Insights on Effective Methods of Lower Extremity Perfusion Assessment

Offering insights from the latest PAD guidelines and research, these authors offer a closer look at non-invasive diagnostic methods and a brief review of medical, endovascular, and surgical treatments of PAD.

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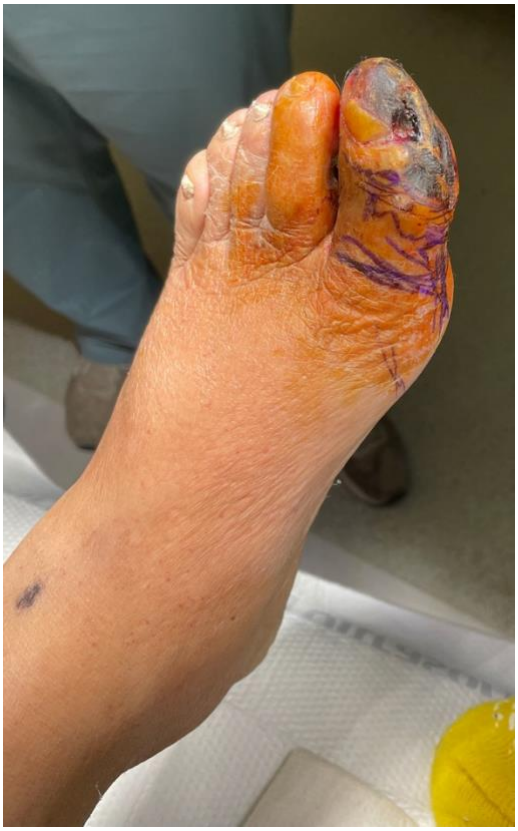


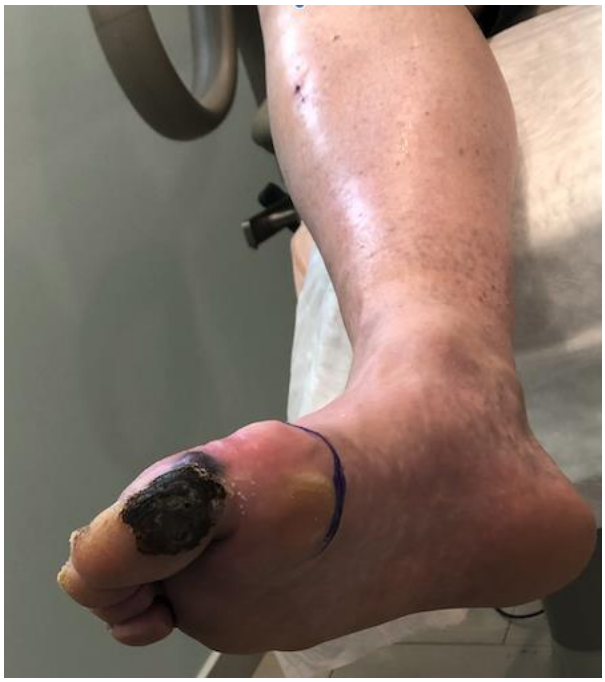
Peripheral arterial disease (PAD) is a condition in which arteries become narrowed or blocked. PAD ultimately can result in a range of serious lower extremity complications, including tissue loss, leg amputation, and death. Accurate and timely diagnosis is important for wound healing and for obtaining an accurate and thorough preoperative workup before any foot and ankle surgery.

Approximately 8.5 million Americans are affected by the significant and costly morbidities of peripheral arterial disease—morbidities that include leg amputations and, in some unfortunate cases, death.[1,2] There is a 20 percent incidence of PAD in patients 75 years of age and older. Despite the prevalence of the disease and associated cardiovascular risk, only 25 percent of these patients undergo treatment.[3]

Early diagnosis and treatment of PAD not only improves the quality of life, but it also saves lives. According to the REACH Registry, approximately 16 percent of patients with PAD have other atherosclerotic changes, such as cerebrovascular disease and/or coronary artery disease.[3] Consequently, patients with PAD have a mortality risk 2 to 3 times greater than patients who do not have PAD, and patients with PAD reportedly die 10 years earlier on average than those without PAD.[4] Remember that PAD is not just a “leg cramping problem” but an ominous sign of declining cardiovascular health that requires our close attention.

Diabetes is an independent and significant risk factor for developing PAD. Currently, there are approximately 25.8 million people with diabetes, or approximately 8.3 percent of the population in the United States.[5] The American Diabetes Association consensus statement presents clinical data that 1 in 3 patients with diabetes mellitus are known to have PAD.[6] The statement urged clinicians to participate actively in the diagnosis and treatment of this disease.

Recognizing the Challenges of Diagnosing PAD



PAD is often associated with claudication, which is intermittent pain in the calf while walking; however, this classic symptom seems to be present in only 10 percent of patients diagnosed with PAD. Fifty percent of the PAD population report being asymptomatic, while the other 40–50 percent report atypical symptoms and/or various leg complaints.[7] The visual and clinical presentations and/or lack thereof make the medical diagnosis of PAD rather challenging. A recent systematic review of clinical studies on PAD found that a physical examination of the lower extremities (e.g., palpation of pulses and "classic findings" such as atrophic skin changes or lack of hair growth) alone is unreliable and "not independently sufficient to include or exclude the diagnosis of PAD."[7] In other words, non-invasive diagnostic approaches such as arterial Doppler tests should be used to diagnose PAD definitively.

What You Should Know About Diagnosing Lower Extremity PAD

When it comes to assessing and diagnosing PAD, we follow a three-step checklist.

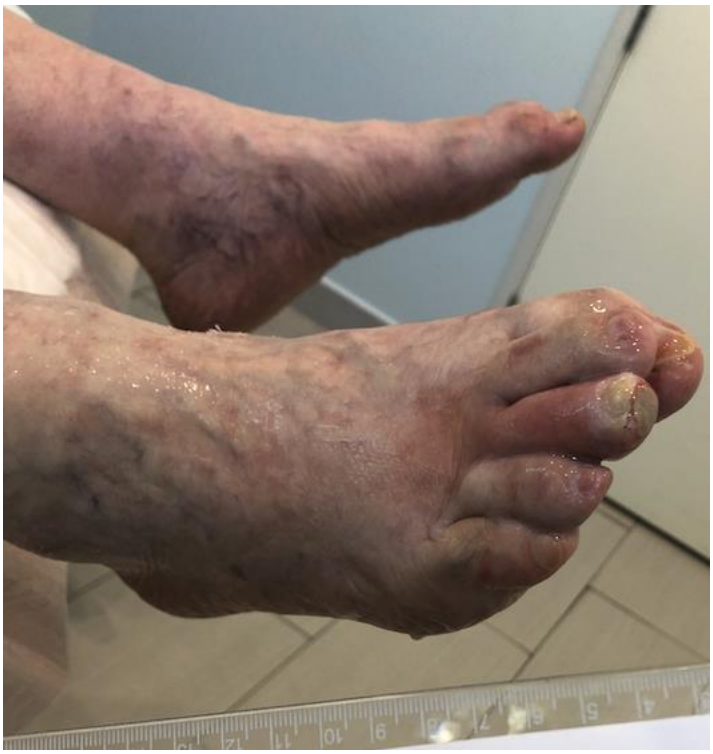
1. Obtain a full history and perform a physical exam to determine the pre-test probability of PAD.
2. For high-risk individuals, perform a non-invasive perfusion test.
3. After a confirmed diagnosis of PAD is made with the use of non-invasive perfusion testing, it is critical to notify the patient and his or her primary care physician. For those suffering from moderate to severe ischemia, an immediate referral to a vascular specialist (i.e., vascular surgeon, interventional cardiologist or interventional radiologist) is also warranted to ensure proper evaluation and treatment of PAD.

The diagnostic protocol for PAD in patients with or at risk for wounds begins with a thorough history and physical exam. It is important to elicit information, especially in older individuals, regarding a history of hypertension, diabetes, dyslipidemia, obesity, multiple stages of renal disease, tobacco use, and family history. The 2011 PAD guidelines from the American College of Cardiology (ACC) Foundation/American Heart Association indicate that people 65 years of age and older are at risk for PAD.[8] The 2005 PAD guideline noted that people 70 years of age and older were at risk for PAD.[6] High-risk candidates included smokers and patients with diabetes 50 years of age and older.[6] A history of coronary artery disease, stroke, claudication, or other types of PAD

(carotid, renal and mesenteric) are also known risk factors. Finally, one should consider the presence of gangrenous wounds or chronic lower extremity wounds (non-healing over four weeks) as PAD risk factors.

The physical examination entails a comprehensive lower extremity vascular examination, including evaluating pedal pulses, capillary filling time, edema, skin condition, and temperature. A thorough history and physical history can determine the pre-test probability for the use of non-invasive testing methods. It is important to note that random screening of PAD with non-invasive testing methods is not recommended as it is a waste of resources and is not reimbursable.

A Closer Look at Non-Invasive Testing Methods for PAD



Peripheral arterial flow in the foot and ankle consists of two categories: macro perfusion and micro perfusion. Macro perfusion involves three major arteries (anterior tibial, posterior tibial, and peroneal arteries) with diameters up to 3 mm. Micro perfusion consists of non-pulsatile arterioles within the skin capillary bed with a diameter of approximately 0.012 mm. There are various non-invasive perfusion testing methods that are commercially available and in wide use. The macro perfusion tests include the ankle-brachial index (ABI), the toe-brachial index (TBI), pulse volume recording (PVR), and the handheld Doppler exam. The two microperfusion tests are transcutaneous oxygen monitoring (TCOM or also called $TcPO_2$) and skin perfusion pressure (SPP).

The ankle-brachial index (ABI) is the best-known non-invasive vascular testing tool. Clinicians perform an ABI test with a handheld Doppler probe and a blood pressure cuff while a patient lies in a supine position, then calculate the ABI by dividing the ankle pressure by the brachial systolic pressure. The ABI has a known sensitivity and specificity of over 90 percent. In terms of interpretation, an ABI below 0.9 is abnormal and diagnostic of PAD. However, non-compressible calcified leg arteries in patients with diabetes or those on dialysis may yield falsely elevated ABI results, sometimes over the non-physiological value (1.4+). Accordingly, this tool is highly unreliable in these populations. Simply put, a low ABI below 0.9 indicates PAD, but seemingly “normal” ABI

values may be misleading or unreliable in ruling out PAD, especially in those with diabetes and patients on dialysis.

The toe-brachial index (TBI) is less influenced by calcification but is limited in application. Analogous to the ABI, the TBI is systolic blood pressure of the great toe divided by the systolic brachial blood pressure. Clinicians can measure toe pressure by placing a small toe cuff around the great toe and attaching a plethysmography probe at the toe tip. The digital arteries in the great toe are less affected by arterial calcification. However, this test is limited if the great toe is wounded or previously amputated. Interpretation of toe pressure and TBI vary in the literature. In general, a toe pressure over 70 mmHg or TBI over 0.5 is normal, and anything below is diagnostic of PAD. In general, we consider toe pressure measurements to be limited in usefulness, and the TBI diagnostic criteria for PAD is too vague to utilize in a clinical setting today.

The pulse volume recording (PVR) is a versatile macro perfusion test, even for patients with arterial calcification. The PVR uses blood pressure cuffs (inflated to 65 mmHg) around the lower limbs, which effectively compresses limb veins while the transducer detects the pressures in pulsatile arterial flow. This facilitates documentation of the arterial waveform. Pulse volume recording has a significant advantage of being unaffected by calcified arteries. This is a morphologic test without numerical values and interpretation may be difficult. One should always pair PVR with other quantitative non-invasive vascular tests. A normal PVR waveform shows a rapid rise and fall with sharp peaks—similar to what one might see with an EKG—while flatter, non-pulsatile flow may represent ischemia and diagnosis of PAD. The PVR waveforms can be triphasic, biphasic, monophasic (or stenotic) on the waveform shape, which one can interpret as mild, moderate, and severe ischemia accordingly.

The Doppler waveform test using a handheld probe may provide a quick macro perfusion analysis. When other diagnostic tools are unavailable or when the patient cannot be in a supine position (i.e., individuals with contracted limbs or morbidly obese patients), a Doppler device may offer a quick method to assess the macro perfusion of the lower extremity. One can elicit Doppler waveforms by applying a Doppler probe at a right angle with conductive gel over the foot and ankle arteries. A clinician may assign minimal ischemia, mild, moderate and severe ischemia based on the morphology of the Doppler waveforms.

Transcutaneous oxygen monitoring is a micro perfusion test with many limitations. Originally developed in the neonatal intensive care unit for the monitoring of newborns, transcutaneous oxygen monitoring measures tissue oxygenation and transcutaneous partial oxygen pressure ($TcPO_2$) in mmHg. The transcutaneous oxygen monitor uses Clarke electrode sensors to measure oxygen molecule permeation through the skin as the heating elements warm the epidermis. This is achieved by placement of the sensors on the patient's skin surface with the use of adhesive plastic fixation rings. Transcutaneous oxygen monitoring is a clinically validated tool that reveals a linear correlation between partial pressure oxygen readings and wound healing potential. In terms of interpretation of the test, normal values are > 50 mmHg, and wound healing

potential drops as $TcPO_2$ values decline.[9] Traditionally, 30 mmHg correlates with a diagnosis of severe PAD or critical limb ischemia (CLI).

Unfortunately, there are many physical limitations to monitoring transcutaneous oxygen. One cannot place the sensor over the plantar foot as the plantar skin is too thick for oxygen permeation. Clinicians cannot monitor transcutaneous oxygen to measure edematous limbs or attach the sensor on dry and flaky skin without compromising the accuracy of the test. These factors eliminate many of our patients as proper study candidates, including most dialysis patients. As the electrodes are highly sensitive to temperature and humidity changes, there is also a significant margin of error when assessing tissue oxygenation level in an exam room (as opposed to a temperature controlled vascular lab). The test is also time-consuming. Skin preparation, calibration, and the testing procedure have a cumulative duration of up to 45 minutes per patient.

Due to these limitations, we have abandoned transcutaneous oxygen monitoring testing in the clinic and replaced it with skin perfusion pressure (SPP) testing. Many recent comparative studies have suggested that SPP has higher accuracy than transcutaneous oxygen monitoring in assessing wound healing potential.[10]

SPP is a newer alternative technology to transcutaneous oxygen monitoring for assessing the skin capillary blood pressure. To measure SPP, one would ensure supine positioning of the patient and place a laser Doppler sensor over the specific skin site with a pressure cuff wrapped around the limb. The computer operates the laser Doppler and pressure cuff in combination with guidance through a gentle inflation/deflation process that detects sufficient arterial compression and identifies the point at which blood flow resumes. This provides SPP measurement in mmHg. SPP is a clinically validated tool with a strong correlation to wound healing potential even in patients with diabetes, and this test is not affected by calcified leg arteries. SPP has fewer physical limitations in comparison to transcutaneous oxygen monitoring and clinicians can measure SPP in plantar skin, edematous limbs or those with dry, flaky skin.[11]

SPP testing is in wide use for the diagnosis of PAD/CLI as well as the assessment and validation of the lower extremity perfusion in catheter labs before and after endovascular intervention procedures.[12] Normal perfusion in lower extremities correlates with SPP values over 50 mmHg. A SPP measurement between 30 and 50 mmHg is diagnostic of PAD while a SPP measurement below 30 mmHg is diagnostic of severe PAD or CLI. Wound healing potential correlates with SPP in a sigmoid curve and wound healing potential drops dramatically when the SPP is below 40 mmHg. We also confirmed this correlation with our own retrospective analysis.[13] In the SPP measurement of 412 limbs and their wound closure time, we validated that SPP measurement over 40 mmHg is a reliable predictor of good wound healing potential.[13]

What the Authors Recommend for the Diagnostic Workup

In our wound care clinic, we use the SPP laser Doppler machine for comprehensive non-invasive vascular testing of the lower extremities. The diagnostic device can

measure SPP in mmHg (micro perfusion test) and record PVR waveforms (macro perfusion test).

The latest clinical study comparing various non-invasive perfusion tests to magnetic resonance angiography found SPP to be the most sensitive in the diagnosis of PAD with a sensitivity of 85 percent while ABI had a sensitivity of 30 percent.[14] In this particular study, ABI failed to diagnose 70 percent of PAD patients tested due to calcified leg arteries. This illustrates the need to incorporate more sensitive testing methods such as SPP and PVR for the perfusion of patients with diabetes and patients on dialysis.

Pertinent Insights on Medical Treatment, Prevention and Risk Reduction of PAD

In the updated 2011 PAD guidelines, the medical treatment of patients with PAD aims to optimize the medical status of each patient to prevent further atherosclerosis and/or atheroembolic processes.[8] Medical treatment of PAD should start with the optimization of cholesterol (LDL below 100 mg/dL), blood pressure (140/90 mmHg), blood glucose (HbA1c below 7%) and weight (body mass index between 18.5 and 24.9 kg/m^2). Physicians should also encourage physical activity of at least 30 minutes for 5 to 7 days per week.

The guidelines also place a new emphasis on smoking cessation.[8] One should ask smokers or former smokers about their tobacco use at every visit and give them assistance in the form of counseling, developing a plan to quit smoking, pharmacotherapy or referral to a smoking cessation program.

Medical optimization and risk reduction can be attempted with the use of antiplatelet therapy and statin therapy. For the use of antiplatelet therapy, the guidelines recommend aspirin (daily dose of 75 mg to 325 mg) or clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi Pharmaceuticals) (daily dose 75 mg) as safe and effective antiplatelet therapy to reduce the risk of myocardial infarction, stroke or vascular death in patients with symptomatic PAD.[20,21]

Statin therapy is evidently beneficial for patients with PAD. The Heart Protection Study randomly assigned 20,536 patients, 6,748 of whom carried a diagnosis of PAD, to either simvastatin 40 mg daily or placebo with a mean follow-up of 5 years.[22] In the overall study population, simvastatin was associated with a 16% relative risk reduction in peripheral vascular events, which was driven primarily by a 20% reduction in non-coronary revascularization. It is noteworthy that this endpoint included not only lower extremity arterial procedures, but also carotid interventions, and there were no differences in the rates of amputation between the 2 groups. Similarly, among 5,861 patients with symptomatic PAD in the REACH (Reduction of Atherothrombosis for Continued Health) registry, statin therapy was associated with a 14% relative risk reduction in a composite endpoint that included worsening claudication, critical limb ischemia, peripheral revascularization, and amputation at 4 years.[23]

There have been several studies now that prove dual antiplatelet therapy (DAPT) has been shown to reduce cardiovascular mortality as seen in the WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) as well as the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51) trial.[24,25] DAPT (aspirin and a second oral antiplatelet agent that blocks the P2Y12 platelet receptor, usually clopidogrel) are generally recommended after infra-inguinal stenting and sometimes after the use of a prosthetic graft.[26]

Direct oral anticoagulants (DOACs) are also frequently prescribed for patients with PAD in order to reduce major adverse cardiovascular events. Previous studies have shown the regression of the atherothrombotic activity in PAD patients with the use of antithrombotic therapy.[27,28] However, in a recent study, DOACs (rivaroxaban, dabigatran, edoxaban, or apixaban) were not found to reduce the risk of cardiovascular death, stroke, myocardial infarction, or amputations when compared to antiplatelet monotherapy.[29] Instead, DOACs displayed effectiveness in the reduction of acute limb ischemia and target lesion revascularization.[29]

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial included a total of 27,395 patients and found combining rivaroxaban and aspirin displayed an overall reduction in cardiovascular death, stroke, or myocardial infarction.[30] This trial showed taking low-dose rivaroxaban and aspirin was favorable compared to higher dose rivaroxaban or aspirin alone.[29] Accordingly, the American Diabetes Association (ADA) Guidelines, endorsed by the ACC, were recently updated to include the use of rivaroxaban (Xarelto, Janssen Pharmaceuticals) 2.5 mg BID with low-dose aspirin daily for the treatment of patients with chronic carotid artery disease/PAD. Interestingly, the COMPASS trial was stopped early due to overwhelming efficacy in the rivaroxaban 2.5 mg BID + ASA treatment arm, as the Kaplan-Meier curve separates very early on between the treatment groups, as the dual pathway inhibition of targeting both the anticoagulation and antiplatelet pathway is effective in PAD management and improving both cardiovascular and major limb endpoints.

One should use statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta blockers in the absence of contraindications or documented adverse effects.[19] If your patients with PAD are not on these medications, it is essential to refer them back to their internist or cardiologist to review their medications to optimize the medical therapy, to be in line with the community standard of care.

What the Literature Reveals About Revascularization and PAD

There is an ongoing debate over revascularization procedures for symptomatic patients with PAD. The treatment choices are divided into endovascular and surgical treatment. Generally speaking, endovascular therapy (angioplasty, atherectomy, thrombolysis, and stenting, etc.) is less invasive and less traumatic for patients, although the application of these modalities may be limited to shorter lesions or incomplete occlusions of main leg

arteries. Surgical treatment (leg bypass and endarterectomy) may be more versatile in treating long and complex lesions, and may create more durable results than endovascular treatments.

On the downside, the surgical procedure selection is limited to the availability of bypass target and conduit. Native veins are ideal while prosthetic polytetrafluoroethylene conduits are inferior in patency and inferior to endovascular therapy.[22] The surgery for leg bypass lasts many hours, and prolonged recovery time may not be suitable for patients with advanced age, multiple comorbidities or dementia.[22]

Although the above comparisons generally hold true, with the advancement of newer catheter and chronic total occlusion re-entry devices, endovascular therapy is certainly expanding beyond the conventional role. Indeed, many advanced institutions are now implementing an “endo-first” approach. In this approach, patients with PAD first go to a vascular interventionalist for an angiogram and endovascular therapy. They subsequently receive referrals if more perfusion is necessary or major leg amputation is required due to overwhelming ischemia and/or infection.

The BASIL study, comparing balloon angioplasty with leg bypass surgery for the treatment of severe limb ischemia, found that the two treatments achieved similar outcomes in amputation-free survival rate.[31,32] However, the study was flawed as it excluded 90 percent of the patients screened as high risk and only one-third of the patients underwent tibial revascularization.

We believe that endovascular intervention can indeed be the first-line therapy for all patients with CLI, given the implementation of a multidisciplinary team approach—advocated by the 2007 TASC-II consensus panel—with sophisticated wound management by wound specialists and prudent intervention by vascular specialists.[22]

In Summary

It is in our patients’ best interest to ensure that clinicians have a heightened awareness of PAD/CLI and the ability to diagnose these conditions with non-invasive tools. We have found that the combination of macro- and microcirculation tests is one of the most effective diagnostic methods to aid in limb preservation. We also advocate for a close collaboration of podiatry and vascular specialists for swift coordination from diagnosis to treatment of PAD/CLI. Advances in wound management, medical therapy and endovascular therapy in recent years have enabled us to preserve many at-risk ischemic limbs that previously would have faced amputation.

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