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Clinical Case Update

Contrast Media Considerations in the Performance of Peripheral Interventions

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Introduction

Peripheral arterial disease (PAD) affects 12% of the adult population and up to 20% of individuals 70 years or older. Its incidence is on the rise, fueled by the raging epidemic of obesity and diabetes mellitus caused by calorie-rich diets and sedentary lifestyles, combined with hypertension and failed attempts at controlling tobacco use.[1-3] Critical limb ischemia (CLI) represents the terminal stage of PAD and it manifests when the restriction to arterial blood flow is so severe that the capillary beds are unable to sustain tissue viability. In patients with diabetes, the risk of PAD is 3 to 4 fold higher and it tends to be more aggressive than in patients without diabetes with a major amputation rate 5-10 times higher. Typical infrapopliteal (IP) diabetic disease is characterized by long, multilevel disease involving all three IP vessels and the elderly (>80-years-old), diabetics, and advanced kidney disease patients tend to exhibit isolated IP disease.[4,5,6] These patients have higher risk for amputation and shorter amputation-free survival compared to those with combined femoropopliteal and IP disease.[7] It is estimated that 1.5 million patients in Europe and 2 million patients in the United States over 50 years of age manifest symptoms of CLI. Although CLI encompasses <5% of all cases of PAD, its prognosis is poor. The one-year mortality and major amputation rates range from 20%-50%.[8-10] It occurs in approximately 1%-3% of all PAD cases[11-13] with an incidence between 500-1000 persons per million per year in Europe and the US.[14-16] Many patients do not progress sequentially along predefined stages from claudication to CLI. As described in select longitudinal studies, some patients with symptomatic PAD develop CLI,[17,18] while data from other studies show that many patients are asymptomatic prior to the development of CLI.[19,20] A staggering 20%-25% of patients with CLI will undergo primary amputation, 50%-60% undergo revascularization (surgical and/or endovascular), and 25% are treated medically.[21]

CLI represents the "point of no return" in the clinical spectrum of the patient with PAD. Surgery and more recently percutaneous endovascular treatments have become the mainstay of management of patients with CLI. Unfortunately, these patients also tend to present with advanced kidney disease, which places them at increased risk of contrast-induced nephropathy (CIN) after traditional contrast-guided endovascular interventions. Due to the extensive multilevel and multivessel involvement, these patients typically require multiple procedures to achieve complete revascularization, and therefore have a repetitive exposure to nephrotoxins, heightening their risk of CIN and adverse outcomes. The utilization of risk assessment tools, as well as preventive strategies, such as the use of hydration and pharmacological agents, have been extensively covered in previous editions of this supplement.[22] The present clinical case update will reflect over the status of adjunctive strategies particularly used in the field of peripheral interventions, as these procedures are typically longer and require larger amounts of contrast than the more largely explored cardiac diagnostic and therapeutic procedures.

Prevention of Contrast-Induced Nephropathy

The most effective preventive strategy for CIN, regardless of the vascular bed being studied, continues to be the reduction in the volume of contrast media.[23] The amount of iodinated contrast (IC) that can be safely administered to patients with baseline chronic kidney disease (CKD) in order to prevent CIN is not known. Cigarroa et al used an empirical formula where the amount of contrast was calculated by multiplying 5 (cc) x body weight (kg) divided by serum creatinine (mg/dL).[24] More recently, strategies focused on limiting the amount of contrast to a maximum of 3 times the calculated creatinine clearance were proposed.[25] Alternative strategies to contrast material have been long sought. In the 1970s, Hawkins pioneered the intra-arterial use of carbon

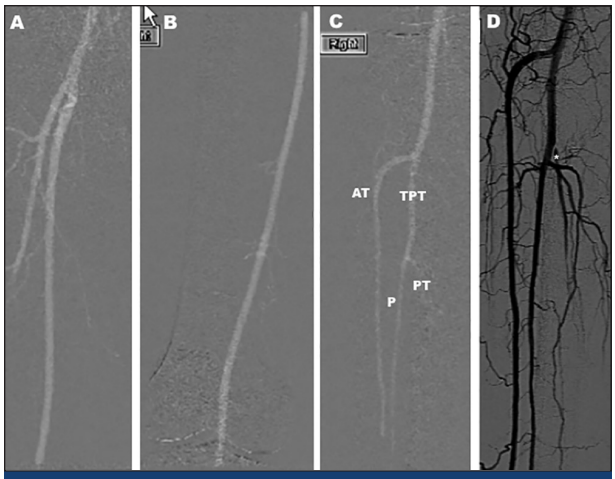

Figure 1. CO_2 angiography in peripheral interventions: common femoral bifurcation into the superficial and deep femoral arteries (A); superficial femoral artery and P1, P2 segments of the popliteal (B). Below-the-knee popliteal artery, anterior tibial (AT), tibioperoneal trunk (TPT), and peroneal (P) are clearly seen. The PT is not well visualized (PT) (C). Tibial vessels are clearly seen with iodinated contrast. Notice PT (*) (D).

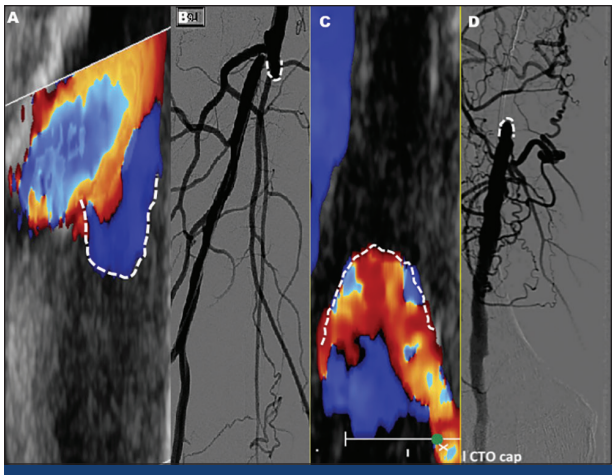

Figure 2. CTO cap analysis can provide operators with pre-procedural information that can aid in determining the interventional strategy. Figure 2 shows the proximal antegrade concave cap in DUS and angiography. This is typically seen in ostial/proximal SFA CTOs (A,B). DUS and angiographic depictions of the distal retrograde concave cap, which is typically seen in the distal reconstitution point of long SFA CTOs, are also shown (C,D). In this case, the ideal approach would be to start at once with antegrade-retrograde combined access and intervention.

dioxide (CO_2) in high-risk patients who were allergic to IC and in those with renal insufficiency.[26] CO_2 is particularly useful in the treatment of atherosclerotic renal artery stenosis and infrarenal abdominal aortic aneurysms.[27,28]

Although CO_2 angiography is a safe and efficacious method for the evaluation of PAD, its use in the evaluation and treatment of PAD has not gained a substantial following. Whether CO_2 angiography-guided endovascular therapy (EVT) can be extended to a broader group of patients is uncertain. Moreover, no prospective study to date has proven the efficacy and safety of CO_2 angiography-guided EVT. CO_2 has no known inherent nephrotoxicity, which renders it a desirable agent for evaluating patients with renal dysfunction.[29-32] In patients with CLI and renal compromise, it presents advantages and disadvantages. Due to its high diffusion capacity (20 times more soluble than oxygen), CO_2 is rapidly eliminated by the lungs during the first pass.[31] However, this same property makes it diffuse rapidly into small collaterals and capillaries located around chronic total occlusion (CTO) caps, limiting visualization in these areas. Due to the low viscosity of CO_2 (400 times less than IC),[33] smaller angiographic catheters may be used, allowing for visualization of distal (including pedal) arterial beds. The visualization during CO_2 injection is secondary to the displacement of the column of blood by the gas, which then acts as a negative contrast agent. The quality and accuracy of the image will depend on the amount of blood displaced by the CO_2. The difficulty sometimes lies in larger vessels where a higher volume of CO_2 is required to displace the column of blood. Furthermore, once the total volume of blood has been displaced, using a higher volume of CO_2 does not improve the vascular image.

CO_2 Properties, Dosing, and Technique

In order to use CO_2 appropriately and safely, a basic knowledge of its properties is essential. CO_2 is a nontoxic, buoyant, and compressible gas that is produced endogenously as a natural byproduct at a rate of approximately 200 to 250 cc per minute.[34] It is transported in the bloodstream to the lungs by three mechanisms: predominantly carried as a bicarbonate ion (83%), bound to hemoglobin (10%), or dissolved in blood (7%). There is no concern for allergy or renal toxicity because CO_2 is present endogenously, which has been confirmed by numerous animal and human studies.[26,35] When CO_2 is injected, it has the potential to fragment into random bubbles depending on how it is delivered. In an attempt to avoid this, the catheter should be purged prior to definitive delivery and a continuous, controlled delivery of the volume of choice should be performed. Although trapping is exceedingly rare, it can be exacerbated by the rapid administration of excessive volumes of CO_2. An excessive volume can be caused by one exceptionally large injection (rare) or by multiple small and repetitive deliveries without allowing enough time between injections (30 to 60 seconds) for the CO_2

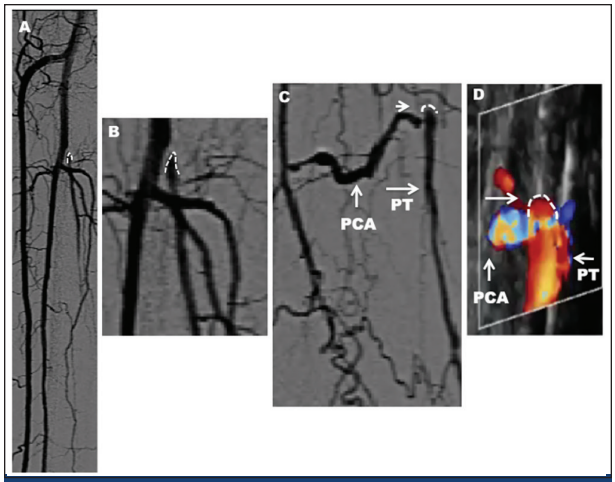

Figure 3. This figure explores angiographic and ultrasound generated CTO cap analysis and iodinated contrast imaging of the tibial vessels. Notice the retrograde concave morphology of the proximal CTO cap in the PT (white dotted line) (A). Amplified image shows the retrograde concave morphology of the proximal cap in the PT (B). Amplified image shows the distal reconstitution of the PT at the level of the ankle via the posterior communicating artery (PCA) (C). Notice the retrograde concave cap of the PT and corresponding reconstitution of the distal PT via the PCA, as seen with EVUS (D).

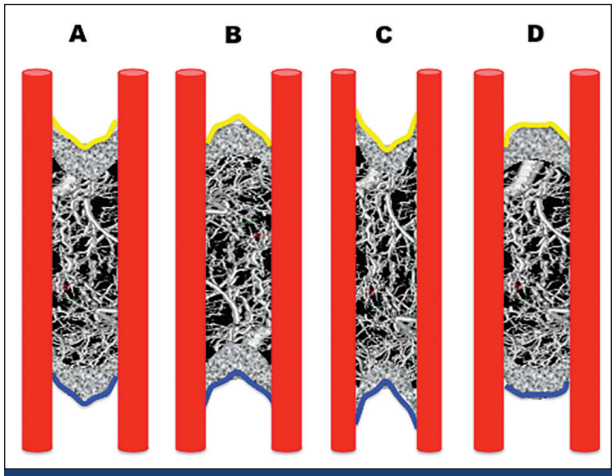

Figure 4. Most commonly found cap combinations: yellow lines denote the antegrade surface of the proximal cap and blue lines represent the retrograde surface of the distal caps. Proximal and distal cap are antegrade concave, thus the best approach is antegrade (A). The proximal cap is antegrade convex, but it has a concave configuration if approached from retrograde access. Given retrograde concavity of the distal cap, the best approach would be retrograde (B). The proximal cap is antegrade concave and the distal antegrade convex (retrograde concave). This is one of the most commonly found cap combinations. In this case the best approach is to start with antegrade-retrograde combined access (C). Antegrade convex proximal cap and retrograde convex distal cap represents the most complex type of CTO and the best approach is combined antegrade-retrograde access. Even then, this type of lesion will require a significant amount of work and likely the need to use reentry tools (D).

to dissolve. Studies looking at CO_2 dosing concluded that a single dose up to 1.6 cc/Kg results in no changes in cardiopulmonary parameters.[36] This dose can subsequently be repeated after 30 to 60 seconds. This amounts to a single dose of 112 cc for a 70-Kg person, which is more than enough to fulfill imaging in any clinical scenario. Due to the tendency of CO_2 to reflux (travel cranially), it is prudent to avoid intra-arterial injections above the diaphragm. Similarly, to reduce the possibility of central cerebral reflux the patient can be placed in the Trendelenburg position. In fact, it is good practice to refrain from arterial delivery of CO_2 if the patient's head is elevated.

Other clinical scenarios that theoretically predispose a patient to untoward embolization include right-to-left shunts and the combination of pulmonary artery hypertension and a patent foramen ovale.[37] An additional rare contraindication is the use of nitrous oxide general anesthesia when using intravenous CO_2, given the potential for nitrogen to diffuse into the CO_2 bubble, causing it to be 5-6 times more occlusive. This potential scenario arises in transjugular intrahepatic portosystemic shunt (TIPS) patients.[37]

A recurrent concern for novice operators is the use of CO_2 in patients with chronic obstructive pulmonary disease (COPD). As a precautionary measure in COPD patients, clinicians should allow more time between injections (2 minutes) to ensure definitive dissolution.

CO_2 in Peripheral Angiography

Several studies have reported the use of CO_2 as an adequate alternative to IC agents in supragenicular vessels, but the diagnostic accuracy to image below-the-knee (BTK) vessels drops by about 50%.[38-40] In a study by Rolland et al, the imaging quality of CO_2 angiography was comparable to IC at the pelvis in 93% and at the thigh in 74% of 120 arteries studied.[40] The same quality was achieved distally in only half of the cases. Oliva et al found no significant differences in the mean stenosis values obtained with CO_2 or IC in any segment for any of the observers.[38] However, imaging of BTK vessels using CO_2 has not shown such favorable results (Figure 1).[41-43]

Several reasons have been postulated to explain this phenomenon:

1. Presence of proximal/inflow CTOs causes slow distal flow and poor filling of the tibial vessels.
2. Aortic injection of CO_2 leads to fragmentation of the CO_2 column by the time it arrives to the tibial arteries, which degrades the image quality.

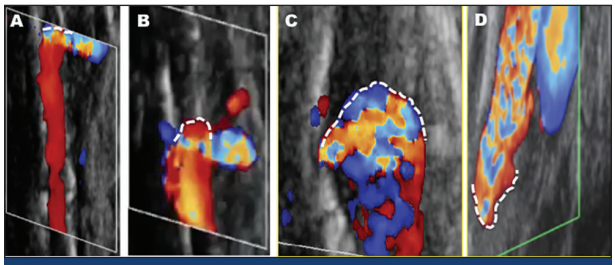

Figure 5. Still frame of a distal CTO cap in the posterior tibial looks like a flat cap (A). The same vessel interrogated during systole shows a retrograde concavity (dotted line) (B). Another example of an antegrade convex (retrograde concave) CTO cap (C). Antegrade concave (retrograde convex) CTO cap (D).

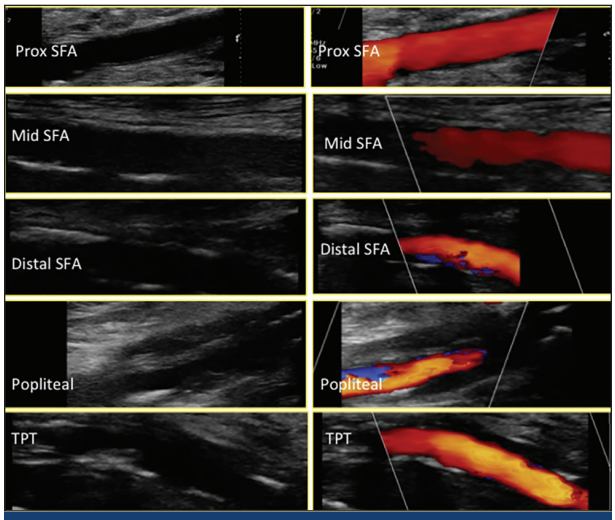

Figure 6. Post-PVI EVUS and duplex shows intact flow in the multilevel target vessels that were treated with flow all the way down to the tibial arteries.

3. Hand injection of CO_2 using 20 or 60 cc syringes: Because CO_2 is loaded under pressure from CO_2 cylinders, these syringes contain indeterminate amounts of CO_2.
4. In contrast to liquid injections, in which the rate of delivery remains constant, the rate of CO_2 delivery increases exponentially toward the end of injection, resulting in inconsistent CO_2 delivery and thus poor vessel filling.[31]

In order to overcome these nuances, it is recommended to proceed with selective and/or suprase-lective CO_2 angiography, which is achieved by advancing the tip of the catheter as close as possible to the target vessel to be imaged. Then, the operator should attempt to deliver the CO_2 injection at a constant rate, avoiding the natural tendency to accelerate the injection towards the end, when there is less gas left in the syringe and therefore less pressure opposing the force applied by the operator. In patients with CLI who do have proximal CTOs, CO_2 can be utilized in combination with IC to minimize the final amount of IC used during the case. In patients with multilevel disease the operator should proceed with staged interventions, even if CO_2 is the agent of choice. Large volumes of CO_2 injections are needed to guide interventions in long SFA CTOs and these have been associated with increased complication rates, mainly as a consequence of CO_2 trapping in the mesenteric arteries. One of the speculations is that large volumes of CO_2 used in long procedures may be coupled with injections that are performed too close to each other, not allowing the lungs enough time to eliminate the gas. In the infrapopliteal space, tibial and pedal CTOs require the use of several modalities including IC, CO_2, and ultrasound, as CO_2 alone is limited in its usefulness due to its tendency to rapidly diffuse into the small capillaries located around areas of total occlusions.

Extravascular Ultrasound (EVUS)

In our lab, we have also used CO_2 in combination with EVUS to enhance the diagnostic accuracy of imaging and to guide interventions. The use of EVUS allows the operator to maneuver wires and interventional devices while significantly decreasing the amount of IC and radiation that are utilized. In selected cases, CO_2 is visualized with EVUS as bubbles going across areas of stenosis, identifying the lumen, which allows the operator to carry diagnostic and therapeutic procedures without virtually using IC. While it is unlikely to completely eliminate the use of IC during endovascular procedures in patients with CLI, the combination of these modalities can definitely decrease the use of IC as well as the radiation exposure for both the patient and the staff performing the intervention.

Historically, EVUS has been used as part of the non-invasive evaluation of patients with PAD in the form of high-frequency duplex ultrasound. As the challenges of complex CLI therapy have increased, EVUS has emerged as an imaging modality that allows guidance for arterial access and endovascular interventions in CLI patients. In recent years the initial presentation of the CLI patient has become more complex, as they present with a more advanced stage of the disease and with more comorbidities, many times requiring the use of exotic arterial access (arterial punctures other than the traditional retrograde common femoral artery approach) in order to efficiently perform CLI interventions. The most commonly used alternative access in CLI patients is the retrograde tibial-pedal access. EVUS has been shown to represent a feasible and safe strategy that can aid

in accessing vascular conduits in CLI patients[44] as well as in guiding the intervention.

EVUS-guided Peripheral Vascular Interventions

CTO Cap Analysis

EVUS provides the operator with the unique ability to visualize CTO caps by showing the heterogeneity and morphology of the CTO cap. This part of the procedure is essential as it helps guide therapeutic decisions, such as which access to attempt and which type of CTO crossing devices to utilize. The characterization of the CTO cap morphology by both angiography and EVUS allows the operators to predict the need for an alternative access (Figure 2). In this example, the lesion has a calcified proximal cap with concave morphology (when approached in traditional antegrade fashion), while the distal cap is antegrade convex (or concave, if it were approached from a retrograde tibial access point). Attempting to cross this lesion from a traditional antegrade approach will likely result in the deflection of crossing tools towards the arterial wall and subintimal plane as the devices approach the distal cap. In lesions where both proximal and distal caps are aligned with a retrograde concave morphology, the use of a support catheter and wire from a retrograde approach increases the likelihood of successful intraluminal crossing as the lesion is being approached from its concave side (Figure 3). Likewise, if both caps have an antegrade concavity, approaching the lesion from the traditional approach should prove successful without the need to obtain tibial access. Figure 4 shows the most frequently seen combinations of CTO caps, and the recommended approaches.

Direct Visualization of Interventional Devices

Every maneuver performed during complex CTO crossing is based on the direct, live, visual feedback provided by EVUS, which continuously tracks the progress of the crossing tools across the CTO caps and through the true lumen without the need to use IC or radiation. The ability to cross the caps and remain in the true lumen increases the number of options available to adequately complete the intervention. In CTOs with densely calcified caps, atherectomy devices can be utilized with EVUS guidance to extensively modify the plaque while directly observing the device coming in contact with the vessel wall and staying within the confines of the lumen. Once the CTO is crossed, the intervention is completed with 2 EVUS-guided steps. The first is EVUS analysis of the vessel diameter (allowing accurate selection of balloon and stent sizes) and guidance of low-pressure balloon inflation. This provides the most accurate feedback of balloon to vessel diameter ratio and decreases the likelihood of barotrauma and unwanted complications. Then, we perform EVUS-guided interrogation of hemodynamic parameters in order to determine if the results are physiologically optimal, in order to conclude the case.

EVUS-guided Lesion Crossing

Understanding the alignment of the proximal and distal CTO caps is crucial, and this information is made readily available to the interventionist with the use of intraprocedural EVUS. The caps may have conflicting alignments (proximal cap is antegrade concave and the distal is antegrade convex) if addressed from the traditional antegrade approach, or may be aligned in such a way that pre-planned retrograde tibial-pedal access should be the chosen strategy (if both caps are retrograde concave, for example) (Figure 3).

The use of live color Doppler video loops at sites of occlusion and reconstitution allows performance of the CTO cap analysis. Still frames at these locations are avoided since the particular frame chosen may be taken during diastole, providing the image with a "flat" appearance, which does not necessarily reflect the true configuration of the cap and would mislead the operator because "flat caps" are generally associated with low flow collaterals (which are a marker of highly complex CTO caps), increased risk of subintimal penetration, complications, and poorer long-term outcomes (Figure 5). Once the concavity of the caps is determined, the interventional strategy is planned. EVUS allows direct hemodynamic evaluation of the result of an intervention without the need to use further radiation and contrast. If flow and velocities have corrected and there is no evidence of complications, the procedure is concluded (Figure 6).

Conclusion

The current status of diagnostic and therapeutic procedures performed in patients with PAD and CLI requires knowledge and experience with a vast variety of techniques in order to improve outcomes and minimize complications. Beyond the usual hydration and pharmacological strategies (which still lack strong support from properly collected, randomized, prospective studies), minimization of contrast volume is by far the one proven method to decrease the incidence of CIN. The use of adjunctive modalities, such as CO_2 angiography and EVUS (alone or in combination), have allowed us to perform highly complex revascularization procedures in patients with CLI using negligible amounts of IC, even in patients with CKD stages 4 and 5.

The use of EVUS to guide endovascular interventions in CLI patients represents a contemporary adaptation of a pre-existing tool in response to unmet needs in the field. This adjunctive modality allows direct arterial visualization during percutaneous access and interventions, identification of CTO caps configuration, advancement of CTO crossing tools and atherectomy devices, as well as adequate choice of balloons and stent sizes. Its use facilitates the successful treatment of complex lesions with less overall use of radiation and contrast (of particular importance given the lengthy nature of these complex procedures and the prevalence of underlying kidney disease among CLI patients). CO_2 angiography should become part of the interventionist's toolbox and its potential combined use with other modalities should amplify the number of patients we may be able to help while minimizing risks and untoward outcomes. It is important to gain experience in its use and to be knowledgeable about its limitations and potential complications. The simultaneous use of contrast-sparing techniques with evidence-based strategies to prevent CIN should allow us to efficiently treat the ever-expanding group of patients with CLI and renal insufficiency.

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Overview
This is an enduring activity based on a Journal article entitled, "Contrast Media Considerations in the Performance of Peripheral Interventions." Critical limb ischemia patients typically require multiple procedures to achieve complete revascularization and are more susceptible to contrast-induced nephropathy as a result of repetitive exposure to nephrotoxins. This clinical case update will reflect on the status of adjunctive strategies used in the field of peripheral interventions, as these procedures are typically longer and require larger amounts of contrast than the more largely explored cardiac diagnostic and therapeutic procedures.

Continuing Education Credits
The CE provider, The Center of Excellence In Education (CEE), is an organization devoted to meeting the educational needs of all levels of healthcare professionals. This educational activity has been planned in accordance with the California Board of Registered Nursing requirements for nursing education for ONE (1) hour of CE Credit.

Physician Assistants (PAs) can submit this module for Category 2 CME for practice-related activities and self-directed activities per National Commission on Certification of the Physician Assistants (NCCPA).

Documentation of awarded credit is provided for licensed registered learners in exchange for completed post test and activity evaluations included in the module.

Target Audience
This activity is designed for Physician Assistant, Nurses, Nurse Practitioners and Allied Healthcare Practitioners and other health care professionals with a special interest in the field of interventional and vascular medicine.

Needs Statement
CEE assesses the educational need for Continuing Medical Education activities through review of the latest evidence-based data and science.

Activity Goals
The goal of this activity is to improve knowledge and competence by the target audience implementing the evidence-based CIN protocols with the intent of improving patient care.

Learning Objectives/Outcomes
By the end of this article, participants should be able to:

1. Define the relationship between peripheral artery disease and chronic kidney disease and how the latter in many instances can worsen the patient's prognosis by not only interfering with therapeutic options but also acting as a compounding risk factor.
2. Demonstrate that the reduction in the total volume of contrast is by far the most effective protective strategy against the development of contrast-induced nephropathy after interventional procedures in patients with peripheral artery disease.
3. Apply the use of formulas to determine the maximal amount of contrast that a patient undergoing a diagnostic or therapeutic invasive procedure should receive in order to minimize their risk of suffering from nephrotoxic effects of contrast agents.
4. Describe alternative techniques to decrease the amount of contrast utilized in invasive diagnostic and therapeutic procedures performed in patients with peripheral arterial disease, such as the use of carbon dioxide and ultrasound-guided peripheral interventions.

Policy
It is the policy of The Center of Excellence in Education to ensure balance, independence, objectivity, and scientific rigor in all of its sponsored educational activities. Commercial support from industry does not influence educational content, faculty selection, and/or faculty presentations, and does not compromise the scientific integrity of the educational activity.

Discussion of off-label product usage and/or off-label product use during cases is made at the sole discretion of the faculty. Off-label product discussion and usage are not endorsed by The Center of Excellence in Education.

Disclosure
Authors, faculty and planners participating in continuing education activities sponsored by The Center of Excellence in Education disclose if they have a relationship with a commercial interest and no conflicts of interest have been identified.

Media Used
Print and online resources are used to complete this activity.

Successful completion of this activity requires a completed post-test and evaluation. You will then print your CE Certificate from the website.

For any CE related inquiry, please contact donnaconrad@shasta.com.

Activity Sponsorship
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Activity Support
This activity is supported by educational funding from Bracco Diagnostics.

Estimated Time for Completion
The maximum time associated for this module conducted is approximately 60 minutes. Participants may only claim CE credits through a completed exam and evaluation form.

Disclaimer
This article does not endorse any commercial products.

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