Original Article

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The use of CO_2 angiography in the treatment of peripheral arterial disease: Our initial experience

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ABSTRACT

Objectives: In this study, we present our initial experience in the use of carbon dioxide (CO_2) digital subtraction angiography (DSA) for the treatment of peripheral arterial disease.

Patients and methods: This retrospective study included a total of six male patients (mean age 63.5±6.9 years; range, 56 to 72 years) with Rutherford Stage 3-4 who were high-risk for chronic renal failure and underwent percutaneous transluminal angioplasty (PTA) due to iliac or femoropopliteal lesions using CO_2-DSA between October 2018 and January 2020. Demographic and clinical characteristics of the patients, ankle-brachial index (ABI) values, and technical success rate were evaluated.

Results: No contrast medium was used in any of the procedure. Technical success rate was 100% and no intraoperative complication was observed. All patients had a non-significant increase in the creatinine levels during follow-up (p=0.076). There was a significant difference between the pre- and postoperative ABI values (p=0.028). All patients were followed in the wards after the procedure and were discharged on postoperative Day 1 with symptomatic recovery.

Conclusion: Our study results show that CO_2-DSA can be used as an affordable and effective alternative in the diagnosis and treatment of peripheral arterial disease with contraindications for iodinated contrast material.

Keywords: Angiography, carbon dioxide, contrast-induced nephropathy endovascular procedure, peripheral arterial disease.

The use of endovascular methods in the treatment of peripheral arterial disease (PAD) has been increasing rapidly with favorable long-term results.[1] These methods are less invasive and can be performed with local anesthesia with early recovery and a shorter length of in-hospital stay.[1]

The use of digital subtraction angiography (DSA) with iodinated contrast material (ICM) is still the gold standard for both diagnosis and treatment of PAD.[2] However, ICM carries the risks of causing severe hypersensitivity reaction and contrast-related nephropathy (CRN).[2,3] The latter typically occurs in patients with prior chronic renal failure (CRF), 24 to 72 h after the injection of the contrast medium.[4] A recent study has shown that the presence of concomitant PAD and CRF may increase the morbidity of interventional vascular procedures.[5]

Alternative methods to ICM such as gadolinium, diluted ICM, and combined hybrid methods can be used to avoid contrast nephropathy.[6] Recently, carbon dioxide (CO_2) DSA (CO_2-DSA) has been used as an alternative to ICM, particularly in patients with renal dysfunction.[7] However, all possess certain limitations. The CO_2 is a non-allergic and non-nephrotoxic gas with high solubility. It is eliminated through the lungs following its rapid solubility, when administered into the vessel.[8] Furthermore, it is cheaper and easier to provide compared to ICM.[9]

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In this study, we present our initial experience in the use of CO_2-DSA for the treatment of PAD in light of the current literature.

PATIENTS AND METHODS

This retrospective study was conducted at Republic of Turkey, Ministry of Health, Ankara City Hospital between October 2018 and January 2020. Of a total of 50 patients, six male patients (mean age: 63.5±6.9 years; range, 56 to 72 years) with Rutherford[10] Stage 3-4 who were high-risk for chronic renal failure and underwent percutaneous transluminal angioplasty (PTA) due to iliac or femoropopliteal lesions using CO_2-DSA were included. Eligible patients were those having atherosclerotic disease of iliac or femoral arteries with symptoms of rest pain to ischemic ulceration of the foot according to the Rutherford classification and those who were either not eligible for surgery due to comorbidities or as they refused open surgery. We only included patients who had risks for CRN with borderline renal functions with a serum creatinine level of 1.4 to 3 mg/dL. A written informed consent was obtained from each patient. The study protocol was approved by the Türkiye Yüksek İhtisas Training and Research Hospital, Ethics Committee (Date: 31.01.2017, No: 29620911-929). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All interventions were performed via PTA through the Luminor® (iVascular, S.L.U., Barcelona, Spain) paclitaxel-coated drug-eluting balloon (DEB) catheter and stenting with the iVolution® (iVascular, S.L.U., Barcelona, Spain) self-expanding nitinol stent (SENS). Serum creatinine levels prior to the procedure and at one day, five days, one month, and three months following the procedure were assessed. All clinical, perioperative, and demographic data including the ankle-brachial index (ABI) values and technical success rate were obtained from the hospital and physician records, including data collected prospectively in the departmental registry.

Procedural technique

Prior to PTA, all patients were evaluated using the Duplex ultrasound. In the routine clinical practice of our department, PTAs are performed under local anesthesia with monitorization by cardiovascular surgeons in the hybrid operating theater. We usually prefer antegrade femoral or contralateral retrograde femoral access. Carbon dioxide was administered using a dedicated injection system (Angiodroid®; Angiodroid Srl, Bologna, Italy) (Figure 1). This system is a digital automatic injector, which ensures stable CO_2 pressure and high accuracy of volumes, as well as a built-in control system to avoid air contamination. The Angiodroid® workstation is movable on steerable wheels and it is similar in size to an iodinated contrast media injector. The Angiodroid® is, to date, the first totally computed CO_2 injection system. Injections can vary between 1 and 100 mL in volume and between 45 and 700 mmHg in pressure (6 and 93 KPa, respectively), with an accuracy for volume delivery of ±1 mL and for pressure delivery of ±1.5%.[11] Notably, no specific injection parameters are recommended, as physicians choose the most optimal dose; however, they must remain within the above safety limits. Once the injector has been prepared for use and activated, it automatically charges the required amount of CO_2 from a 2-L CO_2 cylinder. Afterwards, the injector must be simply connected through a disposable connecting tube to the diagnostic or guiding catheter or sheath of choice and injection is already possible without further delay. Due to the low viscosity of CO_2, even 3-French (Fr) catheters and 22-Gauge tubings or syringes can be used to obtain satisfactory angiographic images with DSA. However, 6-Fr sheaths were used for all patients in the present study and CO_2 was applied at a pressure of 250 mmHg and a volume of approximately 40 mL.

Figure 1. The automatic CO_2 injector (Angiodroid®, Italy).
CO_2: Carbon dioxide.

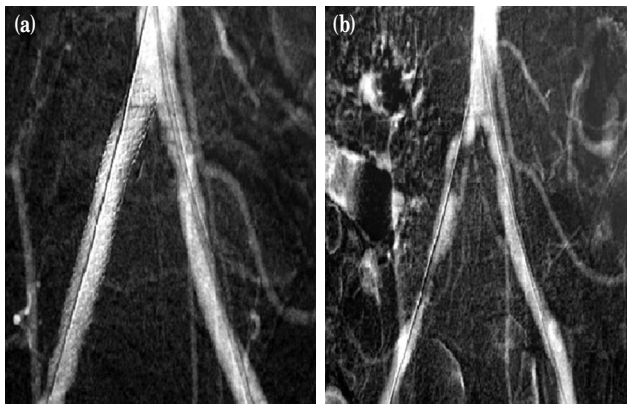

Figure 2. CO_2-DSA of the iliac arteries following stent implantation.
CO2: Carbon dioxide; DSA: Digital subtraction angiography.

All lesions were dilated with paclitaxel-coated balloon (at a vessel/balloon ratio of 1:1 on the basis of visual estimate) for a total inflation time of 3 min at 6 to 12 atm. The balloons were inflated only once. In cases in whom residual stenosis persisted after the repeated dilatation, SENS were implanted (Figures 2 and 3).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max) for continuous variables and in number and percentage for categorical variables. Since the study population was very small sized, no normality test was performed. The Wilcoxon signed-rank test was performed to assess the difference between pre-ABI and post-ABI values. The Friedman test was used to analyze the difference between the pre- and postoperative creatinine values. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline patient demographics and clinical data are shown in Table 1 and Table 2, respectively. Coronary artery disease was present in three patients, five patients were hypertensive, two patients were diabetic, and four patients were current smokers. Hyperlipidemia was present in all patients and chronic obstructive pulmonary disease (COPD) was present in only one patient.

The mean ejection fraction was 52.0±6.1%. The mean preoperative ABI value was 0.5±0.1 and the mean postoperative ABI value was 0.8±0.2. There was a significant difference between the pre- and the postoperative ABI values (p=0.028). The mean preoperative creatinine value was 1.8±0.6 mg/dL. The mean postoperative creatinine value at one and five days were 1.7±0.6 mg/dL and 1.7±0.6 mg/dL days, respectively, while the mean postoperative creatinine value at one and three months were 1.7±0.6 mg/dL and 1.7±0.6 mg/dL, respectively (Table 3). All patients had a non-significant increase in creatinine levels during the follow-up period (p=0.076).

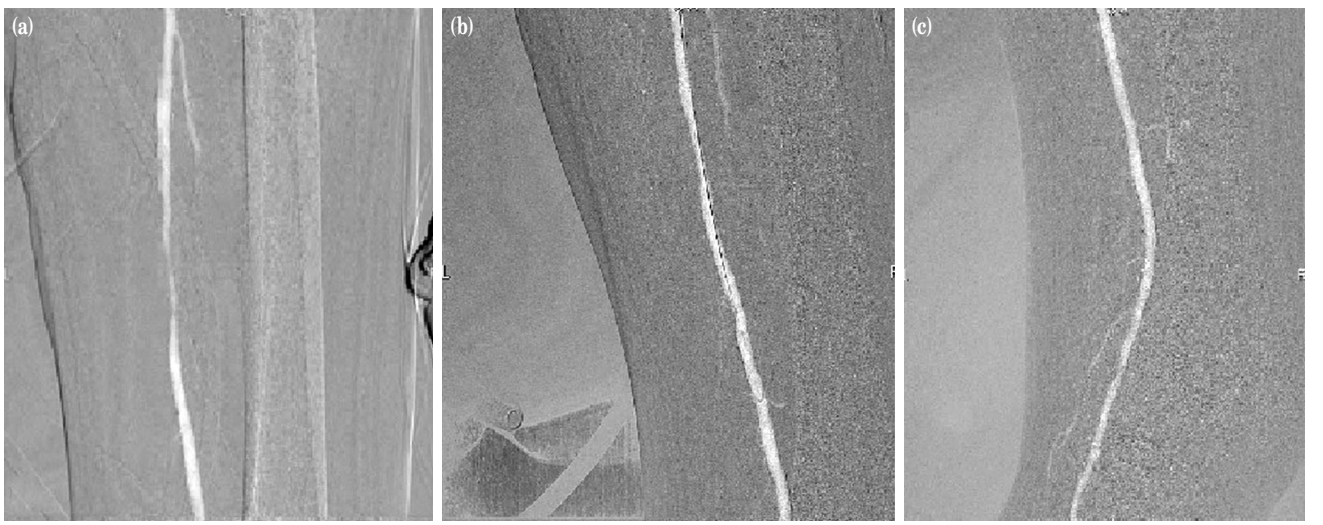

Figure 3. (a) CO_2-DSA showing mid-SFA occlusion. **(b)** CO_2-DSA after surpassing the proximal and mid-SFA. **(c)** Final image following balloon angioplasty of the mid-SFA.
CO_2: Carbon dioxide; DSA: Digital subtraction angiography; SFA: Superficial femoral artery.

Table 1. Demographic data of patients

Patient ID	Age	Hypertension	DM	CAD	Hyperlipidemia	Current smoker	COPD
#1	56	-	+	+	+	+	-
#2	70	+	+	+	+	-	-
#3	61	+	-	+	+	+	-
#4	56	+	-	-	+	-	-
#5	66	+	-	-	+	+	+
#6	72	+	-	-	+	+	-

DM: Diabetes mellitus; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; + Presence; - Absence.

Operative findings are summarized in Table 4. The mean operation time was 60.8±20.1 min and the mean fluoroscopy time was 54.7±19.2 min. Since these procedures were performed using CO_2, no contrast medium was used. The technical success rate was 100% and no intraoperative complication was observed. Two patients were treated using paclitaxel-coated balloon, followed by stent application due to stenosis of the external iliac arteries, whereas the others underwent only paclitaxel-coated balloon application of the superficial femoral artery stenoses.

Table 2. Clinical data of patients

Patient ID	EF (%)	Pre-ABI	Post-ABI	Rutherford stage
#1	55	0.35	0.75	4
#2	50	0.54	0.87	3
#3	42	0.55	1.02	3
#4	60	0.35	0.6	3
#5	50	0.45	0.96	4
#6	55	0.52	0.75	3
P value*		P¹=0.028		

EF: Ejection fraction; Pre-ABI: Pre-interventional ankle brachial index; Post-ABI: Post-interventional ankle-brachial index; + Presence; - Absence; * P value: based on Wilcoxon signed-rank test between pre-ABI and post-ABI values.

Postoperative and follow-up data are summarized in Table 5. All patients were followed in the wards after the procedure and were discharged on postoperative Day 1. All patients had symptomatic recovery. Postoperative acetylsalicylic acid, clopidogrel, and statin were prescribed to all patients.

DISCUSSION

In parallel with the recent technical advancements, endovascular strategies have become well-recognized therapeutic alternatives to bypass surgery, including the patients with chronic total occlusion.[12]

Renal failure following endovascular procedures is a significant cause of mortality and morbidity.[13] Progressive renal dysfunction may be related to various reasons. However, one of the most important reasons is the periprocedural use of ICM. The CO_2-DSA is an alternative method which prevents the use of ICM and renal dysfunction. It is eliminated through the lungs following its rapid solubility, when administered into the vessel.[8] Another advantage of CO_2 is that it can be used in high volumes, even in patients with COPD by leaving intervals between the injections. Carbon dioxide facilitates detection of minor bleeds and small

Table 3. Pre- and postoperative creatinine values

Patient ID	Preoperative creatinine	1st day postoperative	5th day postoperative	1st month postoperative	3rd months postoperative
#1	2.95	2.84	2.88	2.9	2.82
#2	1.75	1.44	1.56	1.54	1.58
#3	1.68	1.4	1.3	1.25	1.3
#4	1.4	1.2	1.2	1.2	1.24
#5	1.71	1.7	1.6	1.65	1.7
#6	1.5	1.58	1.4	1.56	1.54
Mean±SD	1.8±0.6	1.7±0.6	1.7±0.6	1.7±0.6	1.7±0.6
P*=0.076					

ID: Patients series number; SD: Standard deviation; * P value based on Friedman's test between preoperative, postoperative 1st day, postoperative 5th day, postoperative 1st month, and postoperative 5th month creatinine values.

Table 4. Operative data of patients

Variables	n	%	Mean±SD
Operation time			60.8±20.1
Fluoroscopy time			54.7±19.2
Contrast amount (mL)			0±0
Intraoperative complications		0	
Operative success		100	
Balloon dilatation		100	
Stent implantation		33.3	
Intervention site			
Iliac artery	2	33.3	
Superficial femoral artery	4	66.6	

SD: Standard deviation.

Table 5. Postoperative and follow-up data of patients

Variables	n	%	Mean±SD
Duration of hospital stay (days)			1±0
In hospital mortality		0	
Overall mortality		0	
Postoperative complication		0	
Procedure related mortality		0	
Postoperative claudicatio		0	
Symptomatic recovery		6	
Postoperative medication			
Acetylsalicylic acid	6	100	
Klopidogrel	6	100	
Statin	6	100	
Silostazol	0	100	

SD: Standard deviation.

collateral vascular networks. It provides a characteristic parabolic flow pattern at the anterior part of the vessel by staying in an isolated bubble form. It also provides images with a higher quality at the posterior part of the vessel, since the vessel is completely full of blood.[8]

The use of CO_2-DSA was first reported by Hawkins in 1982.[14] Later on, there were few more reports suggesting the use of CO_2-DSA as an alternative method.[14,15] Carbon dioxide gas, as a contrast agent, is not allergenic or nephrotoxic and can be used as a diagnostic and treatment modality in patients allergenic to ICM and those with impaired renal function. Moreover, it is cost-effective and reliable.[16,17] Neither any nephrotoxicity nor allergic reactions were reported in the literature previously.[18]

Diamantopoulos et al.[19] revealed that the use of CO_2 resulted in a 90% of decrease in iodine contrast medium and more than 50% of consequent decrease in the risk of CRN. Fujihara et al.[20] found the risk of CRN following CO_2-DSA to be 5% in their study including 98 patients. Similarly, Stegemann et al.[21] documented the risk of developing CRN as 5% in the CO_2 group and 29% in the ICM group. In our study, the comparison of the preoperative creatinine levels and the postoperative first- and fifth-day creatinine levels revealed a remarkable decrease in favor of the postoperative values. This was probably due to effective hydration of the patients.

Patients with the risk of CRN possess longer hospitalization times and higher hospital costs.[4] The use of CO_2-DSA is essential for such patients, since they may require hemodialysis. None of the patients in our study required hemodialysis and all were discharged at the first post-procedural day, offering a cost-effective therapy.

An important issue is the reliability of CO_2-DSA. Seizures, loss of consciousness, and respiratory arrest due to leakage of CO_2 gas into the cerebral arteries were reported in the literature. Therefore, a recommendation for not using CO_2 injections during the procedures above the diaphragm was made.[22] The CO_2 should not be administered into the cerebral circulation directly due to the possible neurotoxic effects. The CO_2 should be only used during infra-diaphragmatic screening. The use of CO_2 during thoracic aortography, coronary angiography and cerebral arteriography should be avoided.[23] Chao et al.[16] found the incidence of adverse events to be 5.1% in their study involving 605 patients. Eight patients developed abdominal pain, 11 had hematoma of the intervention site, four had transient hypertension, three had vomiting, and one had chest pain and concomitant localized aortic dissection and paresthesia. Mesenteric ischemia due to trapping of CO_2 within the mesenteric arteries is another important complication of CO_2-DSA.[7] Furthermore, CO_2 may cause vapor lock of the pulmonary artery, resulting in hypotension and cardiac arrest.[7]

Although previous studies support the reliability and advantages of CO_2, it is still not widely used during daily practice.[16,18,24] There are minor complications associated with CO_2 angiography which are outweighed by the benefits. In a multi-center, prospective study, Fujihara et al.[20] showed that the complications were mainly minor such as diarrhea, leg, and abdominal pain and non-occlusive mesenteric ischemia was a rare, but major complication. On the contrary, none of the patients in our study had any kind of side effects. Since these interventions are performed using CO_2, no contrast medium is used.

In our study, the technical success rate was 100% and no intraoperative complication was observed. However, low number of patients may have caused study bias. Of note, all patients had symptomatic recovery as evidenced by the improvement of the post-procedural ABI values.

Our study has certain limitations. The main limitations are the small sample size, retrospective design, short follow-up, and the lack of a comparative control group. This study is an initial step for our future studies in which we plan to compare CO_2 angiography and ICM, as it is important for patient health and hospital.

In conclusion, CO_2-DSA can be used as an affordable and effective alternative in the diagnosis and treatment of PAD patients with contraindications for iodinated contrast material. The CO_2-DSA provides a decrease in the contrast volume and renal injury, resulting in shorter hospital stay and reduced hospital cost.

Declaration of conflicting interests

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