The Evaluation and Treatment of Peripheral Arterial Disease

Here's the latest research on PAD.

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Peripheral artery disease (PAD) traditionally is viewed as a chronic condition caused by the buildup of atherosclerotic plaques in the peripheral arteries, leading to complications such as intermittent claudication, ischemic rest pain, ulcers, gangrene, and reduced function in the limbs. However, recent research indicates that the pathogenesis of Critical Limb Ischemia (CLI), a serious complication of PAD, may be primarily an atherothromboembolic condition. A groundbreaking study by Narula, et al.[1] revealed that nearly three-quarters of the arteries from amputated limbs due to CLI contained luminal thrombi, with two-thirds of these arteries showing no significant atherosclerotic lesions. These results suggest a thrombi-dependent mechanism in the development of many PAD and limb-related complications, as the observed stenosis was not due to a local atherosclerotic process.

The risk of amputation due to PAD-related issues is associated with a mortality rate of up to 50% within one year. PAD not only causes severe limb problems but also serves as a warning sign for obstructive atherosclerosis in other parts of the body, including the brain and heart. People with PAD are at higher risk of experiencing ischemic stroke, heart attack, and cardiovascular death. Those who have both coronary artery disease (CAD) and PAD face an even greater risk of cardiovascular mortality compared to those with CAD alone. PAD imposes a significant burden on patients' quality of life and financial health. Globally, approximately 220 million people are affected by PAD, and its prevalence is increasing worldwide.[2]

Smoking Cessation

Smoking is the single greatest modifiable risk factor for the development and progression of PAD. Tobacco smoke triggers inflammation throughout the body, which increases endothelial cell permeability by generating reactive oxygen species. This, in turn, promotes the accumulation of atherosclerosis within the vessel walls. The prevalence of PAD is increased by 2.3-fold in current smokers.[3] Patients with Peripheral Artery Disease (PAD) face smoking-related complications and increased mortality. One study focused on individuals with PAD that underwent angiography for the disease and continued smoking afterward had more than double the mortality and lower extremity amputation rates at a 5-year follow-up.[4] Smoking promotes the development of PAD and increases complication rates, so healthcare providers should prioritize smoking cessation efforts.

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The Basics of Non-Invasive Vascular Work-up

ABI, Segmental Pressure and PVR

Arterial-brachial index (ABI) compares the blood pressure measured at the ankle with the blood pressure measured at the arm. A low ankle-brachial index number suggests a decreased blood pressure at the ankle suggesting poor perfusion from PAD. However, while performing an ABI may be a simple screening tool, it is widely believed that the test is plagued by false-negative screenings. Atherosclerotic plaques as a result of PAD can lead to the inability to compress the arteries at the level of the ankle, and lead to a falsely increased pressure reading and missing the actual blood pressure.

An expanded version of the ABI exam is the use of what is called segmental pressures. As the name suggests, pressures are recorded at

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increased segments in the lower leg, including the thigh, calf, and great toe. This increases the reliability in the exam, thus the atherosclerotic plaques may be decreased in the calf and spare the arteries in the great toe, aiding in an accurate diagnosis.

Pulse volume recording (PVR) (Figure 1) is an air plethysmography waveform analysis test used to detect the segmental volume changes in the limb resulting from the flowing blood as a function of the cardiac cycle. Similar to the segmental blood pressure (SBP) measurements, pressure cuffs are wrapped around the target limb segments. The cuffs are inflated to a target pressure that occludes the venous return yet will not obstruct the arterial flow. This target pressure is typically 65 mmHg and is kept constant throughout the PVR test. The PVR waveform is generated based on the pressure changes in the air inside the cuff as arterial flow passes.

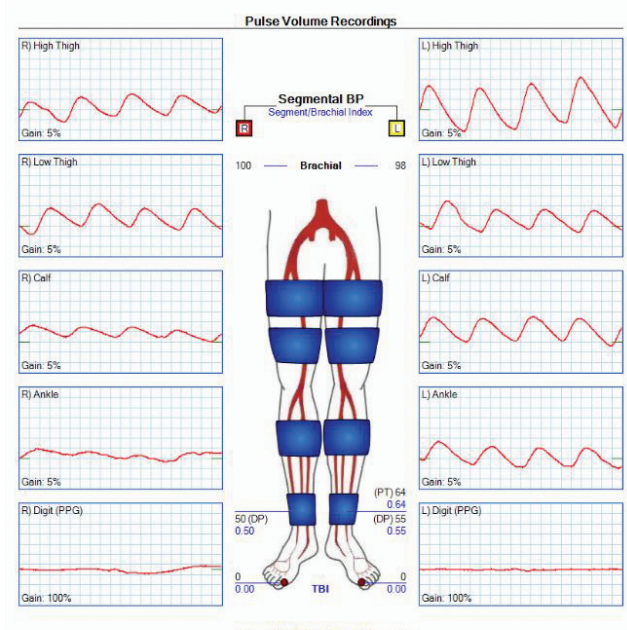

Figure 1: An example of PAD affecting bilateral lower extremities, demonstrating decreased waveforms in the right calf and absent waveforms in both great toes.

Arterial Duplex Ultrasonography

Arterial duplex ultrasonography (Figure 2), otherwise referred to as arterial duplex or arterial ultrasound, relies on the changes in ultrasound signal frequencies reflected from moving red blood cells.

Typically, normal flow is triphasic in nature, indicating that the movement of red blood cells is consistent in speed and direction, with a laminar flow pattern. This is replaced by a biphasic flow when arterial fibrosis, which reduces the elastic recoil, occurs. It should be noted that the diastolic pattern occurs in the triphasic and biphasic patterns when the flow moves for a short period in reverse. If the fibrosis is severe, and stenosis is occurring, the flow may be monophasic, showing a loss of the diastolic, or reverse, flow. This velocity change occurs as pressure remains the same, but the diameter of passage decreases, requiring an overall increase in speed of flow for the volume to pass. The velocity decreases again once flow moves past the stenosis and the diameter of passage increases. However, it should be noted that rather than increase, velocity decreases in cases of severe stenosis at levels of 95% or greater, and disappears altogether at sites of occlusion.

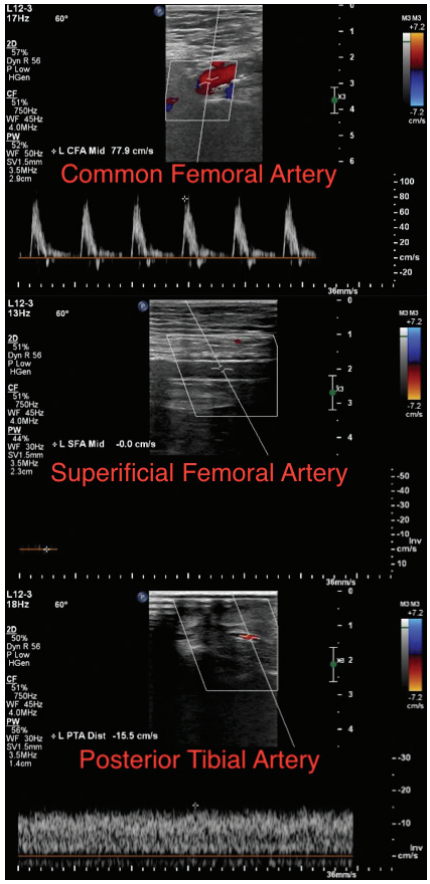

Figure 2: Arterial ultrasound finds triphasic waveforms in the common femoral artery, but complete loss of waveforms in the superficial femoral artery, suggesting occlusion. Downstream a monophasic waveform is present, suggesting some collateral flow feeding the posterior tibial artery.

Transcutaneous Oxygen Measurements

Transcutaneous oxygen measurements (TCOMs or TcpO2), measures oxygen released at the skin. While it does not directly measure circulation, it does provide insight into the oxygen delivery to the skin, which is impacted by the underlying circulation. While inconsistent results may occur,[5] it has often shown to be useful in aiding in the determination of healing potential.[6]

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The examination is performed by applying a series of probes to the surface of the skin for approximately 20 minutes. The probes capture oxygen released from the skin, which provides a result in terms of the total pressure created by the oxygen. Based on previous research,[6] it is believed that results of 40mmHg or greater indicate adequate oxygen perfusion to support

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healing, and results below this may have difficulty in healing. The lower the pressure reading, the lower the likelihood of healing that exists.

CT Angiography

CT angiography is an advanced imaging study that combines a CT scan with a contrast dye injection to produce detailed images of blood vessels throughout the body (Figure 3).

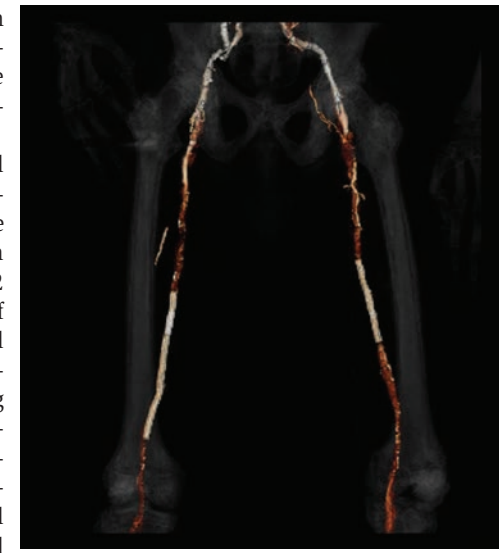

Figure 3: Three-dimensional reconstruction of the arterial flow through the lower extremity demonstrates both previously placed stenting as well as lack of contrast passing through the superficial femoral arteries, suggesting occlusions.

Therapeutic Treatment Options

Statins

It has been observed that cholesterol is a key component of arterial plaques. Elevated levels of lipids and lipoproteins, including total cholesterol, non-HDL cholesterol, and LDL cholesterol (LDL-C), are linked to an increased risk of cardiovascular disease and peripheral artery disease (PAD). Recent studies focusing on statins suggest that reducing lipid levels, especially LDL-C, to the lowest achievable target significantly enhances cardiovascular outcomes. According to guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA), PAD is considered equivalent to a history of heart attack or stroke regarding the use of cholesterol-lowering therapies.

Treatment with moderate-intensity statin therapy using simvastatin resulted in a 17% reduction in peripheral vascular events. These events were defined as noncoronary revascularization, amputation, aneurysm repair, and death related to PAD.[7]

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Antiplatelet and Anticoagulation Therapies

PAD is marked by increased platelet hyperaggregability and enhanced adhesion, along with elevated surface protein expression. This provides the rationale for employing antiplatelet therapy.

Aspirin has demonstrated efficacy in treating symptomatic PAD. Significant evidence supporting its usefulness in PAD first emerged in 2002 through a meta-analysis of randomized trials conducted by the Antithrombotic Trialists' Collaboration,[8] involving over 9,000 patients. The analysis indicated a 23% proportional reduction in serious vascular events—such as nonfatal myocardial infarction, nonfatal stroke, or vascular death. In 2007, the (CLIPS) Critical Leg Ischemia Prevention Study[9], a study involving 366 patients with both symptomatic and asymptomatic PAD, revealed a 64% decrease in relative risk for major vascular events, including ischemic stroke, myocardial infarction (MI), and vascular death with the use of low dose aspirin.

In the 1996 CAPRIE trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events)[10], long-term treatment with clopidogrel proved more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death among patients with atherosclerotic vascular disease. Additionally, clopidogrel demonstrated a safety profile comparable to that of moderate-dose aspirin.

Clinical trial data on warfarin, and more recently rivaroxaban, indicate that anticoagulation may indeed prevent limb-related complications from PAD, as well as reduce overall cardiovascular morbidity and mortality.

Cilostazol

Claudication pain occurs due to peripheral ischemia distal to a stenosis in the arterial supply, typically occurring during exertion as the demand outweighs the available arterial supply. It has been postulated that peripheral vasodilators, such as cilostazol, may be beneficial for treating claudication. The use of cilostazol subtly improved walking distance before the onset of claudication; however, the results were less effective than starting a walking program.[11] Nonetheless, individuals with concurrent neuropathic foot ulceration would be unable to start a walking program.

Arterial Pumps

Arterial pumps utilize high-pressure, rapid sequence, intermittent pneumatic compression (HPIPC) to the foot, ankle, and calf using cuffs attached to the leg (Figure 4). This regimen mimics the beneficial effects of brisk walking. These devices use pressures more than twice those of traditional intermittent pneumatic compression (IPC) devices, designed for venous thrombosis prevention, venous insufficiency, and lymphedema. By compressing all tissues below the knee, a large volume of venous blood is emptied, dropping venous pressure to nearly zero and increasing the arterial-venous pres-

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sure gradient, which enhances arterial flow. Studies have demonstrated the benefit in both wound healing as well as in treating ischemic pain. One study found wound surface area reduced by 57% at 12 weeks and reduced by 71% at 16 weeks for the HPIPC group, compared to 45% and 56% for the control group.[12] Arterial pumps have been shown to be an effective tool in limb salvage and amputation prevention in the population with PAD with no formal revascularization options.[13]

Hyperbaric Oxygen Therapy

When arterial insufficiency is present, damage to tissues is unable to properly heal, leading to chronic wounds and gangrene. The lack of arterial flow leads to a deficiency in oxygen in the tissues.

Hyperbaric oxygen therapy (HBOT) may aid in the recovery of these tissues and allow for wound healing. Oxygen stimulates collagen synthesis, which is essential for healthy tissue formation in a healing wound bed. This synthesis occurs when fibroblasts are activated by lactate produced by macrophages in the wound environment. Increased oxygen levels also lead to higher VEGF gene expression. VEGF, or vascular endothelial growth factor, stimulates neoangiogenesis, the growth of new blood vessels into the wound. Fibroblasts cannot synthesize collagen in a hypoxic state; an oxygen-rich environment is necessary for the proper cross-linking of collagen. When oxygen levels are low and collagen formation stalls, neoangiogenesis also halts, resulting in chronic, non-healing wounds.[14]

Placing a patient in a hyperbaric chamber at 2.5 ATA O2 may raise the oxygen tension to more than 10 times above normal physiological levels. This effectively saturates the plasma and causes hemoglobin to remain fully oxygenated, even on the venous side that further oxygenates this tissue[15].

Within 15 minutes of hyperbaric oxygen therapy, endothelial cells begin to proliferate, and after 120 minutes, fibroblasts start responding, with effects lasting up to 72 hours post-exposure. With high levels of oxygen, red blood cell ability to pass through narrow capillaries improves. Additionally, leukocytes use oxygen to create high-energy radicals, and the rate of radical formation is directly proportional to the available oxygen. These radicals are then utilized by neutrophils to increase phagocytosis of bacteria, thereby cleaning the wound and preventing infection.[16]

Topical Oxygen

For patients who do not meet the criteria for systemic supplemental oxygen delivery, local oxygen delivery devices may be an option. As previously reviewed, HBOT requires patients to breathe 100% oxygen at increased atmospheric pressures, which carries its own risks. Additionally, delivering oxygen to the wound via HBOT requires systemic circulation to

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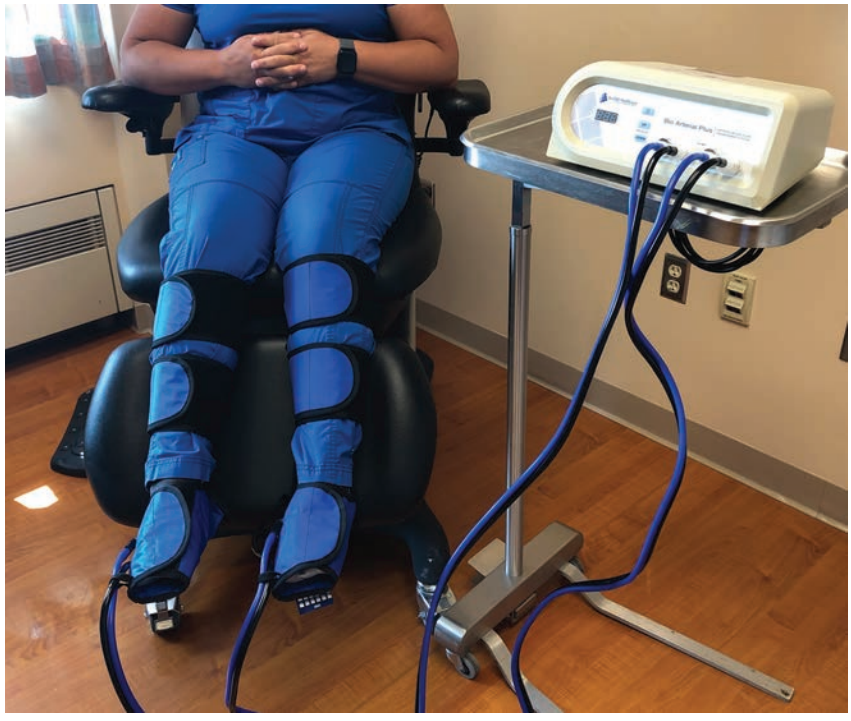

Figure 4: Demonstration of a HPIPC system.

Figure 5: Demonstration of a topical oxygen system.

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transport oxygen-rich blood. In contrast, topical applications of oxygen increase oxygen levels directly at the wound bed, delivering oxygen where it is needed most, and does so while the patient remains at room pressure. This local increase in oxygen enhances oxygen solubility and dissolution by increasing O2 partial pressures.[17]

Topical oxygen can also be administered at the patient's residence, reducing the burden of care and improving compliance. Many hospitals and medical centers lack the monoplace or multiplace pressure chambers required for HBOT, making it inaccessible to many patients. HBOT typically requires patients to visit an equipped medical center five days a week for up to 40 treatments, with each session lasting around two hours. In contrast, topical oxygen administration can take place in the patient's home, improving compliance with therapy (Figure 5).

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While HBOT currently remains the standard for treating non-healing diabetic foot ulcers with supplemental oxygen, new research continues to show promise for oxygen. A 2020 level 1 study utilizing topical oxygen found an impressive 41.7% closure rate at 12 weeks for the study group comparted to only 13.5% for the sham group ($p = 0.010$). Perhaps even more impressive was a post-study follow-up at one year where 56% of the TO2 group closed and remained closed compared to 27% for the sham group ($p = 0.013$).[18]

Interventional Angiography and Vascular Bypass

For patients with occlusions and stenosis of their arterial flow, referral to a vascular surgeon or interventional radiologist that specializes in revascularization is also vital. While available therapies offer assistance, nothing can outcompete restoration of inline flow to the foot. However, using these therapies as an adjunct, in addition to a referral to an arterial disease specialist, will help ensure the best possible outcome. If you are uncertain of which device or medical management is the most appropriate, collaborate with your patient's primary care provider and/or the vascular specialist. Networking with your colleagues may help reduce risks and unforeseen complications.

While not every patient with a foot ulcer has arterial insufficiency or require therapies to improve blood flow, it is important to screen your patients to identify which patients may benefit. **PM**

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