Enhancing Limb Salvage in Critical Limb-Threatening Ischemia

Pedal arch assessment and intervention are a promising step forward.

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Introduction

It is estimated that 237 million people throughout the world and more than 20 million people in the United States suffer from peripheral arterial disease (PAD). This is a significant cause of both the loss of life and loss of limb.[1,2] Peripheral arterial disease is an occlusive disease resulting from atherosclerosis that typically affects the lower extremities, increasing susceptibility to lower extremity amputation and other detrimental cardiovascular pathology.[3]

Critical limb-threatening ischemia (CLTI) is the most advanced and severe form of PAD, characterized by the advanced obstruction of peripheral arteries, progressing to severe pain and ulcerations. Critical limb-threatening ischemia is a major risk factor for lower extremity amputation, with an estimated 30% of patients requiring major lower limb amputation after one year and a 60% mortality rate within five years of diagnosis.[4,5] The severity of the disease and its progression emphasize the importance of quick and proper diagnosis and treatment.

Further adding to the prevalence and devastation of PAD are the rising rates of diabetes mellitus (DM) worldwide. In fact, DM is the eighth leading cause of disease in the world, affecting roughly 537 million people, a number expected to rise to 643 million by 2030 and 783 million by 2045.[6-8] Diabetes Mellitus is a chronic disorder attributed to the body's inability to respond to or produce insulin, resulting in carbohydrate metabolic dysfunction. Chronic insulin resistance progresses to abnormal blood and urine glucose levels, which can precipitate cardiovascular issues such as PAD.

Patients with chronic diabetic foot ulcers (DFUs) commonly suffer from PAD because the underlying etiology of uncontrolled DM can further occlude arteries and exacerbate the severity of PAD. These wounds are typically among the most difficult to heal because of the compromised blood supply being unable to provide sufficient healing factors. The combination of PAD and the loss of protective threshold seen in diabetic peripheral neuropathy puts these patients at the most severe risk of lower extremity amputation.

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Due to the detrimental nature of PAD and its numerous complications, especially in those with DM, a thorough assessment of severity and risk factors is necessary. Fortunately, numerous tools are available to assist in this, including those used to help determine the need for revascularization, such as the WIFI classification system, and those used to help plan revascularization procedures, such as the angiosome concept and, more recently, pedal arch patency. The goal of this paper is to discuss the usefulness and application of these tools while highlighting the importance of more physicians assessing the pedal arch and targeting it for revascularization in PAD-related wounds of the foot.

The WIfI Classification System

The Wound, Ischemia, and foot Infection (WIfI) classification system is the current predominantly-used framework put forth by The Society for Vascular Surgery (SVS) Lower Extremity Guideline Committee for the classification of wounds in patients with CLTI. The system incorporates perfusion along with wound extent and severity of infection by focusing

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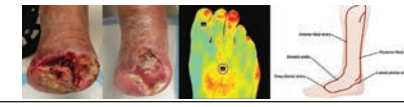

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on three main factors: wound, ischemia, and foot infection. The WIfI system offers a more holistic approach to the identification and classification of CLTI wounds by considering more parameters than other systems, such as the Wagner grading system. While the Wagner grading focuses on the depth of a wound, the WIfI incorporates perfusion measurements to better assess the extent of a wound and provide better diagnostic evidence for determining intervention and treatment options.

The current mainstay test for perfusion assessment within the WIfI classification is the Ankle Brachial Index (ABI), calculated as a ratio of systolic blood pressure at the level of the ankle of the dorsalis pedis or posterior tibial artery divided by the systolic blood pressure in the brachial artery. A concern with ABI is that it solely focuses on the non-specific macrovascular supply of the lower limb but cannot account for micro-perfusion distal to the ankle or the specific location of vascular occlusion.

Figure 1: Pedal arch anatomy
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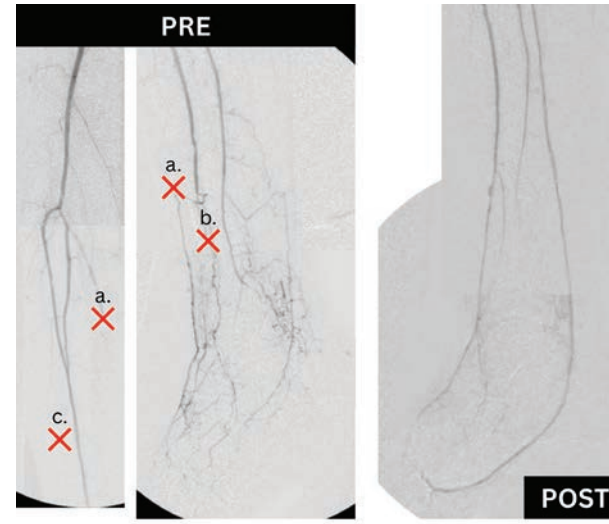

Figure 2: Pre- and post-pedal arch intervention angiogram
(a) Occlusion of the posterior tibial artery; (b) Occlusion of the anterior tibial artery; (c) Occlusion of the plantar circulation and forefoot loop
Images courtesy of Curtis Anderson, MD, PhD, FSIR

The current gold standard of pedal arch evaluation is angiography, a procedure that not only aids in diagnosis but also allows for prompt and immediate treatment when deemed necessary.

Pedal Arch Assessment

A rapid and accurate diagnosis of CLTI is paramount in the prevention of life and limb-threatening complications. Traditionally, the three main pillars of a standard vascular examination include inspection, auscultation, and the evaluation of pulses via palpation or through a handheld Doppler.[9] Determining the exact source of the ischemia is more complicated and necessitates the utilization of more complex instrumentation. The assessment of the patency of the pedal arch, present in approximately 90% of patients and formed by the dorsalis pedis artery (DPA), the lateral plantar artery, a deep perforating artery, and the posterior tibial artery (PTA), can be difficult and requires through examination, but, when done well, has proven to be invaluable as a predictor for wound healing in those with CLTI (Figure 1).[10]

In fact, it has shown significant promise as a prognostic indicator following revascularization, even compared to angiosome-directed revascularization. When compromised, this critical bridge between anterior and posterior pedal circulation has also demonstrated harmful effects on collateral vascular supply between angiosomes.[11]

In a retrospective analysis, Rashid, et al. evaluated the effect of pedal arch quality on patency rates of distal bypass grafts and the direct impact on healing in 154 patients with CLTI, finding that pedal arch patency, rather than the angiosome revascularized, directly affected the rate and time to healing.[12] Furthermore, in a retrospective cohort study consisting of 106 limbs from 85 patients, Kawarada, et al. concluded that, after successful infrapopliteal intervention, patency of the pedal arch was shown to be a better predictor of wound healing than direct angiosome revascularization.[13]

The current gold standard of pedal arch evaluation is angiography, a procedure that not only aids in diagnosis but also allows for prompt and immediate treatment when deemed necessary. In the case of angiography for pedal arch intervention, access is typically achieved in an antegrade fashion to the target artery, usually the common femoral or proximal superficial femoral artery, as described in a 2022 review by Tummala and Briley; however, retrograde femoral access can also be performed to

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target pedal vasculature for intervention.[10,14] After achieving access, the visualization of the arterial supply of the lower extremity using angiography can be performed, and the presence of any occlusion can be noted and treated (Figure 2).

The price of angiography and the potential for complications, however, have led some to seek alternative assessment modalities, such as duplex and Doppler.[15] Some commonly used Doppler-based studies include the ankle-brachial index and segmental pressure measurements.

Pedal acceleration time (PAT) has been used to circumvent the issue of unreliable ABI and segmental pressure results due to pMAC.

Pedal Arterial Calcification

Calcification, resulting in non-compressible vessels, is a problem very common to those with pedal arch disease and can negatively affect the accuracy of both ABI and segmental pressure measurements, and therefore the perfusion assessment within the WIfI classification system.[16-18] Pedal medial arterial calcification (pMAC), resulting from a complex process in which calcium hydroxyapatite crystals form in the tunica media of arteries as a result of the transformation of vascular smooth muscle cells into an osteogenic phenotype, often occurs in the elderly, those with chronic kidney disease, and those with diabetes.[19] Due to the significant association between pedal medial arterial calcification and major amputation and mortality, many providers have turned to the pMAC score as a valuable tool for predicting limb salvage outcomes.[20-23]

A multi-institutional, retrospective study of 176 patients by DiBartolomeo, et al. was conducted to evaluate the usefulness of the pMAC score as a predictor of limb amputation in those who underwent either endovascular or open infrainguinal revascularization treatment for chronic limb-threatening ischemia.[21] The study revealed that patients with a pMAC score of 5 were at significantly higher risk for major limb amputation than those in the 0-1 pMAC group and 2-4 pMAC group ($P = .001$ and $P = .044$, respectively) and had significantly lower amputation-free survival ($P = .008$).

A single-institution retrospective study of 306 by Liu, et al. investigated the relationship between pMAC, hemodynamic change, and major amputation in patients following infrainguinal revascularization for CLTI.[20] The study results showed that the pMAC score is independently associated with persistent distal ischemia and major amputation after successful endoluminal revascularization. A pedal medial artery calcification score of 5 was the

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Figure 3: Pre- and post-pedal intervention in a patient status post left TMA dehiscence probing to midfoot
(A) Pre-pedal intervention; (B) Post-pedal intervention. *Images courtesy of Curtis Anderson, MD, PhD, FSIR*

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only factor independently associated with an unimproved ischemia grade post-revascularization.

Pedal Acceleration Time

Pedal acceleration time (PAT) has been used to circumvent the issue of unreliable ABI and segmental pressure results due to pMAC. Pedal acceleration time is a non-invasive, direct duplex imaging modality shown to be a reliable assessment of pedal perfusion, demonstrating accuracy in those with non-compressible ankle and/or non-obtainable toe pressures.[24,25]

In a retrospective study by Teso, et al. consisting of 73 limbs, a PAT of less than 180 milliseconds was associated with higher limb salvage rates, regardless of whether direct blood flow to the wound bed was achieved.[25] Therefore, they suggest that PAT be added to the WIfI classification system.

De Castro-Santos, et al. conducted a single-center, cross-sectional study on 141 patients with and without diabetes and CLTI to determine PAT's sensitivity, specificity, and accuracy in predicting lower-limb ischemia by comparing the results to ABI and the WIfI classification system.[26] They found PAT to be 85% accurate in detecting an ABI < 0.8 and < 0.6 and 87% accurate in detecting an ABI < 0.4 in patients without diabetes. In patients with diabetes, PAT was 91% accurate in detecting ABI < 0.8, 79% accurate in detecting ABI < 0.6, and 88% accurate

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Figure 4: Kawarada Pedal Arch Classification
(1) Intact pedal arch; (2a) Occlusion of the lateral plantar artery; (2b) Occlusion of the dorsalis pedis artery; (3) Occlusion of the lateral plantar artery and dorsalis pedis artery
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in detecting ABI < 0.4. Pedal acceleration time was also 77% accurate in detecting WIfI classification stages at moderate and high-risk for amputation in patients with and without diabetes.

Outcomes of Pedal Intervention

The outcomes of pedal intervention have been very encouraging (Figure 3). Cheun, et al. conducted a single center retrospective review of 1,768 patients with CLTI and a WIfI grade of 3 or 4.[27] All patients underwent isolated tibial intervention on an average of two tibial vessels and had either good pre-operative runoff (40% of patients), poor pre-operative runoff without pedal intervention (38% of patients), and poor pre-operative runoff with pedal intervention (22%). The results of the review revealed that patients with concomitant pedal intervention had improved 30-day major adverse limb events (MALE) (7% vs. 12%; P = 0.001) and improved 30-day amputation rates (5% vs. 11%; P = 0.001) when compared to the poor pre-operative runoff group with no pedal intervention.

Furthermore, the pedal intervention group had similar 30-day amputation rates and 30-day MALE rates compared to the good pre-operative runoff group (7% in the pedal intervention group vs. 5% in the good runoff group). Wound healing at the three-month mark was also shown to be superior in the pedal intervention group when compared to the poor runoff one without pedal intervention group (55% vs. 25%, respectively; P = 0.001).

Finally, pedal intervention also improved freedom from MALE and amputation-free survival (AFS) five years post-intervention when compared to the poor preoperative runoff group with no pedal intervention (41 ± 8% vs. 17 ± 8%; P = 0.008 and 38 ± 6% vs. 11 ± 6%; P = 0.003, respectively) and was nearly equal to that of the good runoff group (46 ± 4% and 51 ± 5%, respectively).

In a prospective study by Shahat, et al., 120 patients with CLTI and WIfI grade 2, 3, or 4 who had previously undergone endovascular revascularization for infrainguinal arterial disease between April 2019 and April 2021 were divided into groups according to their Kawarada pedal arch types (Figure 4).[28] Pedal arch revascularization (PAR) was attempted in all patients with significant pedal artery disease. Successful PAR was performed in 98 patients.

The results demonstrated that successful PAR, compared to unsuccessful PAR, led to better wound healing rates (86.7% vs 59.1%; P = 0.007), AFS (92.9% vs 72.7%; P = 0.018) and major amputation rates (5.1% vs 40.9%; P ≤ 0.001). Furthermore, unsuccessful PAR was independently associated with failure of wound healing (odds ratio [OR] = 21.64; 95% CI, 4.01-116.69; P ≤ 0.001) and was a significant predictor of major amputation (OR = 22.44; 95% CI, 3.53-142.67; P = 0.001) along with Global Limb Anatomic Staging System (GLASS) (OR = 6.84; 95% CI, 1.30-36.03; P = 0.023 and OR = 24.93; 95% CI, 2.84-218.69; P = 0.004, respectively).

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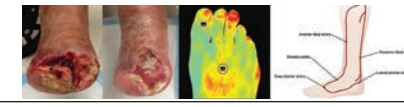

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Conclusion

As the burden of critical limb-threatening ischemia continues to grow alongside the rising global prevalence of diabetes, a more comprehensive and targeted approach to limb salvage becomes increasingly necessary. This paper has explored the evolving landscape of CLTI management, discussing some of the limitations of traditional diagnostic tools such as ABI and highlighting the significance of pedal arch assessment in improving outcomes.

Pedal arch patency, pedal medial arterial calcification score, and pedal acceleration time each provide unique and complementary insights into lower extremity perfusion status, which can guide more effective re-vascularization strategies and ultimately aid in the healing of hard-to-heal chronic wounds such as DFUs. The growing evidence in support of pedal intervention not only reinforces its prognostic value but also highlights its role in enhancing wound healing, reducing major adverse limb events, and improving amputation-free survival.

By integrating these advanced assessment modalities into routine clinical practice, alongside established frameworks like the WIfI classification, clinicians can more accurately stratify risk and tailor interventions. Ultimately, a shift toward greater utilization of pedal arch evaluation and intervention represents a promising step forward in optimizing limb preservation and patient outcomes in those with CLTI. **PM**

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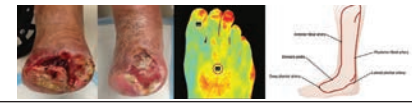

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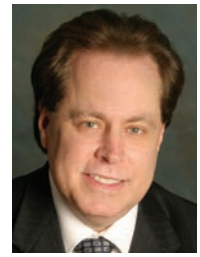

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