Cohort Study

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Comparing the accuracy and safety of automated CO_2 angiography to iodine angiography in peripheral arterial disease with chronic limb ischemia: a prospective cohort study

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Introduction: Diagnostic angiography of peripheral arteries using carbon dioxide (CO_2) is feasible in nearly all areas below the diaphragm. Using carbon dioxide as a contrast material in angiography provides the highest quality diagnostic results in the vascular segments above the knee. However, its diagnostic reliability decreases as it moves toward the distal side of the vessels below the knee. This study investigated the diagnostic accuracy and consistency between CO_2 and iodine contrast angiography in patients with peripheral vascular disease (PVD) with chronic limb ischemia (CLI).

Methods: The study prospectively enrolled 35 patients with PVD and CLI and performed both CO_2 and iodine contrast angiography, comparing the results for each patient. Image quality, stenosis severity, and anatomical location were analyzed.

Results: In this study, a total of 35 patients (19 male) with an average age of 56.91 ± 10.73 were examined. Among them, 13 patients (37.1%) had involvement in the femoral region, 8 patients (22.9%) in the popliteal region, 8 patients (22.9%) in the tibial region, and 6 patients (17.1%) in the foot region. CO_2 angiography produced excellent image quality in 40% of cases, with good quality in another 25.7%. The quality decreased in the popliteal and foot regions. While stenosis assessment was comparable between the two methods in the femoral, popliteal, and tibial regions, there was a significant difference in the foot region. The sensitivity, specificity, positive predictive value, and negative predictive value of CO_2 angiography were all 100% in the femoral and popliteal areas. However, these values were lower in the tibial and foot areas.

Discussion: The study concluded that the use of CO_2 angiography, particularly for vascular lesions above the popliteal cavity, is a valuable and safe method for peripheral vascular examination of the lower limbs. It can serve as an alternative to iodine contrast angiography, especially in patients with kidney failure.

Keywords: angioplasty, automated CO_2 angiography, iodine angiography, peripheral arterial disease

Introduction

Peripheral vascular disease (PVD) is a leading cause of disability and death globally, placing a significant financial strain on healthcare resources[1,2]. Peripheral arterial disease (PAD), a prevalent form of vascular disease, is characterized by the narrowing or blockage of arteries due to fatty deposits or plaques known as atheroma[2–4]. This results in reduced oxygen and nutrient supply to the body part served by the affected artery, leading to pain and numbness. PAD heightens the risk of limb infection, potentially leading to gangrene and limb amputation[5,6]. Furthermore, it escalates the risk of cardiovascular and cerebrovascular diseases[2,4]. Approximately 12% of adults and 20% of individuals over 70 years old are affected by PAD. The prevalence of this disease, along with its complications such as limb ischemia, is

HIGHLIGHTS

- Feasibility and Safety of CO_2 Angiography: Our study demonstrates that CO_2 angiography is a feasible and safe alternative to iodine contrast angiography for peripheral vascular disease (PVD), particularly in the femoral and popliteal regions.
- Comparable Diagnostic Accuracy: In the femoral, popliteal, and tibial regions, CO_2 angiography showed comparable diagnostic accuracy to iodine contrast angiography in terms of stenosis severity assessment.
- Anatomical Location Matters: Image quality was significantly affected by anatomical location, with lower quality observed in the popliteal and foot regions. This underscores the importance of considering anatomical location when selecting CO_2 angiography as a diagnostic tool.
- Potential for Patients With Kidney Failure: The safety and efficacy of CO_2 angiography offer a promising alternative for patients with kidney failure, where iodine contrast angiography is contraindicated.

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increasing due to factors such as obesity, diabetes, high-calorie diets, sedentary lifestyles, hypertension, and smoking[7–10]. Diabetic patients are at a higher risk for PVD, with a 3 to 4 times increased risk compared to nondiabetic patients. They also have a higher risk of complications, including 5–10 times higher risk of limb amputation. In diabetic patients, vascular diseases distal to the popliteal typically involve multiple levels and all three vessels distal to the popliteal[11,12]. These patients often have concurrent coronary artery disease and advanced kidney disease, which further increases their susceptibility to adverse events[13,14]. Additionally, diabetic patients are at a heightened risk for contrast-induced nephropathy following fluoroscopic procedures and endovascular interventions[14].

The treatment of vascular diseases depends on the type and location of the lesion, with open surgery and endovascular procedures being the primary options. The evolution of endovascular procedures for vascular occlusive diseases in the lower limbs is ongoing. These procedures' success and the lesion path's opening are tied to the anatomical and morphological characteristics of the lesion being treated. The TASC guidelines suggest endovascular procedures for group A lesions, while open surgery is advised for type D lesions. However, due to advancements in endovascular techniques, these methods are also being used for type B and C lesions[15].

Revascularization is considered the primary treatment for individuals with severe limb ischemia. Endovascular techniques, which are less invasive and suitable for patients with shorter life expectancies or higher surgical risks, have become widely accepted for treating PVD due to their good and satisfactory clinical outcomes[16,17].

Treatment aims to manage pain, preserve limb function, heal wounds, prevent mobility limitations, improve quality of life, and decrease cardiovascular events, including major amputations[13,14].

Digital subtraction angiography (DSA) using iodine contrast remains the most common invasive method for diagnosis and therapeutic imaging. However, this approach carries a significant risk of contrast-induced nephropathy, particularly in diabetic patients with pre-existing kidney disease[18,19].

Studies have reported an incidence of about 5.1% for contrast-induced nephropathy in patients with chronic kidney disease who undergo peripheral vascular interventional procedures[20].

Diagnostic angiography of peripheral arteries using carbon dioxide is feasible in nearly all areas below the diaphragm. Moreover, all intravascular interventions, including stenting and balloon angioplasty, can be conducted via carbon dioxide angiography[20,21].

Numerous studies have been carried out to explore the advantages of using carbon dioxide as a contrast agent in lower extremity interventional procedures, to minimize complications such as contrast-induced nephropathy and allergic reactions[20,22–25]. The reliability of angiography with carbon dioxide in assessing the severity of stenosis in vessels less than 8 mm in diameter is on par with iodine contrast angiography. This type of angiography also provides a comparable densitometric analysis of stenotic lesions[26–28].

Mild side effects of carbon dioxide angiography can include lower limb and abdominal pain and diarrhea, with death being a rare but possible side effect, for instance, due to mesenteric ischemia. Nevertheless, many studies have identified this technique as a dependable method for diagnostic purposes[29].

This study evaluates the diagnostic efficacy of carbon dioxide angiography compared to conventional iodine angiography in patients with chronic limb ischemia. The analysis focuses on factors including the location of the vessels, the severity of the stenosis, and calcification.

Methods

In this prospective study, we investigated patients with CLI caused by PVD who were admitted to a tertiary center, between 2021 and 2022. We included patients who needed diagnostic or therapeutic angiography for PVD below the diaphragm. Patients who had allergies to iodinated or carbon dioxide contrasts, chronic obstructive pulmonary disease (COPD), previous angiography or angioplasty, heart or vascular wall defects, or a glomerular filtration rate (GFR) less than 60 were excluded from the study

This study was approved by the Institutional Review Board (IRB) of the Tehran University of Medical Sciences, Tehran (Ethical code: IR.TUMS.IKHC.REC.1400.498), and conducted by the Declaration of Helsinki. Furthermore, the work has been reported in line with the STROCSS criteria[30]. All patients provided informed consent before the procedure.

The study by Palena *et al.* in 2015 was used as a reference[31], and with β set at 80% and α at 5%, and the sample size was determined to be 35.

We collected demographic information, such as age and sex, using a prepared form. All 35 included patients underwent iodine diagnostic angiography and the images were saved. Then, all patients underwent CO_2 contrast angiography and its images were also saved. CO_2 was injected into the examined area using an automatic device, with a volume of 20 cc and a pressure of 250 mmHg, through the femoral artery on the opposite side. If angioplasty was required, it was performed accordingly based on iodine angiography. To reduce biases, all CO_2 angiographic images were securely stored and coded, and one month later, the saved images were evaluated by the vascular surgeon without knowing the patient's information (Figure 1). Patients then completed the evaluation forms, ensuring unbiased assessment. All patients received aspirin and ticlopidine or clopidogrel before the procedure. They were also given a saline solution infusion before and after the procedure. Sedatives or analgesics were not given to avoid masking any reactions to the CO_2 injection.

The vascular surgeon blindly evaluated each image (CO_2 and iodine) to determine the need for subsequent angioplasty, giving a yes or no response. For the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) calculations, we used the following definitions based on the paired comparisons of CO_2 and iodine angiography:

- True positive (TP): CO_2 angiography correctly identified a need for intervention that was agreed upon by iodine angiography.
- True negative (TN): CO_2 angiography correctly indicated no need for intervention, and iodine angiography agreed.
- False positive (FP): CO_2 angiography indicated the need for intervention, but iodine angiography did not.
- False negative (FN): CO_2 angiography failed to identify a need for intervention, while iodine angiography necessitated the angioplasty.

The records were based on the qualitative criteria. The images were divided into four groups for quality assessment: excellent

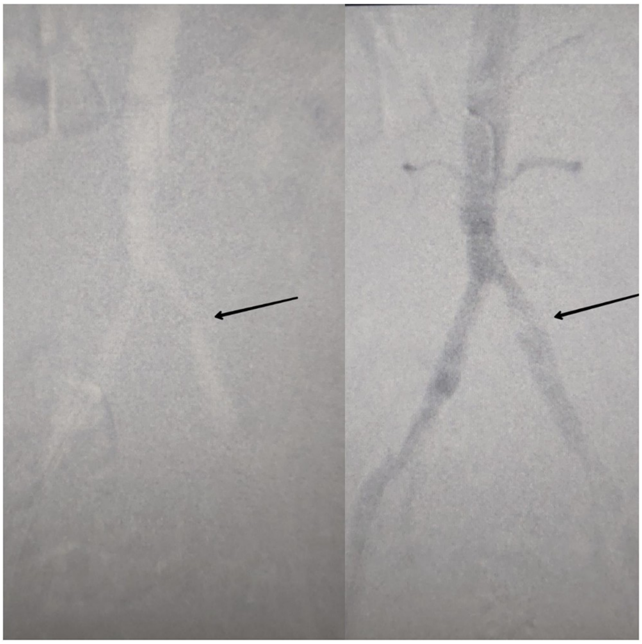

Figure 1. Representative diagnostic angiography with CO_2 (left) and iodine (right) contrast in a 40-year-old man with a lesion in the left iliac artery (arrows) with approximately 50% stenosis.

quality, good quality, low quality, and unacceptable quality. Excellent quality means that all images had sufficient quality for diagnosis and treatment determination without the need for re-imaging. Good quality means that all images were sufficient for diagnosis and treatment determination, but more images were needed before treatment. Low quality means that some or all of the images were insufficient and needed to be re-imaged. Unacceptable quality means that the images were generally not acceptable and needed to be re-imaged.

The diagnostic accuracy of carbon dioxide angiography was assessed by comparing it to angiography with iodine contrast in the recorded cases.

The lower limb arteries are divided into four regions: femoral region, popliteal region, tibial region, and foot region. We determine and record the location of the lesion in one of these areas.

The severity of stenosis in the lesion was assessed by the vascular surgeon. If less than one-third of the contrast could flow through the lesion, it was considered a severe stenosis. Otherwise, the stenosis was labeled non-severe.

The vascular surgeon also checked the severity of calcification in the lesion qualitatively (high/medium/low). If less than one-third of the vessel area was calcified, it was considered low; if between one-third and two-thirds of the vessel area was affected, it was classified as moderate; and if more than two-thirds of the vessel area was involved, it was categorized as severe.

All data were analyzed by SPSS version 26. Descriptive and frequency statistical tests were used to determine the prevalence of variables. The normality of the distribution of continuous variables was assessed via the Kolmogorov–Smirnov test. The paired T-test and the Wilcoxon test were used subsequently to compare the result of normally and non-normally distributed variables. Statistical significance was set at P-value < 0.05.

Table 1

Iodine contrast angiography findings

	Location				
	Femoral	Foot	Popliteal	Tibial	Total
Stenosis grading					
Non-severe	5	0	2	1	8
Severe	8	6	6	7	27
Total	13	6	8	8	35
Calcification grading					
Low	2	2	2	4	10
Moderate	5	1	2	1	9
Severe	6	3	4	3	16
Total	13	6	8	8	35

Results

Demographic findings

The study involved examining 35 patients with an average age of 56.91 ± 10.73 (range: 35 to 76 years). The gender distribution was 16 female patients (45.7%) and 19 male patients (54.3%). All patients had diabetes, and 14 patients (40%) were taking antihypertensive drugs. The study included 13 patients (37.1%) with vascular stenosis in the femoral region, eight patients (22.9%) in the popliteal region, eight patients (22.9%) in the tibial region, and six patients (17.1%) in the foot region.

Iodine contrast angiography findings

The average percentage of stenosis based on iodine angiography was calculated as 59.43 ± 31.64%, the lowest degree of stenosis was 10% and the highest degree of stenosis was reported as 95%.

The severity of vascular stenosis reported using iodine contrast angiography was qualitatively reported as severe in 77.1% of patients and non-severe in the remaining 22.9%. Also, vascular calcification was found to be severe in 45.7% of patients, moderate in 25.7%, and mild in 28.6% of patients (Table 1).

The quality of angiography images with Iodine contrast was excellent in all patients except one case. Only one patient, a 58-year-old woman with 70% stenosis in the foot area, was assessed as having good image quality.

Finally, by using angiography with iodine contrast, it was found necessary to perform angioplasty in 23 patients (65.7%), and 12 patients (34.3%) did not have an indication for angioplasty by performing this diagnostic method.

Table 2

CO_2 contrast angiography findings.

	Location				
	Femoral	Foot	Popliteal	Tibial	Total
Stenosis grading					
Non-severe	5	3	2	2	12
Severe	8	3	6	6	23
Total	13	6	8	8	35
Calcificationgrading					
Low	2	2	3	5	12
Moderate	5	2	1	0	8
Severe	6	2	4	3	15
Total	13	6	8	8	35

Table 3

Quality of CO_2 angiography images in different anatomical regions.

	Location				
	Femoral	Popliteal	Tibial	Foot	Total
Quality of CO_2 angiography images					
Excellent	9	4	1	0	14
Good	3	4	2	0	9
Low	1	0	5	6	12
Total	13	8	8	6	35

CO_2 contrast angiography findings

The average percentage of stenosis determined through automatic CO_2 angiography was found to be 49.71 ± 33.38%, with the least severe stenosis being 5% and the most severe being 95%. Using CO_2 contrast angiography, 65.7% of patients were found to have severe vascular stenosis, while the remaining 34.3% had non-severe stenosis. Vascular calcification was observed in 42.9% of severe cases, 22.9% of moderate cases, and 34.3% of mild cases (Table 2).

The quality of images obtained from CO_2 contrast angiography was rated as excellent in 14 patients (40.0%), good in nine patients (25.7%), and low in 12 patients (34.3%). Table 3 examines the frequency of CO_2 angiography image quality in various anatomical areas. As observed, only one instance of low-quality images was reported in the femoral region and none in the popliteal region. However, all patients with foot region involvement had low-quality CO_2 angiography images, and 62.5% of patients with tibial region involvement had low-quality images. The chi-square statistical test indicated a significant relation between the anatomical location of the vascular examination and the quality of the images obtained from CO_2 contrast angiography (P-value 0.001).

In conclusion, automatic CO_2 angiography reports deemed angioplasty necessary in 19 patients (54.3%), while 16 patients (45.7%) did not require angioplasty based on this diagnostic approach.

Additionally, there were no instances of CO_2 allergy, limb pain, abdominal pain, diarrhea, or any other complications related to CO_2 observed.

Comparison of findings from angiography with iodine contrast and angiography with carbon dioxide contrast

Generally, iodine contrast angiography reported a stenosis level of 59.43 ± 31.64%, while carbon dioxide contrast angiography reported a level of 49.71 ± 33.38%. The Wilcoxon test showed a significant difference between these results (P = 0.012).

Table 4 shows the stenosis levels reported by both methods in different anatomical regions. The smallest difference between the two methods was found in the vascular stenosis of the popliteal area, followed by a minor difference in the femoral area.

The Wilcoxon test was performed to compare the differences between the two methods across four anatomical regions. The pooled analysis revealed a significant difference between the two methods (P-value = 0.012). However, regarding region-by-region analysis, no significant difference in the femoral, popliteal, tibial, and foot regions was found.

The comparison of the stenosis levels reported by the two methods concerning the quality of images obtained from carbon dioxide angiography showed a significant correlation. The Kruskal–Wallis test indicated that the lower the image quality, the greater the difference in stenosis levels reported by the two methods (P-value = 0.001) (Table 5).

Table 4

Stenosis percentage by both methods in different anatomical regions.

	Iodine contrast	CO_2 contrast	P-value
Stenosis percentage			
Femoral	48.46 ± 31.78	47.69 ± 32.64	0.317
Popliteal	56.88 ± 33.37	56.88 ± 33.37	1.000
Tibial	73.13 ± 29.99	52.50 ± 35.25	0.068
Foot	68.33 ± 29.10	40.83 ± 39.04	0.109
Total	59.43 ± 31.64	49.71 ± 33.38	0.012

Table 5

Stenosis percentage by both methods in different anatomical regions.

	Quality of CO_2 angiography images	Iodine contrast	CO_2 contrast
Stenosis percentage	Excellent	64.46 ± 28.04	64.46 ± 28.04
	Good	34.44 ± 30.36	33.89 ± 30.80
	Low	72.08 ± 27.84	44.17 ± 36.11

Sensitivity, specificity, PPV, and NPV of carbon dioxide contrast angiography compared to iodine contrast angiography in determining the need for intervention and calcification severity

Table 6 presents the sensitivity, specificity, PPV, and NPV of carbon dioxide angiography to assess the need for angioplasty in different anatomical regions. The femoral and popliteal regions show the highest levels of sensitivity, specificity, PPV, and NPV. The tibial region is more sensitive in detecting the need for angioplasty compared to the foot region.

Table 7 summarizes the sensitivity, specificity, PPV, and NPV of carbon dioxide angiography in determining the severity of calcification in different anatomical regions. The femoral and popliteal and tibial regions show 100% sensitivity, specificity,

Table 6

Test characteristics of CO_2 contrast angiography compared to iodine contrast angiography in determining the need for intervention.

	Location				
	Femoral	Popliteal	Tibial	Foot	Total
Test characteristics					
Sensitivity	100%	100%	66.7%	50%	82.6%
Specificity	100%	100%	100%	100%	100%
Positive predictive value	100%	100%	100%	100%	100%
Negative predictive value	100%	100%	50%	50%	75%

Table 7

Test characteristics of CO_2 contrast angiography compared to iodine contrast angiography in determining the severity of calcification.

	Location				
	Femoral	Popliteal	Tibial	Foot	Total
Test characteristics					
Sensitivity	100%	100%	100%	66.7%	93.7%
Specificity	100%	100%	100%	100%	100%
Positive predictive value	100%	100%	100%	100%	100%
Negative predictive value	100%	100%	100%	75%	95%

PPV, and NPV. The foot region is less sensitive in detecting the severity of calcification compared to the other regions.

Receiver operating characteristic curve (ROC) for predicting the need for angioplasty

According to ROC analysis, for predicting the need for angioplasty (vascular surgeon comment based on the gold standard test "iodine angiography"), the area under curve (AUC) was calculated as 0.732 and 0.683 regarding iodine angiography and CO_2 angiography, respectively (Fig. 2).

Additionally, Table 8 represents different stenosis percentage cut-offs regarding iodine and CO_2 angiography and attributable sensitivity and specificity for predicting the need for angioplasty.

Discussion

The benefits of using CO_2 gas as a contrast material in vascular imaging, such as its non-nephrotoxicity and lower risk of causing anaphylactic reactions, compared to iodine, have led to an increased interest in its use[25,26,32–36]. Numerous studies have validated its effectiveness as a reliable alternative to iodinated contrast agents in the angiography of vessels above the popliteal cavity and abdominal vessels[18,20,23,35]. However, the accuracy of angiography imaging with carbon dioxide contrast remains a significant challenge of this diagnostic method. The presence of abdominal gases can reduce the quality of images when examining abdominal and pelvic vessels[37]. Additionally, reports suggest that the accuracy of imaging the lower vessels of the popliteal cavity decreases by 50% with this method[23,27,38,39]. In our study, the sensitivity of the CO2 angiography method in the tibial and foot regions decreased by 33.3% and 50%, respectively, compared to the popliteal and femoral regions.

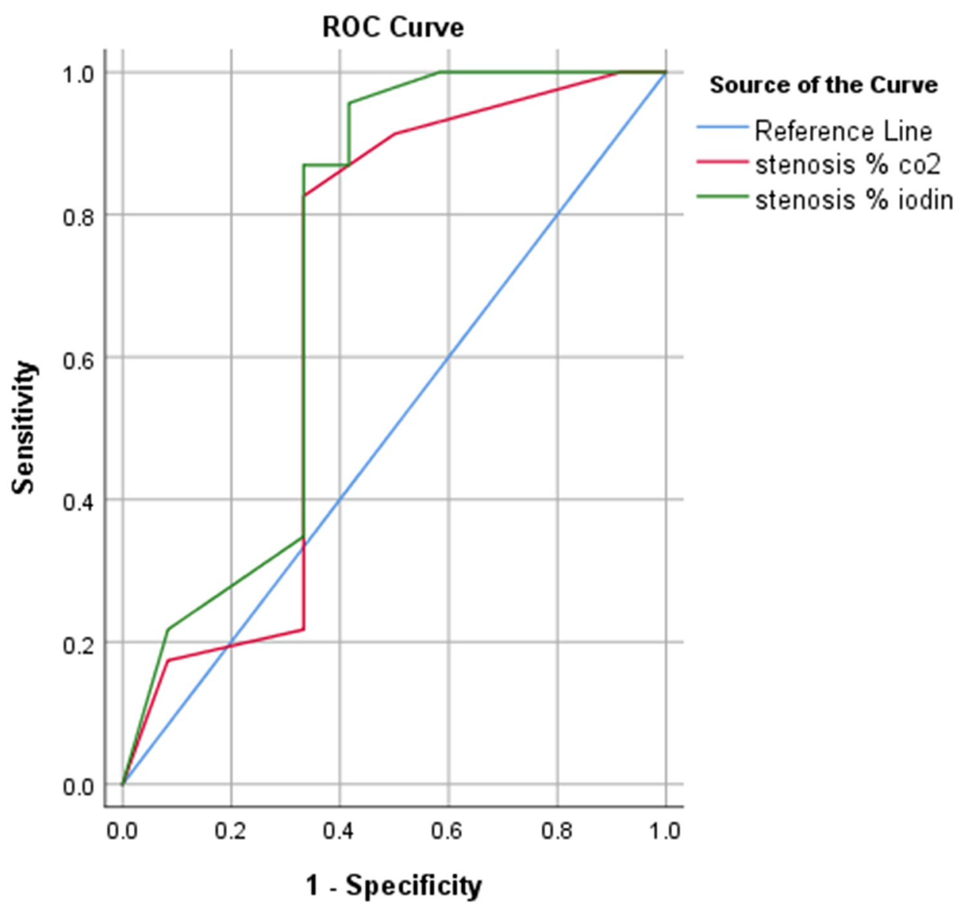

Figure 2. Receiver operating characteristic curve (ROC) for predicting the need for angioplasty (according to CO_2 angiography) based on the stenosis percentage in both iodine and CO_2 angiography.

Table 8

Diagnostic performance of iodine and CO_2 angiography for the need for angioplasty.

Test result variable(s)	Positive if greater than or equal to[a]	Sensitivity	1 – specificity
Stenosis % iodine contrast	9.00	1.000	1.000
	12.50	1.000	0.667
	25.00	0.957	0.417
	32.50	0.870	0.417
	45.00	0.783	0.333
	55.00	0.739	0.333
	67.50	0.652	0.333
	77.50	0.391	0.333
	85.00	0.348	0.333
	92.50	0.217	0.083
	96.00	0.000	0.000
Stenosis % CO_2 contrast	4.00	1.000	1.000
	15.00	0.913	0.500
	25.00	0.826	0.333
	35.00	0.696	0.333
	45.00	0.565	0.333
	55.00	0.522	0.333
	67.50	0.435	0.333
	77.50	0.261	0.333
	85.00	0.217	0.333
	92.50	0.174	0.083
	96.00	0.000	0.000

In our study, we examined 35 patients with CLI, using both iodine contrast material and carbon dioxide contrast material for angiography. The results showed that the image quality was excellent in 97.1% of cases when using iodine contrast material, while only 40% of cases had excellent image quality when using carbon dioxide contrast material, with 34% reporting poor quality. Furthermore, our study revealed a significant correlation between the quality of lower images with angiography using carbon dioxide contrast in the foot and tibial regions. A study by Ali *et al.* in 2023 found that the image quality from angiography with carbon dioxide contrast was higher in areas above the geniculate artery than in lower areas (86.5% vs 66.5%)[40]. Previous studies have indicated that the most common reason for the reduction in diagnostic image quality in peripheral vessel angiography is artifacts caused by patient lower limb movements[41].

In our article, we found that the sensitivity and specificity of carbon dioxide angiography to assess the need for intervention in the femoral and popliteal regions were 100%. However, the diagnostic sensitivity of this method in the tibial and foot regions was 66.7% and 50%, respectively. Despite poorer results in vascular lesions below the popliteal using carbon dioxide contrast in our study, research by Stegemann *et al.* suggested the use of carbon dioxide as an additional or alternative contrast for examining popliteal and lower arteries[42]. Similarly, Scalise *et al.*'s study demonstrated that angiography with carbon dioxide in areas below the knee, with a sensitivity of 97.9%, a specificity of 95.8%, a PPV of 94%, and an NPV of 98.6%, is a suitable method for vascular investigations in these areas[21]. The results of Palena *et al.* study showed that when using carbon dioxide contrast, the sensitivity, specificity, PPV, and NPV for vascular lesions above the knee were found to be 96.8%, 80.0%, 96.8%, and 80.0%, respectively. For lesions below the knee, the values were 93.3%, 83.3%, 96.5%, and 71%, respectively. Additionally, for diagnostic purposes in the foot and below the ankle, the study reported values of 86.6%, 66.6%, 92.8%, and 50%, respectively[41].

Therefore, in some studies, this method has successfully detected lesions even below the knee.

However, other studies, such as the one by Paul Diaz and colleagues, reported insufficient and poor results using arteriography with carbon dioxide, especially at infrapopliteal levels[37]. Ali *et al*'s study also noted a significant decrease in the quality of reports related to vascular lesions below the knee[40].

High-quality images in more distal areas are crucial for determining the need for a revascularization procedure. The absence of suitable images can lead to frequent use of contrasts and exposure to higher radiation doses, increasing complications. It is worth noting that studies reporting higher-quality images of angiography with carbon dioxide in distal body parts used automatic CO_2 injectors[21,31]. It appears that the use of automatic injection methods for carbon dioxide contrast can enhance accuracy compared to the iodine injection method.

Furthermore, lower rates of nephropathy with CO_2 angiography as the third leading cause of renal failure in hospitalized patients were a noteworthy issue[43]. Complications during CO_2 angiography usually are non-severe including leg and abdominal pain, GI upset, and very rarely emergent complications such as non-obstructive mesenteric ischemia, neurotoxicity, and air contamination[44]. The results of CO_2 contrast angiography were consistent with previous findings, with no complications detected[31,39].

This work sheds important light on how CO_2 angiography is used in PVD patients. One of the study's advantages is its prospective design, which makes it possible to evaluate the CO_2 angiography's diagnostic accuracy in comparison to that of iodine angiography. In addition, the study examines how various anatomical sites affect image quality, offering insightful information for medical decision-making. The limitations of the study should be taken into account, though. The findings' generalizability may be constrained by the relatively small sample size (35 patients) and the possibility of selection bias. Second, it may be beneficial and informative to assess the outcomes related to different TASC-II classifications of the lesions and also compare the kidney function during the procedure; however, this was not feasible in our study. Furthermore, because the study's exclusive emphasis was on PVD patients, its conclusions might not apply to other patient populations. These results need to be confirmed and expanded upon by larger cohort and diverse patient studies.

Conclusion

According to the outcomes of this study and previous research, the use of angiography with carbon dioxide contrast, particularly for vascular lesions above the popliteal cavity, is beneficial and safe in the peripheral vascular examination of the lower limbs. It can serve as an alternative to angiography with iodine contrast, especially in patients suffering from kidney failure.

Ethical approval

This study was approved by the Institutional Review Board (IRB) of the Tehran University of Medical Sciences, Tehran

(Ethical code: IR.TUMS.IKHC.REC.1400.498), and conducted by the Declaration of Helsinki. All patients provided informed consent before the procedure.

Consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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None.

Author's contribution

A.A: conceptualization, project administration, investigation, resources, visualization, data curation, writing – original draft. S.J: investigation, data curation, validation, methodology, writing – review and editing, software, formal analysis M.N: conceptualization, validation, supervision, funding acquisition. All authors contributed to the article and approved the submitted version.

Conflicts of interest disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Research Registration Unique Identifying Number (UIN)

Not applicable.

Guarantor

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Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The data and materials used to analyze the study are available from the corresponding author upon reasonable request.

Assistance with the study

None.

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