

## Safety of carboxy-angiography in patients with critical lower limb ischemia

Tursunov Jakhongir Tojiboevich \*

*Department of Interventional Cardiology, "Jacksoft" Clinical Hospital, Tashkent, Uzbekistan.*

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### Abstract

**Background:** Critical lower limb ischemia (CLI) represents the most severe form of peripheral arterial disease, associated with high rates of morbidity, limb loss, and cardiovascular mortality. Timely and accurate vascular imaging is essential for diagnosis, treatment planning, and procedural guidance in patients undergoing endovascular or surgical revascularization. Conventional contrast angiography, while widely utilized, poses substantial risks in patients with chronic kidney disease (CKD), which is frequently present in the CLI population.

**Introduction:** Carboxyangiography, or carbon dioxide (CO<sub>2</sub>)-based angiography, has emerged as a promising alternative imaging modality that avoids the nephrotoxicity and allergic risks associated with iodinated contrast agents. Owing to its low viscosity and high solubility, CO<sub>2</sub> offers distinct hemodynamic and imaging advantages, particularly in infringing interventions.

**Purpose:** This review aims to evaluate the current evidence on the safety of carboxyangiography in patients with CLI, with a focus on procedure-related complications, hemodynamic effects, renal outcomes, and its clinical applicability across varying risk profiles. The review also addresses technical considerations and limitations associated with CO<sub>2</sub> angiography.

**Findings:** Current literature suggests that carboxyangiography is generally safe when used in appropriately selected patients, especially for infringing arterial imaging. The risk of adverse events such as vapor lock, transient hypotension, and neurovascular complications appears low when proper technique and precautions are employed. Importantly, carboxyangiography demonstrates a favorable renal safety profile, making it an attractive alternative in patients with moderate to severe CKD. However, limitations in image quality, operator experience, and contraindications in thoracic or cerebral vascular imaging remain challenges.

**Conclusion:** Carboxyangiography represents a viable and safer alternative to iodinated contrast angiography in CLI patients, particularly those at high risk for contrast-induced nephropathy. Continued refinement of techniques and further prospective data are needed to fully establish its role in routine vascular practice.

**Keywords:** Carboxyangiography; Critical Limb Ischemia; Carbon Dioxide Angiography; Contrast-Induced Nephropathy; Peripheral Arterial Disease

### 1. Introduction

Critical limb ischemia (CLI), also known as chronic limb-threatening ischemia (CLTI), represents the most severe form of peripheral arterial disease (PAD). It is characterized by chronic ischemic rest pain, non-healing wounds, or gangrene attributable to arterial occlusive disease. CLI is associated with high morbidity and mortality rates, with significant risks of limb loss and cardiovascular events. The prevalence of CLI is increasing globally, paralleling the rising incidence of

\* Corresponding author: Tursunov Jakhongir Tojiboevich

diabetes mellitus, chronic kidney disease (CKD), and an aging population. In the United States, approximately 2 million people are affected by CLI, with a 5-year mortality rate approaching 50% and a major amputation rate of 40% [1].

Accurate vascular imaging is essential in the diagnosis, risk stratification, and management of CLI. Angiography remains the gold standard for delineating the extent and severity of arterial occlusive disease. It provides detailed visualization of the vascular anatomy, facilitating the identification of suitable targets for revascularization and guiding endovascular or surgical interventions. Conventional imaging modalities, including digital subtraction angiography (DSA), computed tomography angiography (CTA), and magnetic resonance angiography (MRA), typically utilize iodinated contrast agents to enhance vascular visualization. However, the use of iodinated contrast media poses significant risks, particularly in patients with pre-existing renal impairment.

Iodinated contrast agents are associated with the risk of contrast-induced nephropathy (CIN), a form of acute kidney injury that can lead to increased morbidity, prolonged hospitalization, and higher healthcare costs. The incidence of CIN is notably higher in patients with CKD, diabetes mellitus, and congestive heart failure—conditions commonly coexisting in individuals with CLI. The pathophysiology of CIN involves direct tubular toxicity, renal vasoconstriction, and oxidative stress, culminating in reduced renal perfusion and function. Given the high prevalence of CKD among CLI patients, the use of iodinated contrast agents necessitates careful consideration and risk mitigation strategies [2].

To circumvent the nephrotoxic risks associated with iodinated contrast media, alternative imaging agents have been explored. Carboxyangiography, utilizing carbon dioxide (CO<sub>2</sub>) as a contrast agent, has emerged as a viable option, particularly for patients with contraindications to iodinated contrast. CO<sub>2</sub> is a colorless, odorless gas that is highly soluble in blood and rapidly exhaled through the lungs, minimizing the risk of systemic toxicity. Its low viscosity allows for excellent vascular opacification, especially in the lower extremities, making it suitable for imaging infrainguinal arteries. Moreover, CO<sub>2</sub> does not elicit allergic reactions and is devoid of nephrotoxic effects, rendering it a safer alternative for patients with renal insufficiency or iodine allergies [3]. Despite its advantages, the use of CO<sub>2</sub> angiography is not without limitations. The gas's buoyancy can result in suboptimal imaging of vessels located above the diaphragm, such as the coronary and cerebral arteries. Additionally, there is a risk of gas embolism if CO<sub>2</sub> is inadvertently introduced into the arterial circulation inappropriately. Therefore, the application of CO<sub>2</sub> angiography requires meticulous technique and adherence to safety protocols to mitigate potential complications [3].

This review comprehensively evaluates the safety profile of carboxyangiography in patients with critical lower limb ischemia (CLI), with the goal of informing clinical practice and optimizing its application. It explores the pathophysiological rationale and clinical implications of using carbon dioxide (CO<sub>2</sub>) as a contrast agent in vascular imaging, highlighting its potential advantages in patients at risk from iodinated contrast agents. The review analyzes current evidence on the safety and efficacy of carboxyangiography for the diagnosis and treatment planning of CLI, identifies potential risks and limitations associated with its use, and discusses strategies to mitigate these concerns. Ultimately, it provides practical recommendations for the clinical application of CO<sub>2</sub> angiography, especially in patients with renal impairment or allergy to iodinated contrast, to support its safe and effective integration into vascular care.

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## 2. Principles of Carboxyangiography

Carboxyangiography employs carbon dioxide (CO<sub>2</sub>) as a negative contrast agent in vascular imaging. Upon intra-arterial injection, CO<sub>2</sub> displaces blood within the vessel lumen due to its gaseous nature, creating a transient gas column that appears as a radiolucent area on digital subtraction angiography (DSA). This displacement allows for the visualization of vascular structures without the use of iodinated contrast media. CO<sub>2</sub>'s high solubility in blood facilitates rapid elimination through the lungs, minimizing the risk of systemic toxicity. Carbon dioxide (CO<sub>2</sub>) exhibits unique physical and chemical properties that make it an effective and safe alternative to iodinated contrast agents in angiographic procedures. Its extremely low viscosity, approximately 400 times lower than that of iodinated media—allows it to traverse small-caliber vessels and navigate intricate vascular anatomies with ease. CO<sub>2</sub> is also highly soluble in blood, facilitating rapid absorption and elimination through the lungs, which significantly minimizes the risk of gas embolism. Furthermore, its compressibility requires precise, controlled injection techniques to avoid sudden, forceful delivery. Due to its buoyant nature, CO<sub>2</sub> tends to rise within the vascular system, a characteristic that can either be beneficial or limiting, depending on the specific vascular territory being assessed. These properties collectively support its growing role as a contrast agent, particularly in patients at risk of complications from traditional iodinated agents [4].

The safe and effective use of carbon dioxide (CO<sub>2</sub>) in angiography necessitates specialized equipment and careful technical considerations to optimize image quality and minimize risks. Automated CO<sub>2</sub> delivery systems are strongly preferred over manual injection methods, as they provide precise control over both the volume and pressure of gas administration, significantly reducing the likelihood of complications such as vascular injury or gas embolism. While

standard angiographic catheters are generally suitable for CO<sub>2</sub> angiography, their compatibility with CO<sub>2</sub>-specific delivery systems must be verified to ensure safe usage. Imaging is typically performed using digital subtraction angiography (DSA), which enhances visualization of vascular structures by subtracting baseline images from those captured after CO<sub>2</sub> injection. Patient positioning also plays a critical role due to the buoyant nature of CO<sub>2</sub>; for lower limb imaging, a supine position is standard, whereas a slight head-down tilt may be used during abdominal vascular imaging to direct the gas toward the target vessels [5]. These technical measures collectively support the safe and diagnostically effective application of CO<sub>2</sub> angiography.

Carboxyangiography, using carbon dioxide (CO<sub>2</sub>) as a contrast agent, serves as a valuable imaging alternative for select patient populations, particularly those with renal insufficiency or allergies to iodinated contrast media. Common indications include the evaluation of peripheral arterial disease, especially in the lower extremities; the detection of endoleaks following endovascular aneurysm repair (EVAR); and the visualization of the portal venous system and other abdominal vasculature. However, the use of CO<sub>2</sub> is contraindicated in several clinical scenarios due to safety concerns. It should not be employed for imaging of the coronary, cerebral, or thoracic vasculature, as inadvertent gas embolism in these territories can lead to catastrophic events such as stroke or myocardial infarction. CO<sub>2</sub> angiography is also contraindicated in patients with pulmonary hypertension or significant right-to-left intracardiac shunts, given the potential for hemodynamic compromise. Additionally, concurrent use with nitrous oxide anesthesia is discouraged, as it can impair CO<sub>2</sub> elimination and increase the risk of gas retention. When compared to iodinated contrast agents, CO<sub>2</sub> offers notable advantages. It is non-nephrotoxic and non-allergenic, which makes it a safer alternative in patients with chronic kidney disease or known hypersensitivity to iodinated contrast [6]. Its low viscosity enhances its ability to opacify small or severely stenosed vessels and facilitates imaging in complex vascular anatomies. Furthermore, CO<sub>2</sub> is cost-effective and widely accessible.

Nevertheless, CO<sub>2</sub> has certain limitations. Image quality can be suboptimal, particularly in vascular territories above the diaphragm, due to the gas's buoyant properties and rapid dispersion. Improper administration techniques increase the risk of gas embolism, and its use requires dedicated equipment and personnel trained in CO<sub>2</sub>-specific protocols. Carboxyangiography using CO<sub>2</sub> represents a viable and often preferable imaging method in carefully selected patients. Its safe and effective application hinges on a thorough understanding of its indications, contraindications, physical behavior, technical requirements, and comparative advantages over iodinated contrast agents.

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### 3. Safety Profile: Evidence Review

The safety of carbon dioxide (CO<sub>2</sub>) angiography has been evaluated through various studies, including randomized controlled trials (RCTs), observational studies, and registries. A meta-analysis encompassing seven observational studies and one RCT, involving 754 peripheral angiographic procedures in 677 patients, indicated that CO<sub>2</sub> angiography is generally safe. However, it was associated with a higher incidence of minor, non-renal complications such as limb and abdominal pain, nausea, and vomiting compared to iodinated contrast media (ICM) [4]. In a prospective multicenter trial involving 98 patients undergoing CO<sub>2</sub> angiography-guided angioplasty, the technical success rate was 97.9%. The incidence of contrast-induced nephropathy (CIN) was 5.1%, and CO<sub>2</sub> angiography-related complications occurred in 17.3% of cases. Notably, two patients (2%) developed severe, fatal nonocclusive mesenteric ischemia (NOMI), highlighting the need for caution in certain patient populations [5].

CO<sub>2</sub> angiography can influence hemodynamics due to the gas's physical properties. While CO<sub>2</sub> is highly soluble and rapidly eliminated via the lungs, inadvertent intravascular gas embolism can occur, leading to transient hypotension, tachycardia, and, in rare cases, cardiovascular collapse. A case report described severe hypotension and tachycardia as initial signs of CO<sub>2</sub> embolism during a procedure, emphasizing the importance of vigilant monitoring and prompt management [6]. The use of CO<sub>2</sub> above the diaphragm is contraindicated due to the risk of cerebral air embolism. A reported case of fatal brain injury following CO<sub>2</sub> angiography underscores this risk, where inadvertent CO<sub>2</sub> entry into the cerebrovascular circulation led to severe neurological complications [7]. Respiratory effects are generally minimal, but caution is advised in patients with pulmonary hypertension or significant right-to-left cardiac shunts, as CO<sub>2</sub> may exacerbate these conditions.

Minor adverse events associated with CO<sub>2</sub> angiography include limb discomfort, abdominal pain, nausea, and transient paresthesia. These symptoms are typically self-limiting and resolve without intervention. In a study focusing on patients with critical lower limb ischemia, leg pain was reported in 17.3% of patients during CO<sub>2</sub> injection, but no major complications were observed, supporting the procedure's safety in this population [8]. When comparing CO<sub>2</sub> angiography to ICM, CO<sub>2</sub> demonstrates a lower risk of nephrotoxicity, making it a preferable option for patients with renal impairment. However, CO<sub>2</sub> is associated with a higher incidence of minor, non-renal adverse events. A meta-

analysis reported a decreased incidence of acute kidney injury (AKI) with CO<sub>2</sub> (4.3%) compared to ICM (11.1%), but noted more frequent non-renal adverse events with CO<sub>2</sub> use [9].

#### 4. Special Considerations in CLI Patients

Critical limb ischemia (CLI) represents the most severe manifestation of peripheral arterial disease (PAD), often occurring in patients with multiple comorbidities that complicate both diagnosis and treatment. Among these, diabetes mellitus, chronic kidney disease (CKD), and heart failure are particularly prevalent and significantly influence the safety and efficacy of diagnostic imaging modalities. In this context, carbon dioxide (CO<sub>2</sub>) angiography emerges as a valuable alternative to iodinated contrast media, offering specific advantages for this high-risk patient population [10]. Patients with CLI frequently present with a constellation of comorbid conditions that exacerbate their vascular disease and increase the risk of complications from diagnostic procedures.

- **Diabetes Mellitus:** Diabetes is a major risk factor for PAD and CLI, contributing to endothelial dysfunction, accelerated atherosclerosis, and impaired wound healing. Diabetic patients are more likely to develop infrapopliteal disease and have a higher incidence of limb loss.
- **Chronic Kidney Disease (CKD):** CKD is common among CLI patients, with reduced glomerular filtration rate (GFR) increasing susceptibility to contrast-induced nephropathy (CIN). The use of iodinated contrast agents in these patients poses a significant risk of acute kidney injury, potentially leading to dialysis dependence.
- **Heart Failure:** Heart failure, particularly with reduced ejection fraction, is prevalent in the CLI population. These patients have limited cardiac reserve, making them more vulnerable to volume overload and hemodynamic instability during procedures involving contrast administration.

The administration of iodinated contrast agents in patients with CKD and diabetes significantly increases the risk of CIN, a serious complication characterized by a sudden decline in renal function. Studies have reported CIN incidences ranging from 5% to 10% in high-risk populations undergoing peripheral angiography. The pathophysiology involves direct tubular toxicity and renal vasoconstriction, leading to ischemia and oxidative stress. Given the high prevalence of CKD and diabetes in CLI patients, minimizing or avoiding iodinated contrast exposure is paramount. CLI patients often exhibit hemodynamic fragility due to their comorbid conditions [11]. Heart failure can lead to reduced cardiac output, while CKD and diabetes can impair vascular autoregulation. These factors contribute to an increased risk of hypotension and other hemodynamic disturbances during angiographic procedures. The use of CO<sub>2</sub> as a contrast agent requires careful monitoring, as rapid or excessive administration can lead to transient hypotension and other adverse effects. CO<sub>2</sub> angiography offers several advantages for CLI patients, particularly those with CKD or contrast allergies. CO<sub>2</sub> is non-nephrotoxic and does not elicit allergic reactions, making it a safer alternative to iodinated contrast agents. Additionally, its low viscosity allows for better visualization of small and distal vessels, which is beneficial in assessing infrapopliteal disease common in CLI. However, CO<sub>2</sub> angiography is not without risks. Potential complications include gas embolism, particularly if CO<sub>2</sub> is inadvertently introduced into the arterial circulation above the diaphragm [12]. Patients with pulmonary hypertension or significant right-to-left cardiac shunts are at increased risk of adverse events due to CO<sub>2</sub> administration. Therefore, patient selection and adherence to proper injection techniques are critical to minimize risks.

Recent studies have demonstrated the efficacy and safety of CO<sub>2</sub> angiography in CLI patients. For instance, a prospective study involving diabetic patients with CLI and CKD showed that CO<sub>2</sub> angiography effectively guided endovascular interventions without significant changes in renal function post-procedure. The study reported no complications related to CO<sub>2</sub> use, highlighting its potential as a safe alternative in this high-risk group. CO<sub>2</sub> angiography presents a viable and safer alternative to iodinated contrast agents for imaging in CLI patients, especially those with comorbidities such as diabetes, CKD, and heart failure [13, 14]. While it offers significant benefits in reducing the risk of CIN and providing adequate vascular visualization, careful patient selection and adherence to safety protocols are essential to mitigate potential risks.

#### 5. Renal Safety and Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN), also referred to as contrast-associated acute kidney injury (CA-AKI), is a form of acute renal impairment that occurs following the administration of iodinated contrast media (ICM). The pathogenesis of CIN is multifactorial, involving direct tubular toxicity, renal vasoconstriction, and oxidative stress. ICM can induce medullary ischemia through vasoconstriction and increase the generation of reactive oxygen species, leading to tubular cell injury and apoptosis. Additionally, the high osmolality and viscosity of ICM can exacerbate renal hypoperfusion and contribute to nephrotoxicity [15]. Carbon dioxide (CO<sub>2</sub>) angiography has emerged as a safer alternative to ICM, particularly in patients at risk for CIN. CO<sub>2</sub> is a non-nephrotoxic contrast agent that does not induce the same

hemodynamic changes as ICM. Several studies have compared the incidence of acute kidney injury (AKI) between CO<sub>2</sub> and ICM. A meta-analysis encompassing randomized controlled trials (RCTs) and cohort studies found that the risk of CA-AKI was lower with CO<sub>2</sub> compared to ICM (8.6% vs. 15.2%; relative risk [RR], 0.59; 95% confidence interval [CI], 0.33–1.04). Another study reported that CO<sub>2</sub> angiography during peripheral angioplasty procedures significantly reduced the risk of CIN in patients with chronic kidney disease (CKD) [16].

Further evidence from meta-analyses supports the renal safety profile of CO<sub>2</sub> angiography. A systematic review and meta-analysis comparing the incidence of AKI with CO<sub>2</sub> versus ICM found that CO<sub>2</sub> use was associated with a modestly reduced rate of AKI, although nonrenal adverse events were more frequent [11]. These findings suggest that while CO<sub>2</sub> angiography may not eliminate the risk of AKI, it offers a safer profile compared to ICM, especially in high-risk populations. Patients with critical lower limb ischemia (CLI) and CKD stage 3 or worse are particularly vulnerable to CIN due to their compromised renal function. In this subgroup, CO<sub>2</sub> angiography has demonstrated significant benefits. A prospective multicenter trial evaluating endovascular therapy guided by CO<sub>2</sub> angiography in patients with CKD reported a reduced incidence of CIN and maintained renal function post-procedure [14]. Additionally, CO<sub>2</sub> angiography has been effectively used in diabetic patients with CLI and CKD, providing adequate imaging for intervention without the nephrotoxic risks associated with ICM. CO<sub>2</sub> angiography presents a viable and safer alternative to iodinated contrast agents for imaging in CLI patients, particularly those with CKD stage 3 or worse. While CO<sub>2</sub> angiography is not without risks, its renal safety profile makes it a valuable tool in the management of high-risk patients requiring vascular imaging.

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## 6. Technical Limitations and Challenges

While carbon dioxide (CO<sub>2</sub>) angiography presents numerous advantages in patients with critical lower limb ischemia (CLI), its application is not without technical challenges and limitations that must be carefully addressed to ensure safe and effective imaging. One of the primary physical limitations of CO<sub>2</sub> as a contrast agent is its buoyancy. Due to its lower density compared to blood, CO<sub>2</sub> tends to rise within the vascular system, which can hinder adequate opacification of dependent vessels or those located above the diaphragm. As a result, its use is generally restricted to imaging below the diaphragm, limiting its utility in supra-aortic or coronary territories. Another significant challenge lies in image quality. Compared to iodinated contrast agents, CO<sub>2</sub> provides lower contrast resolution, which can impair visualization of small or heavily calcified vessels, particularly in patients with advanced peripheral artery disease. Additionally, motion artifacts and inadequate vessel filling may occur if CO<sub>2</sub> is not injected using precise timing and controlled delivery systems [17]. Manual injection techniques are associated with variability in flow and volume, increasing the risk of complications such as vapor lock or gas embolism. Thus, automated CO<sub>2</sub> delivery systems are recommended, although they require specific training and experience to operate safely. Furthermore, CO<sub>2</sub> must be delivered in a strictly controlled, non-contaminated environment, as introduction of ambient air may result in dangerous air embolism. Patient-related factors, such as pulmonary hypertension, right-to-left cardiac shunts, or respiratory compromise, also pose limitations due to the risk of hemodynamic instability or systemic embolization [9]. Lastly, limited operator familiarity with CO<sub>2</sub> angiography in some institutions and lack of standardization in protocols may hinder broader adoption despite its recognized renal safety benefits. Collectively, these technical limitations underscore the need for appropriate patient selection, procedural planning, operator expertise, and equipment availability when considering CO<sub>2</sub> angiography in CLI patients.

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## 7. Conclusion

Carboxyangiography utilizing carbon dioxide (CO<sub>2</sub>) offers a valuable and safer alternative to iodinated contrast agents in patients with critical lower limb ischemia, particularly those at high risk for contrast-induced nephropathy due to underlying chronic kidney disease or diabetes. Its non-nephrotoxic and non-allergenic properties make it especially advantageous in this vulnerable population. Despite its clinical benefits, CO<sub>2</sub> angiography is associated with specific technical limitations and potential complications, such as suboptimal image quality in non-dependent vessels and risks of gas embolism if not properly administered. Proper patient selection, adherence to established safety protocols, and operator expertise are essential for minimizing risks. With increasing clinical experience and advancements in delivery systems, CO<sub>2</sub> angiography may become an integral part of diagnostic and interventional strategies in CLI. Future studies and standardized protocols are needed to optimize its use and expand its applicability across a broader spectrum of vascular procedures.

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