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Case Report

Carbon dioxide (CO_2) as an alternative contrast agent in percutaneous transluminal angioplasty procedures for chronic limb-threatening ischemia patients with chronic kidney disease

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ABSTRACT

Background: Chronic limb-threatening ischemia (CLTI) is a very morbid illness that significantly reduces quality of life. The severity of this disease may necessitate revascularization or amputation. Arteriography is frequently performed for the planning of revascularization. Patients with compromised kidney function need alternative contrast agents. CO_2 may be utilized in lower extremity vascular diagnostics and intervention, especially in patients at risk for contrast-induced nephropathy (CIN).
Case Illustration: An 80-year-old female with bilateral leg pain and leg swelling had an ulcer on her toe for 2 weeks. She had a history of intermittent claudication for 1 year, hypertension for 5 years, kidney stones for 2 years, and chronic kidney disease for 1 year. She underwent an ECG, laboratory, USG, DUS, and CT-angiography examination. From her laboratory result, her initial creatinine was 5.02 mg/dL (eGFR 8 mL/m/1.73 m^2). After good hydration, it became 1.28 mg/dL (eGFR 39 mL/m/1.73 m^2). After a CT-angiography procedure, her creatinine level was increased (3.7 mg/dL; eGFR 10.9 mL/m/1.73 m^2). She was diagnosed with CLTI Rutherford V Fontain 3 left lower extremity. She suggested doing an angioplasty procedure with a safer contrast agent. An angioplasty procedure was done at RSSA Malang with CO_2 contrast. After the procedure, her leg pain improved, and her creatinine didn't elevate.
Conclusion: CO_2 angiography might be used as a safe alternative contrast medium in patients with CLTI, which benefits the preservation of renal function and prevents limb amputations.

1. Introduction

Chronic limb-threatening ischemia (CLTI) is known as the final stage of peripheral artery disease (PAD). It is typically caused by multi-level arterial occlusion disease. It is a very morbid illness that significantly reduces the quality of life of persons who have it by causing considerable mortality, limb loss, pain, and other symptoms.[4] Left untreated, an estimated 25% of patients have a risk of limb loss at 1 year. Patients with CLTI still have a high risk of amputation, even after successful revascularization has been done.[1]

A full physical examination should be done on every patient suspected of CLTI.[5] Then, patients suggestive of PAD should undergo non-invasive tests, such as ankle pressure and ankle brachial index, toe pressure and toe brachial index, segmental pressure, TcPO2, skin perfusion pressure, plethysmography, or laser doppler flowmetry. Vascular imaging should be performed on the suspected patient to ascertain the presence, severity, and extent of arterial disease and to assist in guiding decisions regarding revascularization. When considering revascularization, patients with CLTI should have thorough anatomic imaging.[1]

The accuracy and acquisition times of CT angiography (CTA) have significantly improved in recent years. Modern CTA produces high-resolution, contrast-enhanced pictures that are swiftly produced and can be seen in various planes or as three-dimensional reconstructions.[6] Patients who already have renal insufficiency are especially vulnerable to contrast-induced nephropathy, which can be a serious issue. From the National Health and Nutrition Examination Survey (NHANES) data in 2000, it was reported that 24% of patients with chronic kidney disease (CKD) stage 3 or more had PAD as measured by an ankle-brachial index (ABI) less than 0.9. Data from the USRDS in 2010 found that around 46% of dialysis patients in the US had PAD. [7] PAD incidence in CKD patients is correlated with age, with a 28% risk increase by 10 years of age, especially in males.[5]

In the vascular imaging procedure known as CO_2 angiography, carbon dioxide gas is used as a contrast agent in place of iodinated contrast medium. It is useful for patients who have renal failure, contrast allergies, or need large volumes of contrast for complex procedures. [7] CO_2 is a colorless, odorless, inexpensive, and highly soluble gas that does not mix with blood and can be eliminated via the lungs.[6] It is safe and effective for evaluating the aorta, its branches, and runoff vessels. [8] It might be used for endovascular procedures such as angioplasty and stenting, embolization of arteriovenous fistulas and malformations, and endovascular aneurysm repair (EVAR). Using CO_2 as an arterial contrast agent above the diaphragm is not recommended due to the potential for gas embolism in

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the spinal, coronary, and cerebral arteries. Absolute contraindications for CO_2 angiography are thoracic aortography, coronary arteriography, and cerebral arteriography. [8] Nausea and pain may be complained of in CO_2 aortography and celiac arteriography; in lower extremities and peripheral areas, it may cause pain, especially at the site of injection. The pain depends on the doses of CO_2 used; a decrease in the doses of CO_2 often reduces the severity and frequency of pain. [6]

2. Case Presentation

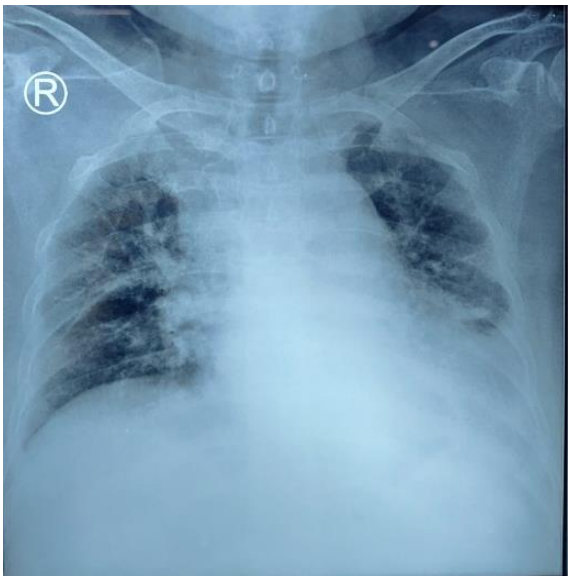

Figure 1. Chest X-ray

An 80-year-old female came with worsening pain in both of her legs with a VAS of 8/10 for 2 months. The pain felt persistent, and it wasn't relieved by rest or any postural changes. She had difficulty walking because of the pain, and it restricted her daily activity. She rubbed her legs frequently to relieve the pain, but it didn't get better. The pain was accompanied by an open wound at her left toe that had a red-black coloration with pus production. The wound was getting bigger day by day. There was cold and numbness on both of her legs. She felt nausea without vomiting and a decrease in appetite for 2 weeks. A complaint of fever, loss of consciousness, slurred speech, half-body weakness, or seizure was denied.

The patient had a history of DOE while doing moderate-to-heavy activity for 2 years, relieved by rest. There was no history of PND, OE, chest pain, bilateral leg swelling, palpitation, or syncope. She had a history of claudication for 1 year and got medication from a cardiologist for 6 months. She had hypertension for 5 years, with the highest systolic blood pressure of 180 mmHg. She routinely controlled herself and took medication from primary care. Two years ago, she was diagnosed with kidney stones in both of her kidneys. She got operated on one month later for her left kidney. The other kidney hadn't been operated on until now because she didn't want to be operated on. 1 year later, she was diagnosed with chronic kidney disease and was suggested to do hemodialysis, but she refused. There was no history of diabetes mellitus (DM) type II, malignancy disease, or CVA. From her family history, there was no history of hypertension, DM type II, CVA, or CVD. She was doing mild to moderate daily activity around her house as a housewife.

Physical examination showed normal vital signs: blood pressure from the left arm was 133/72 mmHg, the left leg was 78/55 mmHg, the right arm was 129/79 mmHg, and the right leg was 71/51 mmHg; heart rate was 90 bpm regular; respiratory rate was 18 tpm; and peripheral oxygen saturation was 99% at four extremities on room air. There was no anemic or icteric sign, no bruit from bilateral carotid arteries, and no thyroid enlargement or increase of JVP on the head and neck examination. Cardiac ictus was displaced to the left with regular S1S2, and there was no murmur or gallop during examination. Normal results were found from the lung and abdominal examinations.

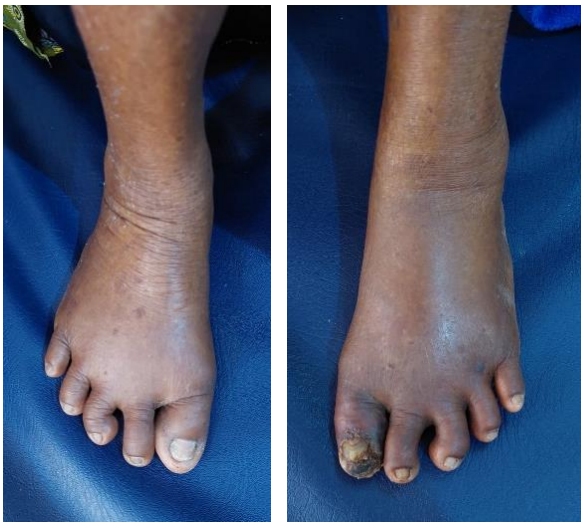

Figure 2. Clinical Appearance of the Lower Extremity

Her upper extremity examination was normal, but her lower extremity examination found a red to black discoloration at her left toe with an open wound measuring 0.5x1 cm. There was no oedema at both of her legs, and an ABI examination showed a score of 0.5 at both of her legs.

From the laboratory examination, her electrolyte serum, faal hemostasis, lipid profile, glucose level, and liver function test were normal. She had a low albumin level of 2.73 g/dL, a high creatinine level of 3.71 mg/dL with an eGFR of 10.931 mL/m/1.73 m^2, and a high uric acid level of 11.2 mg/dL. After the angioplasty procedure was finished, he got a renal function test and a laboratory evaluation, and the result was a creatinine level of 2.8 mg/dL with an eGFR of 14.861 mL/m/1.73 m^2. 1 week after the procedure, she had a creatinine laboratory evaluation of 2.0 mg/dL with an eGFR of 21.806 mL/m/1.73 m^2.

Her ECG examination showed a sinus rhythm with AV-block gr I and poor R wave progression. There was a cardiomegaly with an LVH configuration found on her chest x-ray. She underwent an USG abdomen examination and showed chronic parenchymal renal disease bilateral with nephrolithiasis multiple bilateral without sign of obstruction.

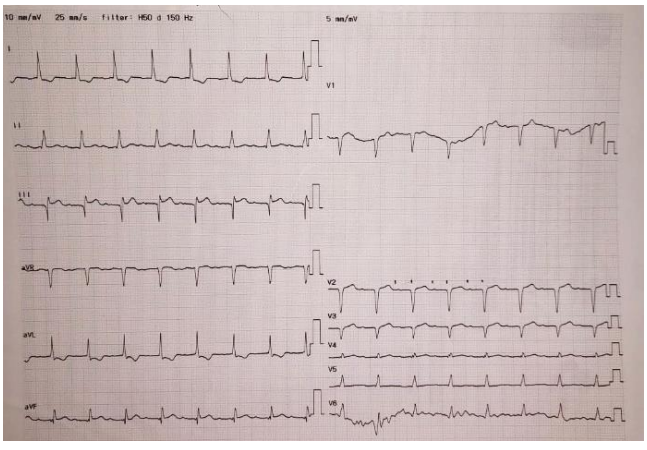

Figure 3. Electrocardiogram

Based on the history and previous examination, duplex ultrasound was performed with the conclusion of CLTI at the bilateral inferior extremity, and it was suggested to do CT-angiography. She came to the previous hospital with a creatinine level of 5.02 mg/dL and an eGFR of 8 mL/m/1.73 m^2. She got good hydration, and her creatinine level improved. CT-angiography was performed at a creatinine level of 1.28 mg/dL and an eGFR of 39 mL/m/1.73 m^2 in the previous hospital. CT-Angiography showed calcified plaque occlusion at bilateral artery tibialis anterior-posterior and artery dorsalis-plantaris pedis; heavy

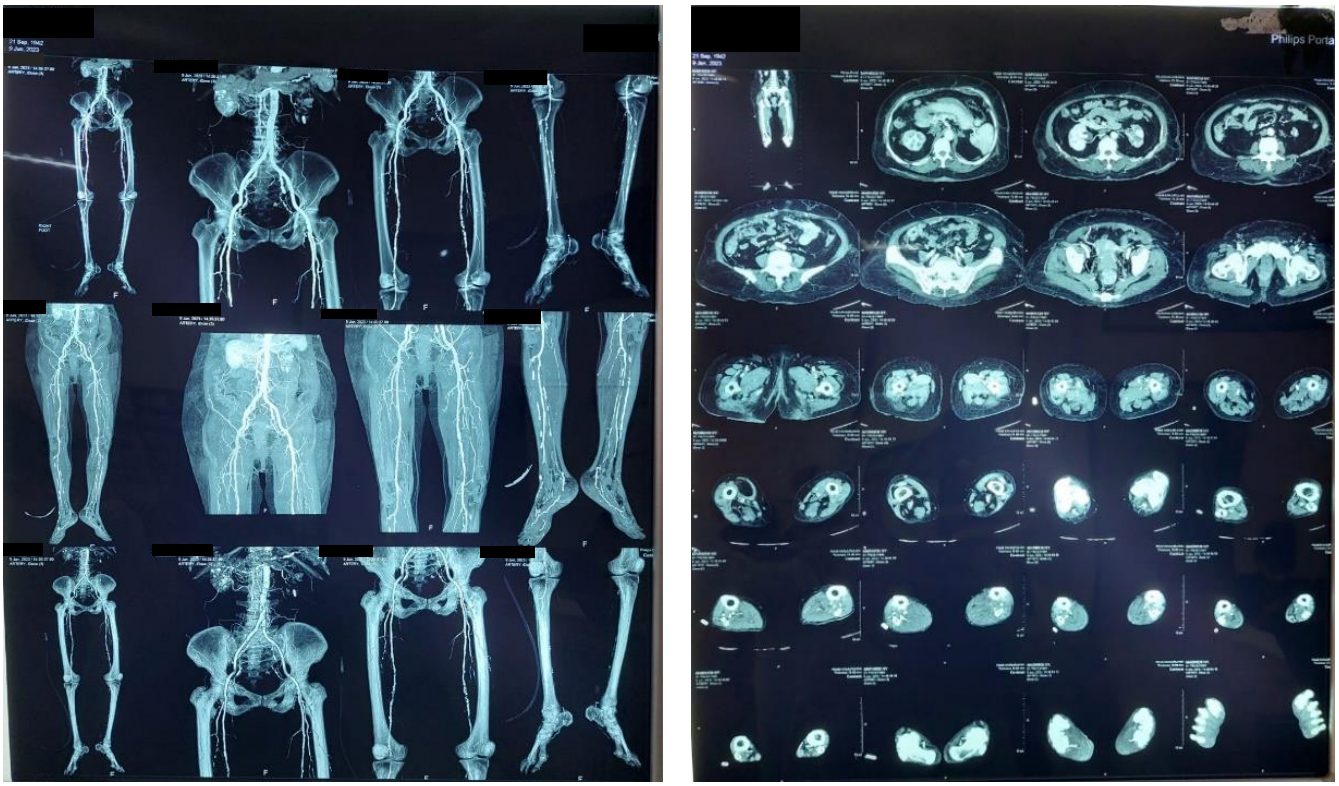

Figure 4. CT-Angiography

stenosis at right artery femoral profunda and left artery peroneal caused by calcified plaque; moderate stenosis at bilateral artery femoral superficial from 1/3 medial-distal, artery popliteal, and right artery peroneal caused by calcified plaque; mild stenosis at aorta, bilateral artery iliac communis, and artery femoral communis caused by calcified plaque; aorta sclerosis and arteriosclerosis at bilateral artery iliac, artery femoral, artery tibialis anterior, artery tibialis posterior, right artery peroneal, and left artery dorsalis-plantaris pedis; it also found a mild right hydronephrosis, left heavy hydroureteronephrosis, and bilateral multiple nephrolithiasis; and spondylosis lumbalis. After CT-angiography was performed, her creatinine level increased to 3.7 mg/dL, and her eGFR was 10.9 mL/m/1.73 m^2. She was diagnosed with CLTI in the left lower extremity Rutherford V Fontaine 3 and planned to do an angioplasty procedure with a safer contrast agent. After the angioplasty procedure, her leg pain improved, and her creatinine level didn't elevate, with a result of 2.8 mg/dL and an eGFR of 14.9 mL/m/1.73 m^2. 1 week after the procedure, her creatinine level evaluation was improved to 2.0 mg/dL, and her eGFR was 21.8 mL/m/1.73 m^2.

3. Discussion

This case report presents a chronic limb ischemia (CLI) patient with comorbid non-haemodialysis chronic kidney disease (CKD) stage V. CKD, especially end-stage renal disease (ESRD), is known as a strong risk factor for peripheral artery disease (PAD) and limb loss. Patients with CLI often have a distal pattern of arterial disease with heavily calcified arteries.[2]

In 1954, Fontaine presented the first classification scheme for the level of ischemia related to PAD, which was solely based on clinical criteria. Rutherford later developed a classification system that includes both subjective and objective data and may be used to describe both acute and chronic limb ischemia. The Wound, Ischemia, and Foot Infection (WIFI) system was recently implemented by the Society of Vascular Surgery (SVS) as a more thorough classification scheme.[6]

The majority of PAD patients are asymptomatic; however, up to 10% are thought to progress to or present with CLTI for the first time (although this estimate appears to vary greatly). The number of women with PAD is growing, and women have a tendency to develop symptoms. [7]

Diabetes, smoking, hypertension, dyslipidemia, chronic kidney disease, obesity, and a sedentary lifestyle are modifiable risk factors for PAD. Left untreated, an estimated 25% of patients have a risk of limb loss at one year. Nevertheless, developments in the management of cardiovascular risk, processes of care, and vascular and endovascular technology may be crucial. [5]

In patients with CLTI, the forefoot is often affected by ischemia and rest discomfort that is worse at night. It is commonly treated with opiate analgesics, has lasted for more than two weeks, and is generally accompanied by a hemodynamic condition of severely reduced perfusion. [9] Gangrene often develops on the forefoot, and ulceration caused byischemiac is often found on the toes.[6]

A thorough physical examination should be performed on all individuals with suspected CLTI. Lower-limb pulse palpation can aid in determining the existence and location of vascular disease. [6] It is crucial not to assess a patient with suspected CLTI while sitting in a chair with the leg hanging down, as this may lead to false assurance about foot perfusion. Some diagnostic techniques, such as ABI, TBI, TcPO2, treadmill tests, and imaging approaches (DUS, CTA, MRA, and DSA), may aid in the diagnosis of patients with suspected CLTI. [6] In all patients with suspected CLTI, AP measurement and ABI calculation are indicated as the first line of non-invasive evaluation. [9] All patients suspected of having CLTI should undergo vascular imaging to assess the presence, extent, and severity of arterial disease and to aid in revascularization decision-making. Imaging should provide comprehensive anatomic staging in patients who are planned for revascularization, utilizing, for example, the GLASS (Global Limb Anatomic Staging System).[1]

GLASS is a new approach used in peripheral artery disease (PAD) that is similar to the SYNTAX system for coronary artery disease (CAD).[2] GLASS focuses on infra-inguinal diseases that start at the origin of the superficial femoral artery (SFA). GLASS combines stages (0–4) for the femoral-popliteal and infra-popliteal in defining infra-inguinal anatomic stages (I–III). The current version of GLASS does not consider multivessel infra-popliteal (IP) revascularization due to a lack of evidence for its effectiveness. Severe calcification, especially in the tibial arteries, is a negative predictor of the success of intervention and indicates a higher risk of amputation. [1]

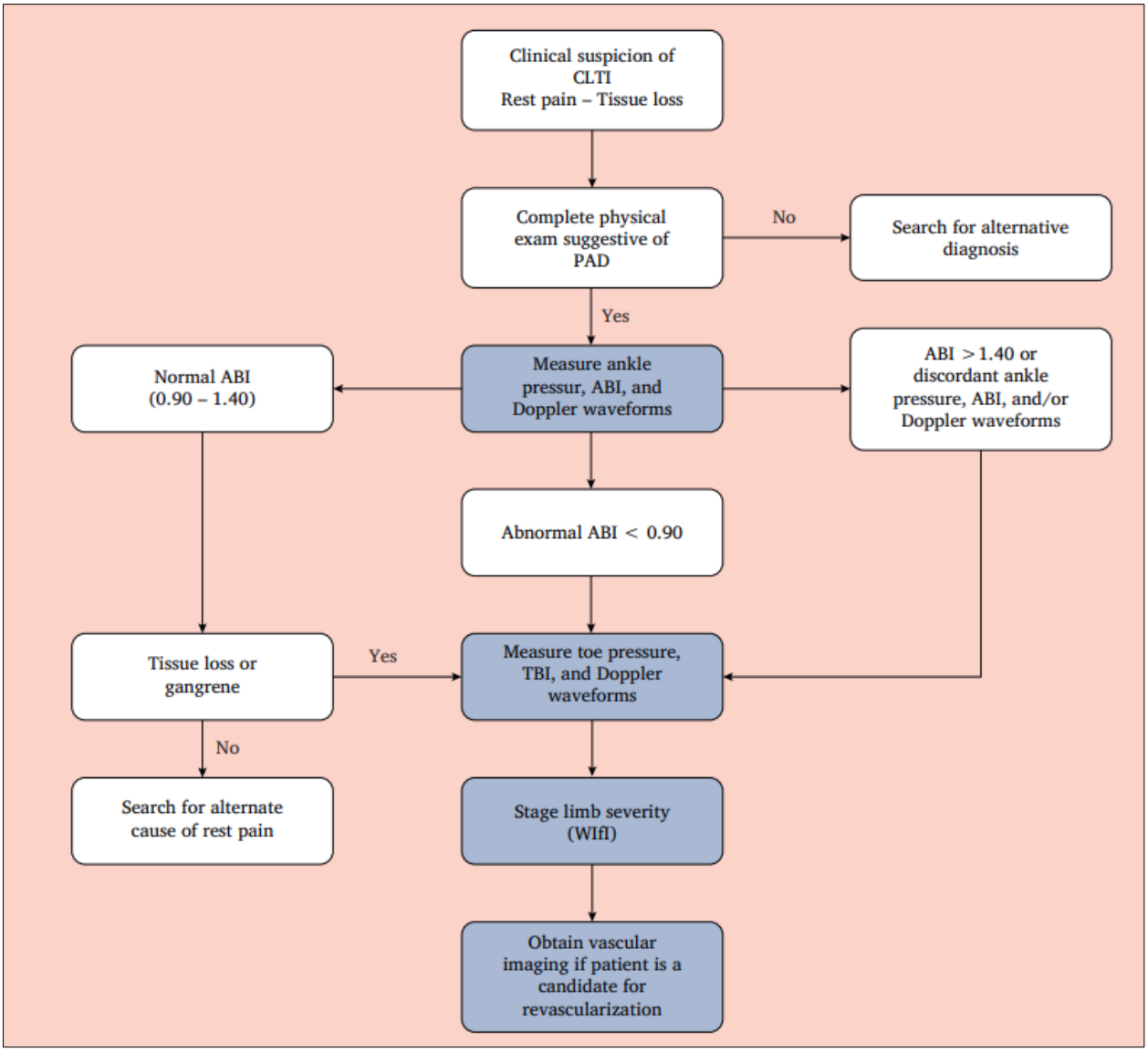

Figure 5. Flow diagram for the investigation of patients presenting with suspected chronic limb-threatening ischemia (CLTI); CLTI: chronic limb-threatening injury; PAD: peripheral artery disease; ABI: ankle brachial index; TBI: toe brachial index.[8]

The goal of CLTI treatment is to save a functional limb and to prevent cardiovascular morbidity and death through comprehensive risk factor management and the best medical therapy available. [1] Antithrombotic therapy, lipid-lowering therapy, lifestyle modification, tobacco cessation, diet and exercise, management of hypertension and diabetes, and management of pain are suggested medical therapies for patients with CLTI. [6]

Although many patients with CLI can benefit from conservative treatment, the severity of the disease may necessitate surgical intervention, including revascularization or amputation. [1] If the patient wants to undergo revascularization and is a suitable operative candidate, arteriography is frequently performed for the next evaluation and planning of revascularization.[2] To successfully restore pulsatile in-line flow to the foot in patients with chronic limb-threatening ischemia (CLTI), particularly those with tissue loss, revascularization is required. The factors that contribute to a successful anatomic outcome differ between bypass grafting and endovascular intervention. [9] Bypass surgery requires adequate inflow and outflow, as well as a suitable autologous conduit. In contrast, the success of endovascular intervention is largely determined by the complexity of atherosclerosis within the target arterial path (TAP) that provides in-line flow to the foot.[1]

Traditionally, angiography procedures utilized contrast chemicals to identify stenosis areas in the targeted artery. It generally uses iodinated contrast media; however, for patients with compromised kidney function or contrast allergies, alternate contrast materials should be considered. [3] Iodinated contrast chemicals offer high-resolution imaging, but they carry the risk of renal injury caused by rapid effects that harm the nephron, such as vasoconstriction, cell apoptosis, and oxidative stress caused by the production of reactive oxygen species. Contrast-induced nephropathy (CIN) can manifest between 24 and 72 hours after contrast injection and can be detrimental to people with preexisting renal impairment. [2]

Contrast-induced nephropathy (CIN) is an increase in the level of serum basal creatinine over 25%, or 0.5 mg/dL, within 48 hours of exposure to a contrast agent. The incidence of CIN in contrast-enhanced computed tomography (CT) is 6%, while that following peripheral angiography is 9%. However, the prevalence may be significantly higher—about >20% and >30% in several patient subsets. [10] Various conditions and factors, including low blood pressure, diabetes, chronic heart failure, being over 75 years old, anemia, a high baseline estimated glomerular filtration rate (eGFR), broad red cell distribution, elevated levels of triglycerides, creatinine, total cholesterol, HDL, LDL, BUN, and natrium, are included as risk factors for contrast-induced nephropathy (CIN). [11] Additionally, raised platelet count, international normalized ratio, blood glucose, volume of contrast medium, and the necessity for intra-arterial balloon pump therapy before imaging are also considered additional risk factors. [12] CIN can affect individuals both with and without chronic kidney disease (CKD),

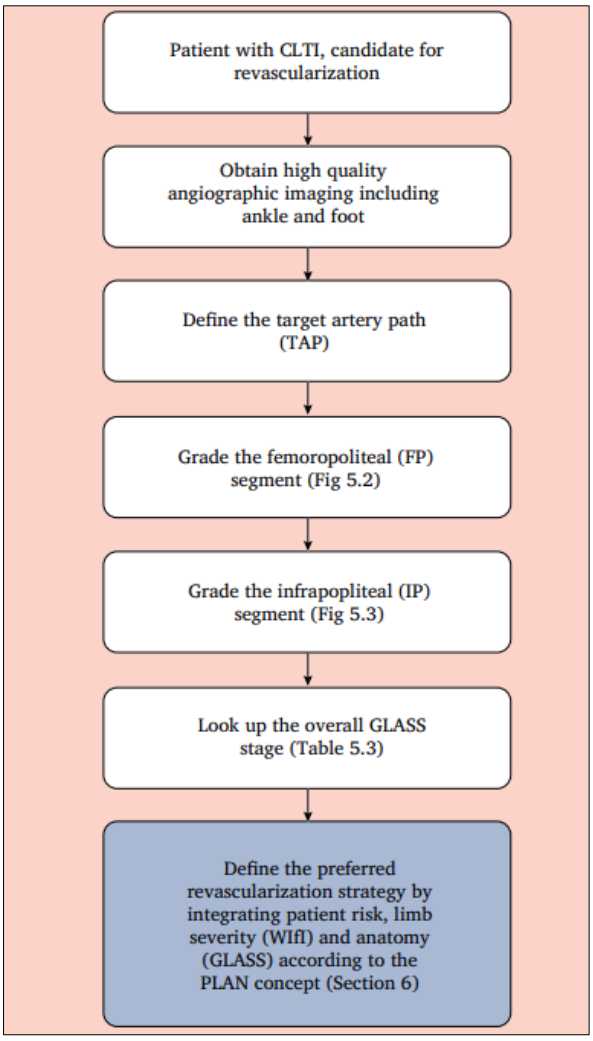

Figure 6. Flow chart illustrating application of Global Limb Anatomic Staging System (GLASS) to stage infra-inguinal disease pattern in chronic limb-threatening ischemia (CLTI); CLTI: chronic limb-threatening injury, TAP: target artery path, FP: femoropopliteal, IP: infrapopliteal, WIfI: wound, ischemic, or foot infection.[8]

but those with CKD are at a higher risk due to their decreased capacity of nephron, increasing their likelihood of CIN.[13] Consequently, it has an increased risk of long-term kidney function decline, cardiovascular events (e.g., myocardial infarct), and mortality. To avoid further kidney injury, CO_2 may be utilized as an alternative contrast agent in lower extremity vascular diagnostics and intervention, especially in patients prone to CIN. [2] CO_2 is used as a contrast agent for imaging both arterial and venous circulations. It is useful for patients with renal insufficiency or a history of hypersensitivity to iodinated contrast medium. [8]

CO_2 acts as a negative contrast agent because of its ability to absorb X-rays and its low density to a lesser extent compared to the blood vessels and vessel wall. [2] CO_2 gas is extremely floatable, allowing it to float in the vascular system, and the visceral arteries can be observed by selective injection with reflux. [4] Unlike iodine contrast, CO_2 does not dilute or mix with blood; therefore, it passes through the blood as an isolated bubble or bubbles and remains undiluted. [3] CO_2 is a non-nephrotoxic and non-allergenic contrast agent, although the quality of image in angiography alone has decreased.[10]

Gas embolism and explosive gas delivery are the two most common problems that might result from CO_2 angiography. Gas embolism is the unintentional mixing of CO_2 with air during delivery. CO_2 is extremely soluble, so it's safe and effective in the arteries and veins below the diaphragm. The blood transports dissolved CO_2 to the lungs, where it is released in one cycle of breath before reaching circulation in the coronary and cerebral regions, thus eliminating the risk of gas embolism. [14] The gas expands when CO_2 leaves the catheter, which explains the phenomenon of explosive delivery. This effect may result in an unpleasant sensation and degrade image quality.

This CO_2 contrast agent limitation can be circumvented by infusing 3 to 5 mL of CO_2 through the catheter to eliminate any fluid or blood, thereby reducing compression of gas and explosive delivery. Any movement can degrade the image quality; however, this constraint is surmountable. CO_2 angiography has minor complications such as gastrointestinal problems, lower extremities, and stomach pain. Non-occlusive mesenteric ischemia is an infrequent major complication. [10]

The use of CO_2 arteriography above the diaphragm in a patient with a cardiopulmonary shunt from left to right may cause an air embolism in the brain. Intra-arterial supradiaphragmatic injections, such as thoracic aortography, coronary arteriography, and cerebral arteriography, carry the danger of causing a cerebral gas embolism due to the air block phenomenon. The concomitant use of NO anesthetic and carbon dioxide should be avoided because the NO may permeate into the bubbles of CO_2 and cause them to become larger, resulting in a pulmonary artery vapor lock. [14] Patients with an intracardiac shunt from right to left should avoid using CO_2 in their venous circulation.Pulmonary hypertension and chronic obstructive pulmonary disease are relative contraindications for intravenous administration of CO_2 contrast agents. The use of CO_2 can increase pulmonary artery pressure and may contribute to the development of pulmonary hypertension.[10]

Advancements in CO_2 delivery and imaging technology have increased the use of CO_2 angiography as a safe alternative to iodinated contrast medium in patients with PAD and CLI, helping to preserve renal function and prevent limb amputations.[10] CO_2 angiography usage has dramatically decreased the frequency of CIN, making it possible for CKD patients to benefit from endovascular operations. [2]

4. Conclusion

Patients with CLI can benefit from conservative treatment, but some of the more severe cases may necessitate surgical intervention, including revascularization or amputation. [1] Arteriography is performed for the next evaluation and planning of revascularization.[2] Arteriography procedures utilized contrast chemicals to identify stenosis areas in the targeted artery. Iodinated contrast chemicals offer high-resolution imaging, but they carry the risk of renal injury caused by rapid effects that harm the nephron. Contrast-induced nephropathy (CIN) can manifest between 24 and 72 hours after contrast injection and can be detrimental to people with preexisting renal impairment. [2] CO2 angiography might be used as a safe alternative contrast medium in patients with CLTI, which benefits the preservation of renal function and prevents limb amputations.

5. Declaration

5.1 Ethics Approval and Consent to participate
Patient has provided written informed consent prior to involvement in the study.

5.2. Consent for publication
Not applicable.

5.3 Availibility of data and materials
Data used in our study were presented in the main text.

5.4 Competing interests
Not applicable.

5.5 Funding Source
Not applicable.

5.6 Authors contributions
Idea/concept: IVN. Design: IVN. Control/supervision: NK. Data collection/processing: IVN. Analysis/interpretation: IVN. Literature review: NK. Writing the article: IVN. Critical review: NK. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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