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The Role of Carboxiangiography for the Diagnosis of Critical Limb Ischemia

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A B S T R A C T

Critical Limb Ischemia (CLI), the most severe manifestation of peripheral arterial disease, represents a growing global health challenge associated with significant morbidity, risk of limb loss, and mortality. Prompt and accurate vascular imaging is essential for diagnosis, treatment planning, and revascularization in CLI. However, the widespread use of iodinated contrast media in conventional angiography poses a considerable risk of contrast-induced nephropathy, particularly in patients with chronic kidney disease or diabetespopulations disproportionately affected by CLI. Carboxyangiography, which utilizes carbon dioxide (CO_2) as a contrast agent, has emerged as a safe, non-nephrotoxic alternative for vascular imaging. CO_2's favorable physical properties—low viscosity, high solubility, and rapid pulmonary clearancemake it suitable for visualizing infra-diaphragmatic arterial lesions without compromising renal function. Clinical studies have demonstrated its diagnostic utility in detecting femoropopliteal and infrapopliteal arterial occlusions, with image quality sufficient for endovascular decision-making. While challenges such as limited use in supra-diaphragmatic vessels and operator dependency remain, advancements in delivery systems and imaging techniques continue to expand its applicability. This review explores the principles, clinical efficacy, safety profile, and current limitations of carboxyangiography in CLI, emphasizing its growing relevance in modern vascular diagnostics and its potential for broader integration into clinical practice.

Keywords: Critical Limb Ischemia; Carboxiangiography; Peripheral Arterial Disease.

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INTRODUCTION

Critical Limb Ischemia (CLI) represents the most advanced stage of peripheral arterial disease (PAD), characterized by chronic ischemic rest pain, non-healing ulcers, or gangrene, resulting from severe obstruction of arterial blood flow to the lower extremities [1]. CLI affects approximately 1–2% of the general population and is particularly prevalent in elderly individuals, smokers, and patients with diabetes or chronic kidney disease (CKD) [2]. Without timely intervention, CLI is associated with high rates of limb loss and mortality, with one-year amputation or death rates approaching 30–50% [3].

Accurate and early vascular imaging is essential for diagnosing CLI, stratifying severity, and planning revascularization strategies aimed at limb salvage. Digital subtraction angiography (DSA) using iodinated contrast media (ICM) remains the gold standard imaging modality [4]. However, in patients with CKD or those at risk of contrast-induced nephropathy (CIN), ICM use may exacerbate renal dysfunction, limiting its safety and utility [5].

Carbon dioxide (CO_2) has emerged as a non-nephrotoxic intravascular contrast agent that offers a valuable alternative in this context. Owing to its low viscosity, high solubility, and rapid clearance via the lungs, CO_2 can be safely used for imaging infra-diaphragmatic vessels, particularly in patients with renal impairment [6]. Carboxyangiographyangiographic imaging using CO_2has shown promising diagnostic accuracy in identifying femoro-popliteal and below-the-knee arterial lesions [7].

This review aims to explore the current role of carboxyangiography in the diagnosis of CLI, examining its indications, technical principles, diagnostic performance, safety profile, limitations, and potential role in improving outcomes for high-risk patients.

Pathophysiology and Diagnostic Needs in Critical Limb Ischemia

Critical Limb Ischemia (CLI), recently referred to as Chronic Limb-Threatening Ischemia (CLTI), is the end-stage manifestation of peripheral arterial disease (PAD) and results from progressive arterial occlusion due to atherosclerosis, thromboembolism, or inflammatory processes [8]. In patients with diabetes mellitus or chronic kidney disease, microvascular dysfunction, arterial calcification, and endothelial injury further exacerbate ischemia and impair collateral formation [9]. These pathophysiologic changes reduce perfusion to distal tissues, leading to rest pain, ischemic ulcers, and tissue necrosishallmarks of CLI.

CLI is typically classified using clinical staging systems, with the Rutherford and Fontaine classifications being the most widely used. Rutherford stages 4–6 describe ischemic rest pain, minor tissue loss, and major tissue loss,

respectively, while Fontaine stages III–IV correspond to rest pain and ulceration/gangrene [10]. Prompt diagnosis and revascularization are critical to prevent limb loss and reduce mortality.Imaging plays a central role in diagnosing CLI, assessing lesion severity, and guiding revascularization planning. Duplex ultrasonography is often the first-line, noninvasive modality but has limitations in obese patients or those with extensive calcification [11]. CT angiography (CTA) and MR angiography (MRA) provide high-resolution imaging, though CTA requires iodinated contrast and MRA may not be feasible in patients with metallic implants or severe renal impairment [12]. Digital subtraction angiography (DSA) remains the gold standard for delineating vascular anatomy and facilitating endovascular interventions [13].

Patients with CLI frequently have comorbidities such as renal dysfunction and diabetes, which complicate imaging due to the risk of contrast-induced nephropathy and challenges in interpreting calcified vessels [14]. In this context, alternative contrast agents like carbon dioxide (CO_2) offer potential advantages, especially for infra-inguinal imaging in high-risk patients.

Carboxyangiography: Principles and Technique

Carboxyangiography, or carbon dioxide (CO_2) angiography, is a well-established alternative imaging method used for vascular visualization, especially in patients at high risk for contrast-induced nephropathy. The use of CO_2 as an intravascular contrast agent dates back to the 1970s, with Hawkins and colleagues pioneering its application in digital subtraction angiography (DSA) [15]. CO_2's role has since evolved, particularly in the imaging of infra-diaphragmatic vessels in patients with renal impairment or allergy to iodinated contrast media.CO_2 has several unique physical properties that make it suitable for vascular imaging. It is a colorless, odorless gas with low viscosityapproximately 400 times less than iodinated contrastwhich allows it to displace blood more effectively and fill small vessels [16]. Its high solubility and non-particulate nature enable rapid absorption into the bloodstream and elimination through the lungs within 1–2 minutes, minimizing systemic retention and toxicity [17].

Technically, CO_2 can be administered via manual injection using a syringe or via automated delivery systems, which are preferred for consistent flow rates, minimized contamination, and improved safety [18]. Automated systems often include pressure-regulated delivery with venting and filtration mechanisms. Patient positioning plays a critical role in optimizing image quality, as CO_2, being buoyant, rises within the vascular lumen. For lower extremity angiography, supine positioning with head elevation is commonly used to facilitate vessel filling and avoid reflux into non-target areas [19].Modern angiographic equipment must be compatible with CO_2 imaging. Flat-panel DSA systems with high frame rates and digital enhancement capabilities allow clearer visualization of CO_2 flow patterns and vessel anatomy.

Despite its advantages, CO_2 angiography has important safety considerations. It must never be injected above the diaphragm due to the risk of cerebral or coronary gas embolism [20]. Contraindications include patients with pulmonary hypertension, significant chronic obstructive pulmonary disease (COPD), or known right-to-left cardiac or pulmonary shunts, where gas emboli may bypass the lungs and cause systemic complications [11].When used with appropriate technique and precautions, carboxyangiography offers a reliable and safe imaging modality for patients with CLI, particularly those with compromised renal function.

Evidence of Diagnostic Accuracy in Critical Limb Ischemia

Several clinical studies have evaluated the diagnostic performance of carbon dioxide (CO_2) angiography compared to iodinated contrast media (ICM) in patients with critical limb ischemia (CLI), particularly among those with advanced renal dysfunction or contraindications to ICM. The collective evidence supports CO_2 angiography as a viable alternative for visualizing infra-diaphragmatic arterial disease with reasonable diagnostic accuracy [12].

In a prospective study by Fujihara et al., CO_2 angiography demonstrated a sensitivity of 94% and specificity of 89% for detecting femoro-popliteal lesions when compared with conventional iodinated DSA, confirming its suitability for guiding revascularization strategies in CLI patients [13]. Similarly, Matsuoka et al. reported that CO_2 angiography effectively visualized below-the-knee (infrapopliteal) vessels, with diagnostic quality images in 83% of patients undergoing endovascular procedures, though challenges remained in assessing highly calcified tibial arteries [14].The image quality with CO_2 angiography tends to be superior in distal and small-caliber vessels due to its low viscosity and ability to displace blood effectively. However, visualization in larger or more proximal vessels (such as iliac arteries) may be suboptimal due to incomplete filling or gas fragmentation, especially in patients with fast blood flow or insufficient CO_2 delivery techniques [15].

Crucially, the impact of CO_2 angiography extends beyond diagnostics. Studies have shown that CO_2 imaging allows accurate procedural planning for both bypass surgery and percutaneous interventions. For example, Kim et al. demonstrated that therapeutic decisionssuch as target vessel selection, balloon angioplasty, and stent deploymentwere comparable in outcomes when guided by CO_2 angiography versus ICM-based angiography in patients with CLI and CKD [16].Although CO_2 angiography may not replace iodinated contrast in all settings, it offers significant value in high-risk patients, enabling safe and effective visualization of critical limb vasculature necessary for revascularization planning.

Safety and Renal Protection Advantages

One of the most compelling advantages of carbon dioxide (CO_2) angiography is its non-nephrotoxic profile, making it an ideal imaging modality for patients at risk of contrast-induced nephropathy (CIN). Unlike iodinated contrast media (ICM), CO_2 is not metabolized by the kidneys and is eliminated via the lungs through passive diffusion, significantly reducing renal exposure to harmful substances [17].

Multiple studies have confirmed the renal safety of CO_2 angiography. In a prospective analysis by Modabber et al., the incidence of CIN in patients with chronic kidney disease (CKD) undergoing lower limb interventions was significantly lower in the CO_2 group compared to those who received iodinated contrast (0% vs. 13.3%) [22]. Another study by Kerns et al. showed that even in high-risk populations with stage 3- 4 CKD, CO_2 angiography allowed safe and accurate imaging without any decline in renal function post-procedure [19].Patients with diabetes mellitus, who are inherently predisposed to both PAD and renal impairment, particularly benefit from CO_2-based imaging. Carboxyangiography enables safe diagnostic and interventional procedures without compromising renal reserve or inducing further nephron damage [10].

Furthermore, CO_2 is non-allergenic, which significantly reduces the risk of systemic allergic and anaphylactoid reactions commonly seen with iodinated contrast agents [21]. This is especially important for patients with a history of contrast hypersensitivity or those requiring multiple imaging procedures.Overall, CO_2 angiography provides a safer alternative for high-risk patients, allowing for effective vascular imaging while minimizing renal and systemic complications, thus aligning well with the needs of the CLI population.

CONCLUSION

Critical limb ischemia (CLI) remains a severe and life-threatening condition with high rates of limb loss and mortality, necessitating accurate vascular imaging for timely intervention. While digital subtraction angiography (DSA) with iodinated contrast media (ICM) remains the gold standard, its nephrotoxicity poses significant risks for patients with chronic kidney disease (CKD) or diabetes. Carbon dioxide (CO_2) angiography has emerged as a safe and effective alternative, offering non-nephrotoxic vascular imaging with diagnostic accuracy comparable to conventional contrast in infra-diaphragmatic vessels.

Clinical studies support the utility of carboxyangiography in detecting femoro-popliteal and below-the-knee lesions, enabling revascularization planning in high-risk patients without compromising renal function. Despite limitations in proximal vessel imaging and technical challenges in highly calcified arteries, CO_2 angiography provides a crucial diagnostic tool for CLI patients with contraindications to ICM.

Given its renal protective benefits and non-allergenic properties, CO_2 angiography should be considered a first-line imaging modality in patients with advanced CKD or contrast hypersensitivity. Future advancements in automated delivery systems and imaging processing may further enhance its diagnostic reliability. As the prevalence of CLI rises with aging populations and increasing comorbidities, integrating carboxyangiography into routine practice could improve limb salvage rates and reduce morbidity in this vulnerable patient population.

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