Cone-Beam CT and Advanced Perfusion in CLI Interventions

Objectively measuring tissue perfusion at the site of tissue loss using two- and three-dimensional techniques.

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Critical limb ischemia (CLI) is a global challenge with increasing incidence and high prevalence among patients with diabetes.[1] Foot ulceration is a common precursor to limb amputation and is often the result of macrovascular and microvascular complications of diabetes, such as accelerated atherosclerosis, sensory neuropathy, and autonomic and proprioceptive alterations.[2] To avoid amputation, rapid and effective revascularization is recommended. With current endovascular revascularization techniques, an endovascular-first approach has been supported in the most recent TASC Steering Committee guidelines.[3] There is evidence that direct revascularization of the wound-related artery utilizing the angiosome concept is preferred over indirect revascularization; however, this has been subject to debate.[4] Unfortunately, despite the best revascularization techniques, some patients' wounds fail to heal and progress to amputation, likely because the diabetic foot complications in these patients are related to microcirculatory perfusion alterations rather than macrocirculation defects.[5]

There are important questions that endovascular specialists need to consider when planning an intervention for CLI:

- Is macrovascular revascularization likely to improve wound healing?
- If so, should an angiosome-based revascularization strategy of the wound-related artery be used?
- Should multiple tibial and pedal arteries be revascularized?
- When is revascularization adequate to provide wound healing?

To effectively answer these questions, it would be ideal to measure tissue perfusion at the site of the tissue loss, preferably before and after revascularization. Noninvasive objective measures of tissue perfusion include toe blood pressure, transcutaneous oxygen tension,[6] and skin perfusion pressure, but these may be difficult to measure during the CLI intervention.[7] Perfusion CT has become an established technique in the diagnosis of cerebral ischemia[8] and oncologic applications, particularly in the liver. Qualitative and quantitative evaluation of parenchymal perfusion by generating maps of blood volume, blood flow, mean transit time, and permeability surface are possible. Foot CT perfusion before and after revascularization has been shown to be feasible and has demonstrated an objective improvement in mean transit time.[9] With the advent of cone-beam CT to modern angiography units, we have the opportunity to evaluate CT perfusion during CLI interventions.[10]

ANGIOGRAPHY-BASED PERFUSION TECHNIQUES

There are two main options for angiography-based perfusion during CLI intervention: two-dimensional (2D) and three-dimensional (3D) techniques. Two-dimensional CT perfusion (termed *perfusion angiography*) has been most widely used[11,12] and utilizes a postprocessing software algorithm that does not require additional digital subtraction angiography for analysis. Digital subtraction angiography of the foot is usually acquired in the lateral projection (Figure 1) with numeric density values allowing calculation of time to peak, peak density value, and area under the (time-density) curve using 2D perfusion-enabled angiographic software. It is important to have a catheter in the same position before and after revascularization (typically the popliteal artery) with an identical contrast injection volume and rate (eg, 20 mL of diluted contrast at 3 mL/s). Although misregistration artifacts

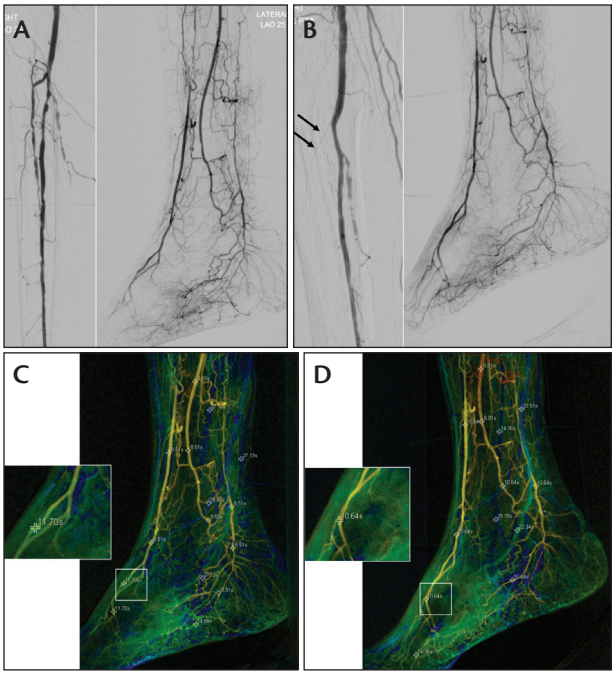

Figure 1. Two-dimensional cone-beam CT perfusion in a 76-year-old woman who presented with a great toe ulcer. Preliminary angiography demonstrated an extensive occlusion of the proximal and mid-anterior tibial artery. There also was high-grade stenosis of the tibioperoneal artery with a good-quality peroneal artery below it, providing collaterals to reconstitute arteries to the foot, including the distal anterior tibial artery (A). The tibioperoneal trunk stenosis was revascularized with a drug-eluting stent, providing indirect revascularization. An attempt to reconstruct the anterior tibial artery (direct revascularization) resulted in occlusion of the proximal segment (arrows), but the distally reconstituted anterior tibial artery was not changed (B). Baseline 2D CT perfusion angiography using i-Flow software (Siemens AG Healthcare). The numbers assigned to each artery represent the time to arrival of contrast after contrast injection via a catheter in the popliteal artery prior to revascularization. Note the time to arrival in the dorsalis pedis artery was measured at 11.7 seconds (C). Two-dimensional CT perfusion angiography after revascularization. The time to arrival of contrast in the dorsalis pedis artery decreased to 10.6 seconds. The great toe ulcer healed within 6 weeks following revascularization (D).

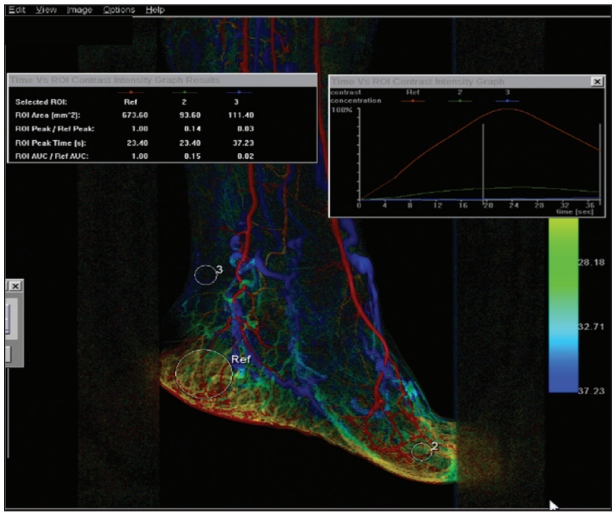

Figure 2. Two-dimensional CT perfusion study used to calculate optimum imaging delay for a 3D perfusion study. Note the plateau of tissue contrast concentration in the measured ROI between 20 and 24 seconds. Based on this study, an injection delay for the 3D perfusion study of 20 seconds was selected.

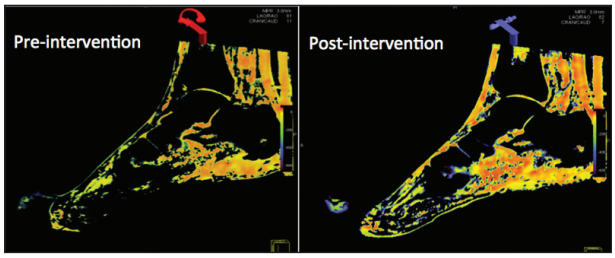

Figure 3. Three-dimensional CT perfusion in an 82-year-old patient with a plantar foot ulcer before and after successful posterior tibial artery revascularization. Note the improved perfusion demonstrated as increased color signal intensity.

due to patient motion may be problematic, studies have shown improved perfusion parameters after successful macrovascular revascularization in the majority of cases.[11,12] A smaller number of cases have shown no improvement in perfusion despite successful macrovascular revascularization, suggesting that these patients have dominant microvascular disease as a cause of their tissue loss.[11,12] Recently, Reekers et al evaluated the possibility of pharmacologic stimulation of foot microcirculation via a locally administered competitive α-adrenergic receptor antagonist (tolazoline).[13] Perfusion angiography was performed before and after administration of tolazoline to test and quantify a capillary resistance index, a parameter for the remaining functionality (reserve capacity) of the microcirculation in CLI patients.

There has been much less experience with 3D perfusion angiography in CLI patients. Although this technique is technically more challenging, it provides a method of directly measuring volumes of normal and ischemic tissue before and after revascularization. This technique has been evaluated in a collaborative project between Auckland Hospital and Siemens Medical. In

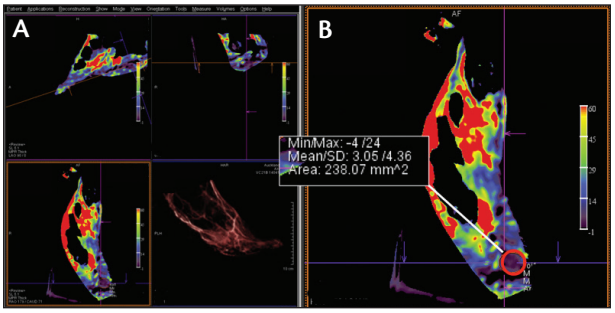

Figure 4. Three-dimensional CT perfusion study of a 78-year-old patient with a heel ulcer prior to revascularization. The workstation allows active scrolling through the 3D data set in axial, coronal, and sagittal planes (A). An ROI measurement of the soft tissues of the heel provides a mean parenchymal blood volume of 3.05 mL of blood per 1,000 mL of tissue (B).

the initial phase of the study, imaging and reconstruction parameters were optimized. In all cases, contrast was injected via a 5-F straight catheter in the ipsilateral popliteal artery before and after the intervention. Iodixanol (Visipaque, GE Healthcare), an iso-osmolar, nonionic dimer was the contrast agent used, as this produces minimal thermal sensation and is less likely to provoke patient motion. Contrast was diluted 50:50 with normal saline, and 20 mL was injected at 3 mL/s for all cases. The foot was immobilized in a radiolucent foam support to minimize motion. The optimum imaging delay after contrast injection was calculated using a 2D perfusion angiogram (Figure 2). The 3D parenchymal blood volume study was acquired at a "steady state" of tissue perfusion. The 3D perfusion angiogram involves rotational angiography, typically a 6-second acquisition with a 28-cm field of view. The 3D data sets are color displayed for perfusion signal intensity (Figure 3). Region-of-interest (ROI) measurements can be placed on normal and ischemic tissue before and after revascularization. Parenchymal blood volume is measured and represents the volume of blood (mL) divided by 1,000 mL of tissue (Figure 4).

To date, 35 CLI patients have been evaluated with 3D perfusion angiography before and after endovascular treatment. In 25 (71%) patients, perfusion angiography demonstrated improved perfusion of tissue in the wound-related angiosome after revascularization (Figure 5). Interestingly, 23 (92%) of these patients had complete wound healing by 3 months. Of the remaining patients, three cases were revascularization failures in that the tibial disease was unable to be crossed with a guidewire and treated. However, seven (20%) patients were successfully revascularized

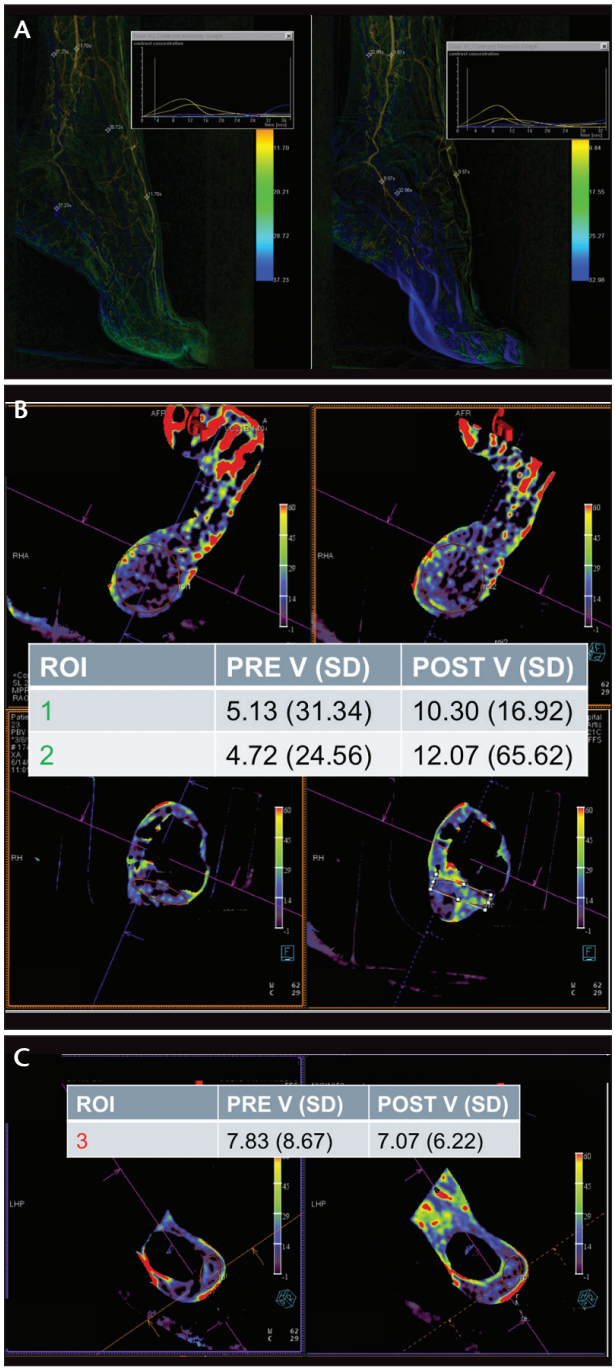

Figure 5. Three-dimensional CT perfusion study of a 68-year-old patient with significant tissue loss overlying the Achilles tendon. Two-dimensional CT perfusion angiography before and after revascularization demonstrated improvement in time to arrival of contrast after treatment (A). Three-dimensional CT perfusion angiography confirmed improved tissue perfusion in several areas of the heel (B). An area over the Achilles tendon did not show improved perfusion. This ulcer had not completely healed by 3 months (C).

but did not have improved tissue perfusion in the wound-related angiosome. Although there are possible technical contributors for this, the findings suggest a dominant microvascular cause pathology for the tissue loss in these cases. At 3 months, only three (43%) of these patients had complete wound healing.

The 3D perfusion technique is still evolving, and there are outstanding technical challenges to overcome. For example, ROI samples that include bone or large vessels can produce spurious results. The value of pharmacologic stimulation with 3D perfusion angiography also requires evaluation. It is also unclear what tissue perfusion threshold is required to facilitate wound healing. Despite these reservations, initial experience suggests this technique holds promise in guiding endovascular therapy during CLI interventions.

CONCLUSION

The aim for intervention for CLI is to provide improved perfusion to the wound-related tissues. In this regard, a technique to objectively measure tissue perfusion during the intervention would be of considerable benefit. Cone-beam CT perfusion angiography holds promise but is still undergoing evaluation and development. Both 2D and 3D techniques have merit and may ultimately be complementary techniques. ■

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Disclosures: None.