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Pathophysiology of Intermittent Claudication in Peripheral Arterial Disease

By WILLIAM R. HIATT, M.D.

Peripheral arterial disease (PAD) is associated with an increased risk of cardiovascular mortality and substantial functional limitation. Patients with claudication have exercise-induced ischemia in the muscles of the leg that limits walking distance and exercise capacity. The initial disease process is atherosclerosis that results in arterial stenoses and occlusions in the arteries supplying the muscles of the lower extremities. Limited blood flow during exercise results in an oxygen supply/metabolic demand mismatch. Claudication discomfort is relieved by rest. While the primary pathophysiology is a limitation in blood flow, the abnormal hemodynamics (reduced limb pressure and flow) do not completely explain the functional limitations experienced by the patient. Patients with claudication acquire ischemia-reperfusion injury that can alter oxidative metabolism in skeletal muscle. Indices of the metabolic state of the muscle better explain the functional impairment than does the reduction in blood flow. Restoration of blood flow with angioplasty or bypass surgery can improve, but not normalize, exercise performance. Exercise training can significantly reduce the severity of claudication and also improve exercise performance. This occurs without a consistent change in limb blood flow, but with favorable effects on skeletal muscle metabolism. This issue of *Cardiology Rounds* discusses the complex pathophysiology of claudication and provides a basis for treatment decisions and novel therapeutic strategies.

PAD is one of the major manifestations of systemic atherosclerosis, affecting 12% of the adult population and up to 20% of elderly persons. Given the strong association with coronary and carotid disease, these patients are at high risk of cardiovascular events, including myocardial infarction (MI), stroke, and death.[1] Patients with PAD have significant functional disability.[2] In many, exercise limitation is directly related to the development of the symptoms of claudication, which is typically exercise-induced discomfort in the calf that is associated with reversible muscle ischemia. Symptoms may also occur in the thigh or buttocks. Claudication only occurs with exercise and is characterized by cramping and aching in affected muscles that force the patient to stop walking, which relieves the discomfort. Patients with claudication have a severe limitation in treadmill exercise performance, with a 50% reduction compared with healthy, age-matched controls.[3] As a result, they have a marked decrease in ambulatory activity and quality of life.[2] The major treatment goals in PAD are:

- preventing the progression of systemic atherosclerosis
- reducing the risk of fatal and nonfatal ischemic events
- relieving the symptoms of claudication
- improving functional capacity and enhancing quality of life.

Understanding the multiple pathophysiologic mechanisms associated with claudication is critical in the overall management of the patient with PAD and the development of potential new therapies.

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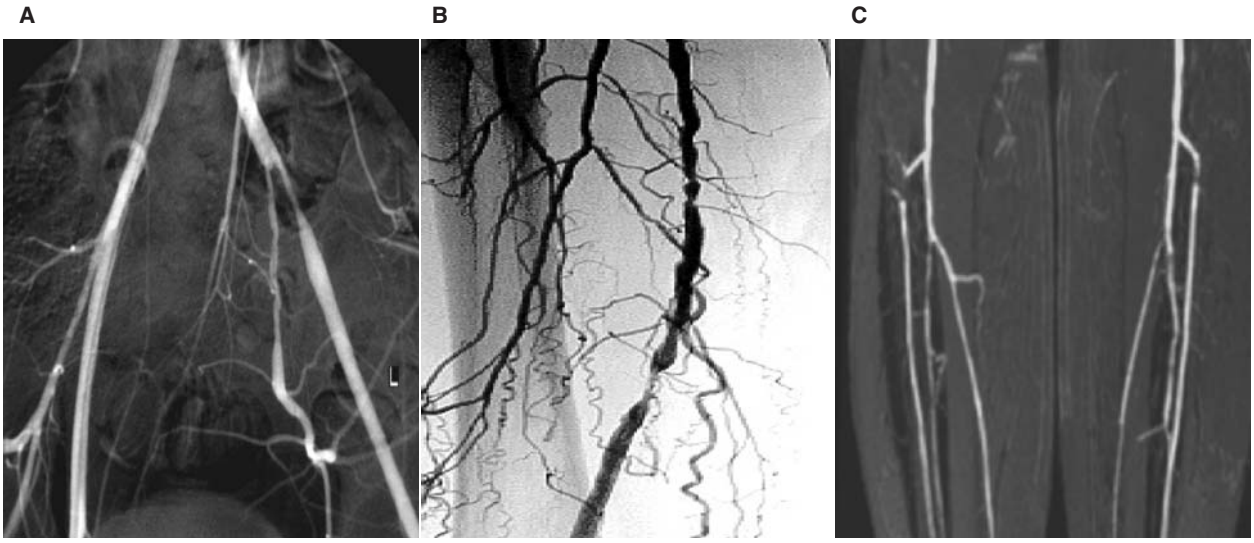
Figure 1: Typical distribution of arterial lesions in peripheral arterial disease.



Panel A shows a stenosis of the left external iliac artery

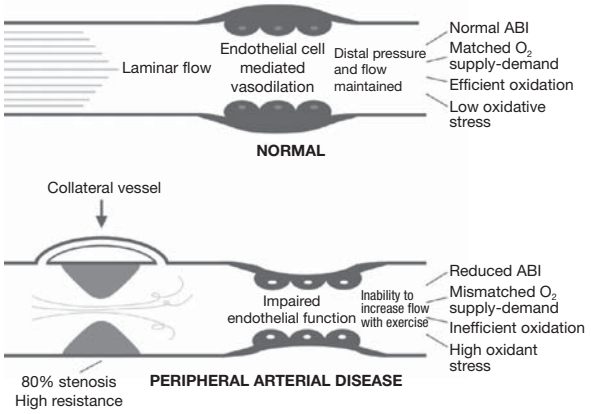
Panel B shows several stenoses in the superficial femoral artery

Panel C shows extensive disease of the tibial vessels in the calf.

Hemodynamic abnormalities in PAD

Patients with PAD develop atherosclerotic occlusive lesions in the arteries supplying the lower extremities. Numerous arterial segments may be affected, including the inflow vessels (aorta and iliac arteries), as well as the femoral, popliteal, and tibial vessels in the leg (Figure 1). Thus, blood flow limitation to active muscle is the primary pathophysiologic event. Factors that influence blood flow delivery include the degree and length of the stenosis, blood viscosity, and blood flow velocity (Figure 2). Multiple or sequential arterial occlusions can further compromise the circulation, while the development of collaterals can partially compensate for the arterial insufficiency. These hemodynamic effects lead to a decrease in ankle blood pressure relative to the arm. When the ratio of ankle-to-arm systolic pressure is <0.90, the patient has evidence of PAD.

Figure 2: Hemodynamic changes in peripheral arterial disease



The top figure represents normal conditions where large vessel blood flow is laminar, endothelial function is maintained, and distal oxygen delivery matches metabolic demand. The bottom figure represents PAD where an arterial stenosis or occlusion causes turbulent flow, endothelial function is impaired and oxygen delivery is insufficient to meet demand. In the healthy condition the ankle-brachial index is > 0.90 (and typically 1.10), whereas in PAD, the ABI is < 0.90 at rest, with a further decrease after exercise.

While arterial flow limitations are of critical importance in the pathophysiology of claudication, the hemodynamic status of the limb poorly correlates with exercise performance. Blood pressure in the ankle or flow in the calf do not reliably predict treadmill walking time.[4] This lack of a consistent relationship between limb hemodynamics and claudication-limited exercise suggests that factors distal to the arterial obstruction likely contribute to the functional limitations of PAD.

Oxidative stress in PAD

Muscle ischemia during exercise and reperfusion after claudication-limited exercise is associated with an increase in oxidant stress.[5] The production of oxygen-free radicals may be a unifying mechanism of vascular and skeletal muscle injury in PAD. Repeated episodes of ischemia during exercise and reperfusion during recovery may promote oxidant injury to endothelial cells, muscle mitochondria, muscle fibers, and distal motor axons. Mitochondria are the major source of free radicals within the cell and, therefore, somatic mutations in mitochondrial DNA are an important marker of oxidant injury.[6] These mutations are readily demonstrated in muscle from patients with PAD. For example, patients with PAD have an increased frequency of mitochondrial DNA 4977 bp deletion mutation.[7] Thus, they have increased levels of both

local and systemic oxidant stress that, over time, contribute to the functional limitations seen in these patients.

Alterations in skeletal muscle metabolism

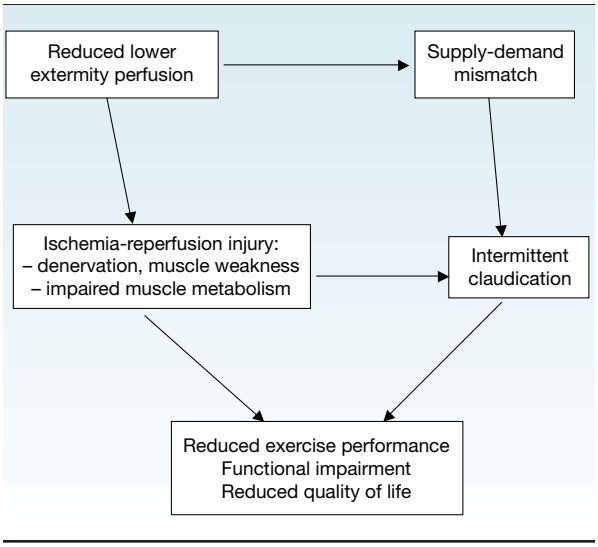
Muscle mitochondrial content and mitochondrial enzyme activities reflect the functional status of the individual. In healthy subjects, muscle mitochondrial content positively correlates with peak oxygen uptake, indicating the importance of muscle oxidative capacity in determining exercise performance in the individual.[8] In PAD, the marked limitation in walking activity and resultant sedentary behavior would be expected to result in a decrease in muscle mitochondrial enzyme content and activity (detraining). In contrast, several studies have revealed increased mitochondrial content in muscle of patients with PAD.[9-11] This increased mitochondrial expression appears to be a direct consequence of, and is proportional to, the severity of the occlusive disease as assessed by leg hemodynamics.[9] Thus, alterations in skeletal muscle mitochondria in PAD appear to reflect the severity of the underlying occlusive disease process. Increased mitochondrial content might improve oxygen extraction under ischemic conditions or could reflect a compensatory mechanism for any intrinsic abnormality in mitochondrial oxidative capacity.

Patients with PAD may develop changes in the activity of enzymes critical for oxidative metabolism in the affected skeletal muscle. A potential site of such impairment is the electron transport chain, which is vulnerable to free radical injury.[12] Skeletal muscle from legs affected by PAD has reduced mitochondrial NADH dehydrogenase of complex I and ubiquinol-cytochrome c oxidoreductase (complex III) activity.[13] These observations suggest that electron transport chain activity is affected by ischemia-reperfusion injury in PAD and may contribute to metabolic dysfunction in PAD.

The changes in enzyme activities and electron transport chain function might be expected to reduce the ability to perform oxidative metabolism. During normal metabolic conditions, fuel substrates such as fatty acids, protein, and carbohydrates are converted to acyl-CoA intermediates for complete oxidation in the Krebs cycle. These coenzyme A-coupled intermediates are linked to the cellular carnitine pool through the reversible transfer of acyl groups between carnitine and coenzyme A.[14] One of the functions of carnitine is to serve as a buffer for the acyl-CoA pool by the formation of acylcarnitines. Thus, conditions of metabolic stress, or failure to further metabolize an acyl-CoA, lead to acyl-CoA accumulation. Transfer of the acyl group to carnitine results in the accumulation of corresponding acylcarnitine.[15]

Patients with PAD have alterations in carnitine metabolism. This is evident by the accumulation of short-chain acylcarnitines in plasma as well as skeletal muscle in legs affected by arterial disease.[16, 17] This accumulation of acylcarnitines implies that acyl-CoAs are not being efficiently oxidized, given that the acyl-CoA pool is in equilibrium with the acylcarnitine pool. Importantly, acylcarnitine accumulation may have functional significance in that patients with the greatest accumulation have the most reduced treadmill exercise performance.[17] Thus, the degree of metabolic abnormality (as defined by acylcarnitine accumulation) is a better predictor of treadmill exercise performance than the ankle brachial index (ABI), emphasizing the importance of altered skeletal muscle metabolism in the pathophysiology of claudication.

Figure 3: Pathophysiology of claudication and reduced functional capacity in PAD.



An overall pathophysiologic scheme is proposed in Figure 3. Atherosclerotic occlusions of the peripheral arteries limit arterial perfusion to the lower extremities. During exercise, the resultant oxygen supply/metabolic demand mismatch is associated with claudication that severely limits exercise performance and quality of life. An additional consequence is ischemia-reperfusion-induced oxidant stress injury throughout the vascular bed. Muscle denervation and alterations in muscle metabolism further limit performance.

A pathophysiologic approach to the treatment of claudication

Exercise training: Exercise training is an important treatment for claudication.[18] A supervised program of treadmill-based walking exercise can induce a training response characterized by large improvements in treadmill exercise performance, peak oxygen consumption, and quality of life. The benefits and mechanisms of improvement have been reviewed in a study by Stewart et al.[18] Possible mechanisms underlying the training response in PAD include improvements in endothelial function, skeletal muscle metabolism, and blood viscosity, and a reduction in systemic inflammation.[18] Exercise training may also improve leg blood flow and oxygen delivery, but the observed

changes are inconsistent and not generally correlated with the training response. In addition to hemodynamic and metabolic mechanisms, improved biomechanics of walking also contribute to increased walking ability by decreasing the oxygen requirements to sustain a given level of constant load exercise.[19] The clinical response also appears to be specific to the type of exercise used in the training program. A training regimen based on treadmill walking produces greater functional outcomes when compared with strength training.[19]

Exercise training-induced adaptations can be related to the metabolic alterations in PAD, as detailed above. Physical training is an important modifier of mitochondrial expression and can thus change the intracellular environment resulting from the demands of exercise. Better metabolic function may be a final common mechanism for the diverse responses induced by training. Consistent with this concept, training of PAD subjects is associated with a decrease in plasma and muscle acylcarnitine contents; these changes relate to the magnitude of improvement in exercise capacity derived from the training.[11] A metabolic component to the training benefit is also consistent with the greater impact of aerobic training as compared with strength training.[19]

Thus, progressive walking exercise addresses many aspects of the non-hemodynamic components of claudication pathophysiology. The benefit of exercise training is as effective in improving exercise performance as successful revascularization and provides further evidence that components of the pathophysiology of claudication (other than large vessel hemodynamics) contribute significantly to the functional limitations in these patients.[20]

Revascularization: Surgical bypass for patients with claudication has been shown to improve exercise performance.[20] This clinical benefit is related to improvements in limb perfusion; however, most patients still experience claudication and have a limited exercise performance.[21] This may be due to the inability to bypass every occlusive lesion and, thus, the capacity to increase exercise-induced changes in blood flow is not normalized to meet muscle metabolic demand. Alternatively, abnormalities in skeletal muscle structure and function may contribute to persistent limited exercise performance in PAD.

***Pharmacotherapy*:** Vasodilators decrease arteriolar tone; however, numerous controlled trials have found no convincing evidence of clinical efficacy for any of these medications in patients with claudication.[22] For example, prostaglandins modulate arteriolar tone, but recent trials with the oral prostaglandin beraprost did not demonstrate any improvement in treadmill exercise performance or quality of life.[23] There are several potential pathophysiologic explanations for the lack of efficacy of these drugs in treating claudication. During exercise, resistance vessels dilate distal to a stenosis or occlusion in response to ischemia. Vasodilators have little effect on these already dilated vessels and may decrease resistance in unobstructed vascular beds, leading to a "steal" of blood flow away from under-perfused muscles. Vasodilators can also lower systemic pressure, leading to a reduction in perfusion pressure. Thus, vasodilating medications do not favorably address the pathophysiology of claudication or result in a treatment benefit.

Cilostazol is an FDA-approved drug for treatment of claudication. It has pharmacodynamic properties that inhibit platelet aggregation and vascular smooth muscle proliferation, and improve the lipid profile and vasodilation. How these potential mechanisms relate to the clinical benefit of cilostazol is unknown. Despite the lack of a direct relationship between the pharmacodynamic properties of cilostazol and the clinical benefits, a meta-analysis of 6 randomized trials indicated a significant benefit on exercise performance and quality of life.[24]

Ranolazine, dichloroacetate, glucose-insulin-potassium solutions, L-carnitine, and propionyl L-carnitine alter ischemic muscle metabolism by shifting the balance of fuels oxidized from fatty acids towards glucose.[25] This metabolic shift is associated with an improvement in the ratio of ATP production to oxygen utilized, which is advantageous when oxygen is limiting. A recent study demonstrated that ranolazine improved exercise performance in patients with angina, which is, in many respects a cardiac equivalent to claudication, without any changes in systemic hemodynamics.[26] Orally administered L-carnitine and propionyl-L carnitine may have metabolic benefits by providing an additional source of carnitine to buffer the cellular acyl CoA pool. In this way, carnitine may enhance glucose oxidation under ischemic conditions.[27] Propionyl-CoA generated from propionyl-L-carnitine may also improve oxidative metabolism through its anaploretic actions in priming the Kreb's cycle, secondary to succinyl-CoA production. Propionyl-L-carnitine has been shown to improve treadmill performance and quality of life in patients with claudication.[28, 29]

Administration of L-arginine may improve vascular endothelial function and muscle blood flow in patients with PAD.[30] In patients with claudication, L-arginine supplementation does not consistently improve treadmill exercise performance.[31] Several studies have revealed that statins have a beneficial effect on exercise performance in patients with claudication.[32] Statins also improve endothelial function and have other favorable metabolic effects. The functional

benefit of statins is not due to regression of atherosclerosis or gross change in limb hemodynamics.

The observed effects of these metabolic modifiers in PAD provide clinical evidence that alterations in muscle metabolism have functional importance and contribute to the pathophysiology of claudication. Treatment with metabolic agents that do not alter systemic or local hemodynamics, can improve the clinical and functional status of the patient.

Conclusions

Patients with PAD and claudication have a profound limitation in exercise performance. Large vessel obstruction impairs the delivery of oxygenated blood to skeletal muscle during exercise, resulting in a supply/demand mismatch. Arterial hemodynamics and large vessel blood flow do not fully account for the exercise limitations observed in patients with claudication. Changes in the microcirculation, skeletal muscle structure, and metabolic function significantly contribute to disease pathophysiology. Understanding these multiple components of exercise limitation provides insight into treatment approaches that address the spectrum of abnormalities seen in patients with claudication.

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