ml/min/1.73 m^2; stage 3B: eGFR 30–44 ml/min/1.73 m^2; stage 4: eGFR 15–29 ml/min/1.73 m^2; stage 5: eGFR < 15 ml/min/1.73 m^2. Post-contrast AKI was defined as a 1.5–1.9x or ≥ 0.3 mg/dl creatinine increase within 48 h after the endovascular revascularization procedure [17]. Comorbidities and cardiovascular risk factors (arterial hypertension, coronary heart disease, cerebral artery disease, diabetes mellitus, nicotine abuse, hypolipoproteinaemia) were also assessed from the patients' history.

Endovascular revascularization

Indications for endovascular revascularization were based on the recommendations of the European and German guidelines for the treatment of peripheral artery disease [3, 18]. All endovascular revascularization procedures were performed according to the recommendations of the curriculum for interventional therapy for arterial disease [19].

Informed consent was received from all patients before the procedure and before inclusion in the study. To reduce the risk of post-contrast AKI all patients were hydrated. The pre- and post-procedure hydration was performed according to the recommendations in the consensus paper of the working group "Heart and Kidney" of the German Society of Cardiology by intravenous administration of saline (sodium chloride 0.9%) at a rate of 1 ml/kg body weight 12 h before and up to 12 h after the intervention [20].

For the CO_2-guided endovascular revascularization, patients were put into a slight Trendelenburg position (10°–15°). Heart rate, oxygen saturation, electrocardiogram and blood pressure were continuously monitored during the entire procedure. All complications appearing during the procedure were registered. CO_2 was used primarily as the main contrast agent. In some patients, additional iodinated contrast medium was injected to gain absent vascular information that could not be displayed by CO_2. Time interval between two CO_2 injections was at least 2 min. Approximately 20 ml CO_2 for an iliac and 10 ml CO_2 for femoropopliteal or crural vascular images were injected. Examination duration, fluoroscopy time, radiation dose, iodinated contrast medium and CO_2 volume were measured and compared to the reference group. After successful endovascular revascularization, all patients received platelet inhibition

or anticoagulation according to the recommendation in the guidelines [3, 18].

Statistical analysis

Metric data are presented as mean ± standard deviation (SD), nominal data are shown as quantities and percentages. Metric variables were compared using the Mann–Whitney U test (e.g. ankle-brachial-index, iodinated contrast medium). Single nominal variables were evaluated by Fisher's exact test (e.g. female gender). Multiple nominal variables were analysed with χ^2 test (e.g. localization of lesions). Logistic regression analyses were used to evaluate factors which are related to the development of post-contrast AKI. Collected data were evaluated with SPSS software (IBM SPSS Statistics, Version 24). Two-sided P-value ≤ 0.05 was defined statistically significant.

Results

A total of 313 patients were analysed. The CO_2-endovascular revascularization group consisted of 102 patients, thereof 16 (15.7%) undergoing exclusively CO_2-guided endovascular revascularization without any additional iodinated contrast medium. In 86 (84.3%) subjects in the CO_2-endovascular revascularization group, additionally iodinated contrast medium was used. The comparative group consisted of 211 patients undergoing endovascular revascularization by use of iodinated contrast medium alone.

Table 1 Baseline data

	CO_2-EVR	ICM-EVR	p-value
Patients, n (%)	102 (32.6)	211 (67.4)	
Women, n (%)	37 (36.3)	52 (24.6)	**0.044**
Age, mean ± SD, years	74.8 ± 8.7	72.4 ± 9.3	**0.007**
BMI, mean ± SD, kg/m^2	26.2 ± 4.7	27.1 ± 5.0	0.183
Comorbidities/risk factors			
Hypertension, n (%)	94 (94.0)	187 (91.7)	0.645
Hyperlipidaemia, n (%)	77 (77.8)	123 (60.3)	**0.003**
Coronary heart disease, n (%)	68 (68.7)	146 (71.2)	0.688
Diabetes Mellitus type II, n (%)	50 (50.5)	112 (54.4)	0.542
History of smoking, n (%)	51 (51.5)	100 (48.5)	0.714
Cerebral artery disease, n (%)	34 (34.3)	75 (36.6)	0.799
Medication			
ASS, n (%)	49 (48.5)	83 (42.6)	0.388
Clopidogrel, n (%)	47 (46.5)	108 (56.0)	0.141
Marcumar, n (%)	36 (35.6)	55 (28.5)	0.233
Heparin, n (%)	4 (4.0)	9 (4.7)	1.0
Fontaine stage			0.536
Claudicants, n (%)	37 (36.3)	85 (40.7)	
CLTI, n (%)	65 (63.7)	124 (59.3)	
Localization			**0.027**
Aorto-Iliac, n (%)	5 (5.0)	3 (1.4)	
Femoropopliteal, n (%)	44 (43.6)	80 (37.9)	
Below-the-knee, n (%)	21 (20.8)	32 (15.2)	
Combined, n (%)	31 (30.7)	96 (45.5)	

Bold values denote statistical significance at the $p < 0.05$ level

ASS acetylsalicylic acid, *BMI* body mass index, *CLTI* chronic limb-threatening ischaemia, CO_2 carbon dioxide, *EVR* endovascular revascularization, *ICM* iodinated contrast medium, *SD* standard deviation

Baseline characteristics

The baseline characteristics of the CO_2- and iodinated contrast medium-endovascular revascularization groups are presented in Table 1.

CO_2-endovascular revascularization patients were significantly more often female (p = 0.044), were older (p = 0.007) and had a higher frequency of hyperlipidaemia (p = 0.003) and higher femoropopliteal and below-the-knee treated lesions (p = 0.027) than patients in the iodinated contrast medium-endovascular revascularization group. All other parameters were indifferent between both groups.

Procedural characteristics and outcome

All CO_2-endovascular revascularizations were performed by three experienced operators with 64, 24 and 14 CO_2-endovascular revascularizations, respectively. CO_2 angiography provided excellent image quality in femoropopliteal and iliac segments (Figs. 1-2). Limited image quality (mainly in crural segments) required the use of additional iodinated contrast medium in n = 86 (84.3%) of all CO_2-endovascular revascularization patients. There were no procedure-related severe complications due to endovascular revascularization in either group. Fifteen patients (14.7%) in the CO_2-endovascular revascularization group reported transient (5–20 s) leg pain directly after CO_2 injection.

Pre- and post-procedural values of ankle-brachial-index, eGFR and procedural outcome data are presented in Table 2.

Overall endovascular revascularization procedural success rate was 96.5% with no difference between groups.

Regarding the types of endovascular revascularization procedures, stenting additional to angioplasty was performed more often in the iodinated contrast medium- than in the CO_2-group (65.9% vs. 46.1%; p = 0.001). While the procedure time did not differ between groups, the dose area product was significantly higher in the CO_2- than in the iodinated contrast medium-group (p = 0.009).

Post-contrast AKI occurred within 48 h after endovascular revascularization in 12 (11.9%) patients in the CO_2- and in 33 (15.6%) patients in the iodinated contrast medium-group (p = 0.491). However, only one of the patients

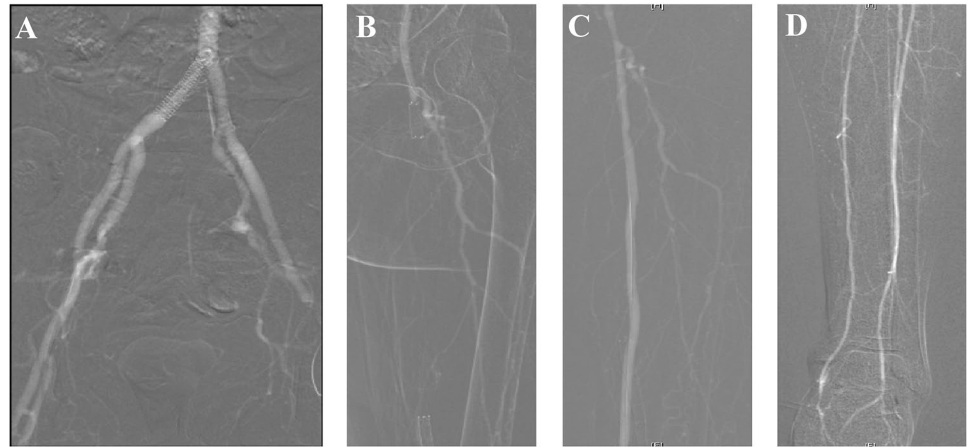


Fig. 1 Representative images of CO_2-guided endovascular interventions. **a** Postprocedural CO_2 angiography of pelvic arteries after stenting of the right common iliac artery. **b** CO_2 angiography shows full occlusion of the femoro-popliteal bypass. **c** Postprocedural CO_2 angiography showing successful revascularization of the femoro-popliteal bypass. **d** CO_2 angiography showing excellent image quality of the crural arteries up to the ankle level

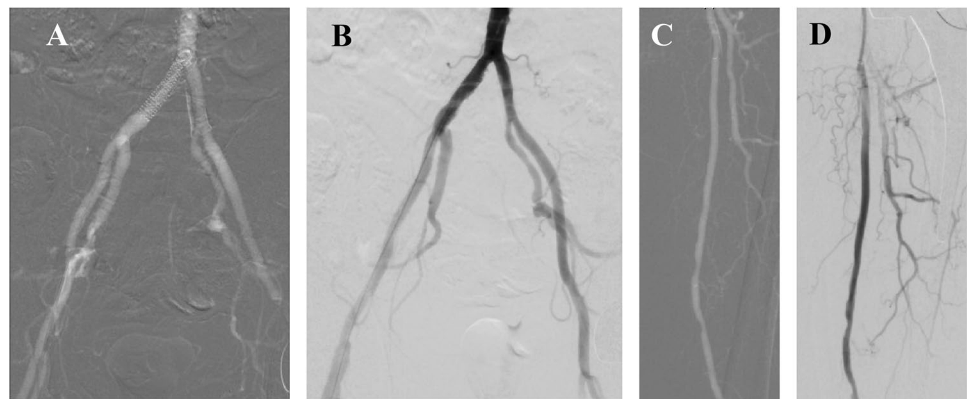


Fig. 2 Images of CO_2- and iodinated contrast medium-guided endovascular interventions. Iliac arteries visualized with CO_2 angiography (**a**) in comparison with iodinated contrast medium angiography (**b**) in the same patient. Femoropopliteal arteries visualized with CO_2 angiography (**c**) and iodinated contrast medium angiography (**d**) in the same patient

Table 2 Haemodynamic and procedural outcome

	CO_2-EVR	ICM-EVR	p-value
ABI before EVR, mean ± SD	0.53 ± 0.29	0.46 ± 0.25	**0.043**
ABI after EVR, mean ± SD	0.80 ± 0.27	0.72 ± 0.26	**0.011**
ABI increase, mean ± SD	0.28 ± 0.24	0.28 ± 0.25	0.865
eGFR before EVR, mean ± SD	32.4 ± 11.8	33.1 ± 15.6	0.326
eGFR after EVR, mean ± SD	34.2 ± 13.1	36.3 ± 19	0.232
ICM, mean ± SD, ml	41.9 ± 31.6	118.9 ± 51.1	**< 0.001**
CO_2, mean ± SD, ml	114.5 ± 53.4	0 ± 0	**< 0.001**
Dose area product, mean ± SD, cGy*cm^2	6.025 ± 6.926	4.281 ± 4.722	**0.009**
Examination duration, mean ± SD, min	92.3 ± 35	101.8 ± 47.2	0.255
Successful EVR, n (%)	99 (99.0)	201 (95.3)	0.113
Additional Stenting, n (%)	47 (46.1)	139 (65.9)	**0.001**
Adjunctive use of thrombectomy devices (Rotarex®), n (%)	13 (12.7)	16 (7.6)	0.149
Directional atherectomy, n (%)	3 (2.9)	1 (0.5)	0.103
Post-contrast AKI, n (%)	12 (11.9)	33 (15.6)	0.491
Hospital stay, mean ± SD, days	6.3 ± 5.7	7.1 ± 7.3	0.327
Haemoglobin drop, mean ± SD, g/dl	0.64 ± 0.97	0.84 ± 1.07	0.055

Bold values denote statistical significance at the $p < 0.05$ level

ABI ankle-brachial-index, *AKI* acute kidney injury, *CO_2* carbon dioxide, *eGFR* estimated glomerular filtration rate, *EVR* endovascular revascularization, *ICM* iodinated contrast medium, *SD* standard deviation

receiving CO_2-only endovascular revascularization (n = 16) had a post-contrast AKI.

Post-contrast AKI prevalence and additionally needed iodinated contrast medium volume depending on lesion localization are shown in Table 3.

Additional iodinated contrast medium volume was lower in femoropopliteal than in crural CO_2-endovascular revascularizations (30.8 ± 31.7 ml vs. 49.3 ± 24.6 ml, p = 0.005). Fifteen (34.1%) femoropopliteal CO_2-endovascular revascularizations were performed with less than 10 ml additional iodinated contrast medium. Post-contrast AKI occurred in 5 (11.6%) femoropopliteal, 1 (20.0%) iliac and 3 (14.3%) crural CO_2-endovascular revascularizations. Big diameter changes of the vessel e.g. post-stenotic dilation/aneurysm were detected as a limitation of CO_2. In these cases, the use of iodinated contrast medium is essential to improve image quality.

The amount of iodinated contrast medium volume used additionally to CO_2 was inversely related to the volume of endovascular revascularization procedures, i.e. it decreased over time with the increase in the number of performed procedures. For operator 1, who performed almost 2/3 of all CO_2-endovascular revascularizations, not only did the amount of additional iodinated contrast medium (47 ± 23 ml vs. 32 ± 26 ml) decrease over time, but so did the procedural time (96 vs. 82 min.) and the radiation dose (6.685 vs. 2.573 cGy*cm^2) (all P < 0.01) when comparing the first 20 vs. the last 20 CO_2-endovascular revascularizations.

Predictors of post-contrast AKI within 48 h after endovascular revascularization

Regarding the whole cohort, baseline eGFR was inversely related to post-interventional post-contrast AKI: A baseline eGFR decrease of 1 ml/min/1.73 m^2 increased the risk of post-contrast AKI by 5.9% (p < 0.001). CKD stage > 3B and the contrast amount were significantly and incrementally associated with post-interventional post-contrast AKI as illustrated in Figs. 3a, b.

Compared to patients with CKD stage 3A, there was no significant risk of post-contrast AKI at CKD stage 3B [odds ratio (OR) 1.302; 95% confidence interval (CI) 0.378–4.489; p = 0.676]. Patients with CKD stage 4 (OR 4.246, 95% CI 1.349–13.368; p = 0.013) and CKD stage 5 (OR 10.861; 95%

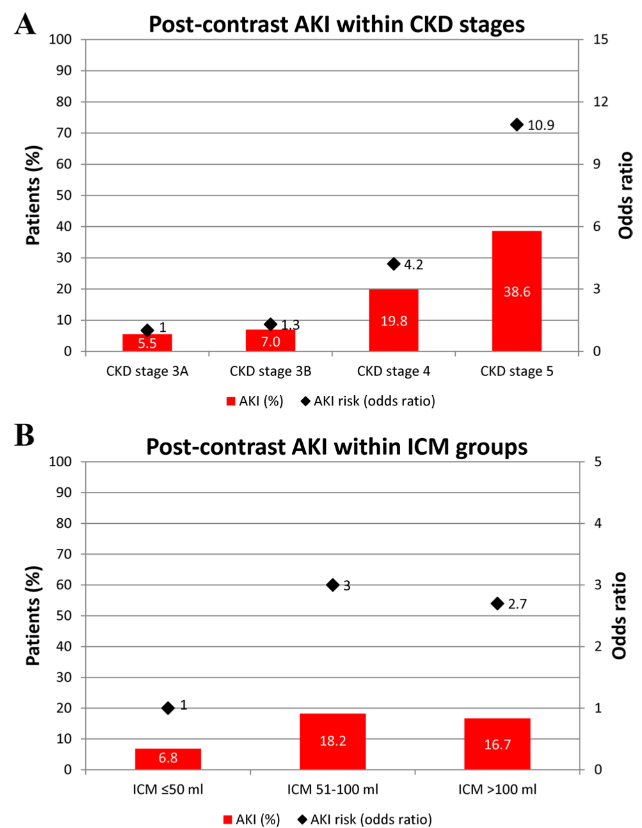


Fig. 3 Post-contrast AKI within CKD stages and iodinated contrast medium groups (CO_2 and iodinated contrast medium-endovascular revascularization groups combined). **a** The percentage of patients with post-contrast acute kidney injury (AKI) according to CKD stages is displayed (red bars). With decreasing renal function, the percentage of patients with post-contrast AKI increases from 5.5% with CKD stage 3A up to 38.6% with CKD stage 5. Black diamonds display the odds ratio for post-contrast AKI at different CKD stages. **b** The percentage of patients with post-contrast acute kidney injury (AKI) according to iodinated contrast medium volumes is displayed (red bars). With increasing iodinated contrast medium volume, the percentage of patients with post-contrast AKI increases from 6.8% (iodinated contrast medium ≤ 50 ml) up to 18.2% (iodinated contrast medium 51–100 ml) and 16.7% (iodinated contrast medium > 100 ml). Black diamonds display the odds ratio for post-contrast AKI in different iodinated contrast medium groups. *AKI* acute kidney injury, *CKD* chronic kidney disease, *ICM* iodinated contrast medium

Table 3 CO_2-endovascular revascularization group: post-contrast AKI prevalence and iodinated contrast medium volume depending on lesion localization

	Iliac	Femoropopliteal	Crural	Combined
Patients, n	5	44	21	31
Post contast-AKI, n (%)	1 (20.0)	5 (11.6)	3 (14.3)	3 (9.7)
ICM, mean ± SD, ml	56.0 ± 27.9	30.8 ± 31.7	49.3 ± 24.6	48.9 ± 32.1
ICM < 10 ml, n (%)	0 (0.0)	15 (34.1)	1 (4.8)	5 (16.4)

AKI acute kidney injury, *CO_2* carbon dioxide, *ICM* iodinated contrast medium

CI 3.349–35.225; $p < 0.001$), however, had a significantly higher risk for developing a post-contrast AKI (Fig. 3a).

Besides the impact of pre-existing CKD, an analysis of all patients revealed that the incidence of post-contrast AKI was directly related to the amount of iodinated contrast medium used during the endovascular revascularization procedure. While patients receiving 50 ml or less iodinated contrast medium had the lowest risk, patients receiving 51–100 ml iodinated contrast medium (OR 3.037; 95% CI 1.163–7.933; $p = 0.023$) and more than 100 ml iodinated contrast medium (OR 2.733; 95% CI 1.042–7.169; $p = 0.041$) had a significantly higher risk for developing a post-contrast AKI (Fig. 3b).

The post-contrast AKI risk within combined groups of CKD stage and iodinated contrast medium volume is shown in Fig. 4. When combining the risk factors, i.e., baseline CKD stage and the amount of procedural iodinated contrast medium intake, it turns out that at CKD stages 3A and B the amount of iodinated contrast medium did not affect the risk of post-contrast AKI. However, at CKD stages 4 and 5 iodinated contrast medium increased the risk of post-contrast AKI incrementally in relation to the amount of iodinated contrast medium. The highest risk for post-contrast AKI was seen at CKD stage 4 with the highest iodinated contrast medium amount (OR 37.714; 95% CI 3.927–362.234; $p = 0.002$).

Chronic limb-threatening ischaemia (Fontaine stages 3 and 4) was significantly associated with post-interventional post-contrast AKI as illustrated in Fig. 5. Compared to claudicants, patients with chronic limb-threatening ischaemia had a significantly higher risk for developing a post-contrast AKI (OR 3.438; 95% CI 1.542–7.668; $p = 0.003$).

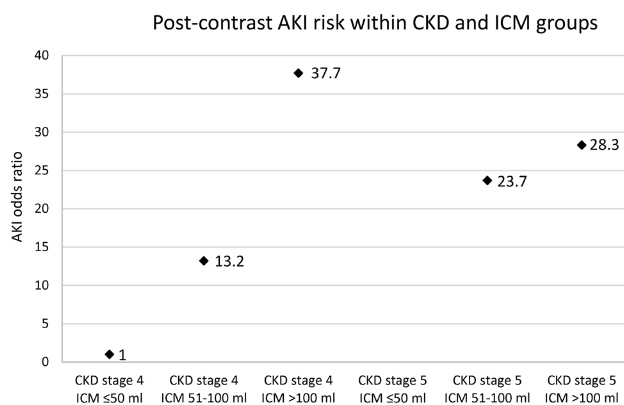


Fig. 4 Post-contrast AKI risk within CKD and iodinated contrast medium groups (CO_2 and iodinated contrast medium-endovascular revascularization groups combined). CKD stages and iodinated contrast medium groups are combined in nine groups. Black diamonds display the odds ratio for post-contrast AKI. Odds ratios are 1 for the three groups, i.e. CKD stage 3 and iodinated contrast medium volume ≤ 50 ml, CKD stage 3 and iodinated contrast medium volume 51–100 ml, CKD stage 3 and iodinated contrast medium volume > 100 ml (data not shown). At CKD stages 4 and 5, iodinated contrast medium increases the risk of post-contrast AKI in relation to the amount of iodinated contrast medium. At CKD stage 4 the odds ratio for post-contrast AKI is 13.2 (95% CI 1.489–117.004; $p = 0.02$) for iodinated contrast medium volume 51–100 ml and 37.7 (95% CI 3.927–362.234; $p = 0.002$) for iodinated contrast medium volume > 100 ml. The corresponding values at CKD stage 5 are 23.7 (95% CI 2.666–210.583; $p = 0.005$) and 28.3 (95% CI 3.289–243.252; $p = 0.002$). There was only one patient with CKD stage 5 and iodinated contrast medium volume ≤ 50 ml, hence there is no odds ratio value in this group. *AKI* acute kidney injury, *CKD* chronic kidney disease, *ICM* iodinated contrast medium

Discussion

CO_2-angiography is an effective and safe alternative to iodinated contrast medium to perform endovascular revascularization in peripheral artery disease patients with concomitant CKD. The diverse characteristics of the patients and of the lesions in the study cohort and the various endovascular revascularization procedures demonstrate that the technique is suitable not only for simple short-lesion balloon angioplasty but also for more sophisticated endovascular revascularizations such as atherectomy and rotational thrombectomy for the treatment of long, multilevel total occlusions. Stenting additional to angioplasty was performed more often in the iodinated contrast medium group. Image quality of CO_2-angiography was excellent in iliac and femoropopliteal segments. In 16 (15.7%) patients complete endovascular revascularization was performed without any iodinated contrast medium. Additional iodinated contrast medium was mostly needed in crural segments, particularly

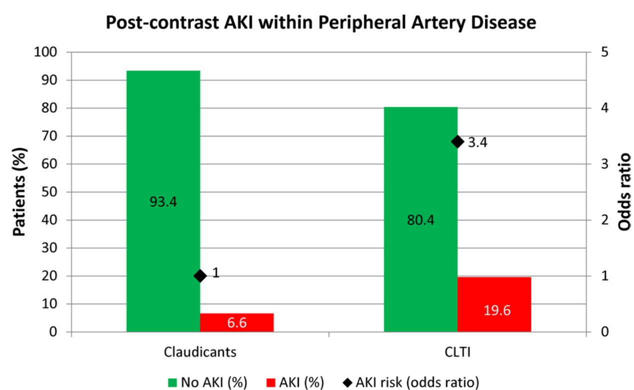


Fig. 5 Post-contrast AKI within peripheral artery disease stages (CO_2 and iodinated contrast medium-endovascular revascularization groups combined). The percentage of patients without (green bars) and with (red bars) post-contrast acute kidney injury (AKI) according to peripheral artery disease stages is displayed. The percentage of patients with post-contrast AKI increases from 6.6% (claudicants) to 19.6% (critical limb-threatening ischaemia). Black diamonds display the odds ratio for post-contrast AKI. *AKI* acute kidney injury, *CLTI* chronic limb-threatening ischaemia

with poor outflow, to provide faultless image quality and to amplify the decision making. Three operators performed all CO_2-angiographies (operator 1 = 64 sessions, operator 2 = 24 sessions, operator 3 = 14 sessions). In our study, the amount of iodinated contrast medium volume that was used additionally to CO_2 was inversely related to the volume of endovascular revascularization procedures and to the experience of the examiners: The more examinations we performed the less additional iodinated contrast medium was needed because of the better understanding of properties such as the ideal CO_2 injection volume and speed, position of the patient and moment of radioscopy. Hence, increasing experience with CO_2-angiography will lead to more CO_2-only-angiographies without additional use of iodinated contrast medium.

In some of the previous studies complications and side effects such as nausea, abdominal pain and even lethal nonobstructive mesenteric ischaemia have been reported [21]. A previous meta-analysis showed comparable incidence of adverse nonrenal events in patients receiving CO_2-angiography [22]. We did not observe any of these severe complications or side effects in our cohort. Only few patients complained about transient leg pain immediately after CO_2-injection which could be managed conservatively without the need for analgetics.

Pre-existing CKD (≥ CKD stage 3) and the total amount of iodinated contrast medium were found to be predictors of post-contrast AKI. Up to CKD stage 3 iodinated contrast medium use did not result in increased post-contrast AKI, irrespective of the iodinated contrast medium volume. However, at CKD stages 4 and 5 the amount of iodinated contrast medium was disproportionately related to the odds of post-contrast AKI (OR 13.2 for iodinated contrast medium 51–100 ml and 37.7 for iodinated contrast medium > 100 ml). These results match with current guidelines that outline post-contrast AKI occurring in patients with eGFR < 30 ml/min [10]. Consequently, CO_2-angiography should be used especially in patients with eGFR < 30 ml/min to reduce iodinated contrast medium volume and associated post-contrast AKI. Critical limb-threatening ischaemia was also found to be a significant predictor of post-contrast AKI. Therefore, these patients should also be primarily treated with CO_2-angiography-guided endovascular revascularization.

CO_2-angiography did not result in extended examination duration. However, the significantly higher radiation exposure to the patients and to the examiner is of concern and needs to be reduced, especially considering the fact that CKD patients are at higher risk for developing cancer when e.g. taking immunosuppression medication. Development and application of dedicated radiological software tools are underway and may help to reduce exposure to radiation in the future.

Another interesting observation in this study was the higher stenting rate in the iodinated contrast medium compared to the CO_2 group (65.9% vs. 46.1%; $p = 0.001$). Actually, one would expect higher rates of stenting in the CO_2 group considering the fact that—compared to patients with normal kidney function—patients with renal failure have more calcified and complex lesions therefore they more often require stenting for unsatisfactory results after only balloon dilatation. Limitations in imaging quality could not be a factor for the higher stent rate in one group since iodinated contrast medium was additionally used in all cases where CO_2 angiography did not show satisfactory image quality. As we do not have detailed information about lesion morphology and complexity we can only speculate about the underlying reasons for the higher stenting rate in the iodinated contrast medium group. The reasons for the higher stenting rate in the iodinated contrast medium group and its impact on long-term outcome has to be explored in specific, prospective studies.

The fact that even patients with exclusively CO_2-angiography without any, or with only a very low amount of iodinated contrast medium developed post-contrast AKI indicates that AKI is a multifactorial rather than a mono-causal process mainly determined by the application of iodinated contrast medium. It has been shown that restoration of blood flow to ischaemic tissue can result in adverse metabolic changes such as acidosis, hyperkalaemia and myoglobinaemia which can eventually lead to diverse organ damage including progressive kidney dysfunction (called as myonephropathic metabolic syndrome) [23]. However, our data clearly demonstrate that if patients with pre-existing CKD at stages 4 and 5 receive more than 50 ml of iodinated contrast medium their risk of developing AKI disproportionately increases (up to 37-fold). In these patients every effort should be made to avoid or at least minimize the amount of iodinated contrast medium so as to lower the risk of AKI. Our data demonstrate that CO_2-guided angiography and endovascular revascularization are eligible and appropriate measures to reduce or even replace iodinated contrast medium and the associated risk of developing AKI in patients with concomitant CKD and peripheral artery disease.

Limitations

Our study has some limitations that have to be addressed: firstly, the data presented in this study are derived from a single-centre, non-randomized trial including a cohort of consecutive patients over a 3-year period; therefore, confounding by selection bias is inherent to the study design. Furthermore, the iodinated contrast medium and CO_2-endovascular revascularization groups were matched regarding risk factors but differed in mean age and gender

which limits the direct comparison between both groups. The lack of detailed information about lesion morphology and complexity, both of which affect the short and long-term interventional outcome, is another limitation of the study. We did not assess the impact of iodinated contrast medium on renal function and its impact on overall outcome beyond 48 h after iodinated contrast medium application. Assessment of long-term follow-up in these patients is important since post-contrast AKI has been shown to be associated with progressive loss of kidney function and higher mortality rates [24, 25]. Therefore, prospective, randomized studies are necessary to evaluate the short- and long-term-impact of CO_2-angiography on renal function and the subsequent outcome in patients with concomitant CKD and peripheral artery disease.

Author contributions TJ, MM, NM designed the study; MM, HR, NM performed the revascularization procedures; TJ, NM, CE, EF performed the statistical analysis; TJ wrote the manuscript in consultation with NM; all authors contributed to the interpretation of the results, provided critical feedback and helped shape the research, analysis and manuscript.

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Compliance with ethical standards

Conflict of interest TJ and MM have no conflicts of interest; EF reports grants from Bayer and Pfizer outside the submitted work; KG reports travel support from Sanofi, personal fees from Bayer and Novo-Nordisk, and has been on the advisory board of Amgen, all outside the submitted work; JS reports travel support from Daiichi Sankyo outside the submitted work; CE reports travel support from Bayer Vital outside the submitted work; HR reports personal fees from Bristol Myers Squibb, Daiichii Sankyo, DiaPlan, MedUpdate, NeoVasc, and Pfizer, all outside the submitted work. He acted as a consultant for NovoNordisk, Pluristem, and Pfizer. He took part in the conduction of multicentre trials of Bard, Bayer, Biotronik, Novartis, and Pluristem; NM reports personal fees from Bayer Vital, Bard, Cordis and Medtronic, all outside the frame of the submitted work.

Ethics approval The study protocol was approved by the ethical committee of the Westfälische-Wilhelms-University of Muenster.

Consent to participate Informed consent was obtained from all patients before inclusion in the study.

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