Pathophysiology of Intermittent Claudication in Peripheral Artery Disease

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Peripheral artery disease (PAD) affects more than 200 million adults worldwide. Patients with lower extremity PAD have a heightened risk for cardiovascular events because of the systemic nature of atherosclerosis, and benefit from treatment with risk factor-modifying therapies. Limb symptoms in PAD include intermittent claudication and diminished walking ability. Arterial obstruction from atherosclerotic lesions initiates limb ischemia; however, decreased perfusion incompletely determines the clinical expression of PAD and its response to therapy. Potential mechanistic drivers of claudication in addition to arterial obstruction include inflammation, vascular dysfunction, reduced microvascular flow, impaired angiogenesis, and altered skeletal muscle function. An improved understanding of the pathophysiology of limb symptoms has the potential to accelerate development of novel therapeutic strategies to increase functional capacity in patients with PAD.

Key Words: Blood flow; Claudication; Exercise; Ischemia; Peripheral artery disease

There is growing recognition of the effect of peripheral artery disease (PAD) on cardiovascular health. Recent studies indicate that, globally, over 200 million adults have PAD, which is an expression of systemic atherosclerosis and well-established as heightening the risk for cardiovascular events. The limb manifestations of PAD induce considerable suffering. Patients with PAD experience intermittent claudication, characterized as exertional leg pain that limits walking ability, and often times, disability. Current medical therapies to reduce the burden of lower extremity symptoms in patients with PAD are limited. Revascularization by endovascular intervention or surgical reconstruction is used to treat lifestyle-limiting claudication if patients do not respond adequately to medical therapy including exercise training. Indeed, lower extremity revascularization with endovascular approaches has undergone a dramatic increase in use. Though endovascular therapy improves blood flow and function, there are significant associated risks, and durability may be limited, especially in infragenual disease. Abundant evidence demonstrates the benefits of exercise therapy in claudication, yet the mechanisms underlying the beneficial effects remain incompletely defined. Thus, an improved understanding of the pathophysiology of limb symptoms in PAD is critical to accelerate the development of novel therapies.

Global Epidemiology of PAD

A set of recent international studies highlights the worldwide prevalence of PAD. The Global Burden of Disease study estimates a more than 30% increase in deaths and disability attributable to PAD between 2005 and 2015, which is largely determined by population aging. PAD prevalence escalates with advancing age, affecting 1 in 10 adults older than 70 years. In addition to age, smoking and diabetes are the strongest risk factors for PAD across the world. A comprehensive global evaluation of PAD found that its prevalence and risk factors are similar in high-income countries to low- and middle-income countries. Lower socioeconomic status is a newly recognized risk factor for PAD. Importantly, there has been a greater increase in PAD prevalence in low- and middle-income countries, rising by 28.7% from 2000 to 2010 as compared with 13.1% in high-income countries. The changing burden of PAD is also greater in women as compared with men.

The health implications of PAD derive from both its limb and cardiovascular manifestations. Consistent with the systemic nature of atherosclerosis, polyvascular disease is common in patients with PAD. In the REACH registry, 61% of PAD patients had concomitant coronary artery disease (CAD) and/or cerebrovascular disease. Thus, the presence of PAD portends a high risk for subsequent cardiovascular events. A meta-analysis of over 48,000 participants in population-based cohort studies demonstrated that a low ankle-brachial index (ABI) predicted a 2-fold risk of death, cardiovascular death, and major coronary events at all ranges of the Framingham Risk Score. Further, the elevated risk of cardiovascular events is present in both symptomatic and asymptomatic patients. Patients with atherosclerotic disease in more than 1 vascular territory have particularly poor outcomes. In the over 5,000 Japanese
Table. Medical Therapies for Symptomatic Peripheral Artery Disease

<table>
<thead>
<tr>
<th>Cardiovascular risk reduction</th>
<th>Leg symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
<td><strong>Pharmacologic treatment</strong></td>
</tr>
<tr>
<td>• Treatment with aspirin or clopidogrel is recommended</td>
<td>• Cilostazol is effective to increase walking distance</td>
</tr>
<tr>
<td>• Benefits of vorapaxar as additional antiplatelet therapy are uncertain</td>
<td></td>
</tr>
<tr>
<td><strong>Statin agents</strong></td>
<td><strong>Exercise programs</strong></td>
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<tr>
<td>• Treatment with a statin medication is indicated</td>
<td>• Supervised exercise program is recommended in patients with claudication</td>
</tr>
<tr>
<td><strong>Antihypertensive therapy</strong></td>
<td>• Structured community or home-based exercise program with behavioral change techniques can be beneficial alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking can be beneficial</td>
</tr>
<tr>
<td>• Antihypertensive therapy should be used to treat hypertension</td>
<td></td>
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<tr>
<td>• ACE inhibitors or ARBs can be effective in reducing the risk of cardiovascular ischemic events in patients with PAD</td>
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<tr>
<td><strong>Smoking cessation</strong></td>
<td></td>
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<tr>
<td>• Advice to quit and development of a strategy for cessation that includes pharmacotherapy and smoking cessation program</td>
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</table>

Adapted from the American College of Cardiology/American Heart Association 2016 Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease. ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

patients studied in the REACH registry, the incidence of the composite outcome (cardiovascular death/myocardial infarction/stroke/hospitalization) was highest in patients with PAD, and the presence of PAD in patients with cerebrovascular disease was associated with a doubling of the 1-year rate of stroke and myocardial infarction. Thus, PAD is a key atherosclerotic marker, and its diagnosis and treatment may afford an opportunity to reduce the risk of a cardiovascular event.

Risk reduction therapy continues to be underutilized in patients with PAD. Successful implementation of medical therapy to target cardiovascular risk is critical to reducing the cardiovascular morbidity and mortality in PAD. Medical therapy for cardiovascular risk prevention in PAD has been reviewed elsewhere and updated in the recent AHA/ACC lower extremity guidelines. As outlined in the Table, several therapies have proven efficacy to reduce cardiovascular risk in PAD and are recommended as guideline-directed therapy.

**Functional Effect of PAD**

Patients with PAD suffer from limb disability. Traditionally, functional limitation has been ascribed to intermittent claudication, the classical PAD symptom characterized by leg pain with activity that resolves with rest. Intermittent claudication is present in only 10–20% of PAD patients. However, a large proportion of PAD patients report atypical leg symptoms that restrict walking ability. Patients with reduced ABI, a ratio of the ankle and brachial systolic pressures, have impaired functional ability regardless of symptom status. In prospective studies, both symptomatic and asymptomatic patients with PAD are at risk for progressive functional impairment. The walking limitations in PAD patients are multifactorial in origin and are reflected in the self-restriction of activity to reduce the occurrence of leg discomfort.

Reduced walking function in patients with PAD is associated with poor clinical outcomes. Quality of life is reduced in patients with PAD, reflecting lower extremity pain and activity restriction. Studies that have assessed patients with a walking impairment questionnaire and measurement of walking times demonstrate that reduced walking ability is associated with higher rates of cardiovascular events and death. A recent meta-analysis of 10 studies demonstrated that shorter walking distance was associated with higher cardiovascular and all-cause deaths. Declines in self-reported exercise performance enhance prediction of mortality risk in PAD. Lower physical activity also predicts progression of PAD with greater decline in the ABI over time. Thus, therapeutic approaches that restore functional capacity in patients with PAD may have a wide-ranging health-promoting effect.

**Pathogenesis of Limb Complications and Walking Impairment in PAD**

Arterial obstruction by flow-limiting lesions underlies the lower extremity manifestations of PAD. In a demand-ischemia model, intermittent claudication reflects inadequate augmentation of skeletal muscle perfusion during exercise. Several lines of evidence, however, indicate that the drivers of the limb symptoms in PAD are more complex. Atherosclerotic disease occurs in the context of multiple disease processes that interfere with exercise ability. Potential mechanisms are detailed in the Figure and the current evidence supporting the role of reduced blood flow, vascular dysfunction, altered muscle metabolism, impaired angiogenesis, and inflammatory activation in producing limb discomfort and functional limitation is discussed in this section.

**Reduced Limb Perfusion Caused by Arterial Obstructive Lesions**

Reduced limb blood flow because of atherosclerotic disease characterizes PAD. Measurement of the ABI evaluates the severity of atherosclerosis impairing blood flow between the aorta and the ankle. Obstructive lesions create drops in both blood pressure and flow that are additive to reducing the ankle pressure. With exercise, the flow to the lower extremity increases and magnifies the pressure drop across fixed lesions, increasing the sensitivity to detect PAD. Recent studies highlight the clinical import of an abnormal exercise ABI with additive prognostic value for future limb revascularization and death compared with the resting ABI alone. Inadequate perfusion with exercise, which...
is caused by fixed lesions, is clearly a key component underlying limb symptoms in PAD. However, multiple studies indicate that the generation of limb ischemia in PAD has multiple determinants.

The anatomic severity of obstruction is an imprecise predictor of clinical status and course. It is well-established that patients with PAD have impaired functional status compared with individuals with a normal ABI.7,39 Yet some studies have shown just modest correlation between ABI and walking ability,40,41 and other studies have found no association between ABI and the magnitude of functional limitation.42 Limb blood flow, assessed by other techniques, has shown inconsistent associations with functional measures. Magnetic resonance imaging-based measurement of calf blood flow was moderately related to walking distance,43 but plethysmography-based calf blood flow showed no association with treadmill walking or change in walking time.42 Prospective studies confirm that individuals with an abnormal ABI have a greater decline in walking ability at 2-year follow-up.44 However, the association between the magnitude of the reduction in ABI and functional outcomes is less clear. Taken together, the available evidence indicates that anatomic disease does not fully govern the clinical status of patients with PAD.

Vascular Dysfunction in PAD

Arterial insufficiency in PAD reflects both fixed and dynamic reductions in blood flow. A healthy vascular endothelium produces several vasodilator substances, including nitric oxide,45 which has pluripotent vascular benefits such as inhibiting platelets, reducing smooth muscle proliferation, preventing leukocyte adhesion, and promoting angiogenesis.46 Diminished nitric oxide bioactivity in the leg impedes the augmentation of blood flow with exercise.47 Vascular dysfunction may also exacerbate the vasoconstrictive effects of catecholamines and limit flow-mediated dilation.48 Together, the effects of abnormal endothelial function may worsen clinical symptoms in PAD.

Several studies have described the clinical relevance of endothelial dysfunction in PAD. Measures of endothelium-dependent vasodilator function, including brachial artery flow-mediated dilation and acetylcholine-induced vasodilation, are lower in patients with PAD.49-51 Both conduit and microvascular endothelial function were evaluated in 1,320 subjects, including 377 with PAD, and compared with patients with CAD; the patients with PAD had more severe impairment of multiple metrics of vasodilator function.52 The presence of endothelial dysfunction in patients with PAD is consistent with a systemic disruption of vascular function. Impairment of the hyperemic blood flow response is associated with functional impairment in PAD.53 There is evidence connecting greater brachial flow-mediated dilation to greater physical activity in daily life in patients with PAD.54 Recent studies related impaired brachial flow-mediated dilation with reduced self-reported walking ability and 6-minute walk test.55,56 Interestingly, patients with PAD have decreased superficial femoral artery flow-mediated dilation associated with lesion severity.57 Arterial stiffness measures, including higher pulse pressure and augmentation index, also are associated with reduced walking time in patients with PAD.58,59 Endothelial dysfunction measured by brachial flow-mediated dilation and reactive hyperemia predicts a higher risk of events after vascular surgery.60-62 Whether endothelial dysfunction predicts progressive functional impairment has not been evaluated.

Impaired Angiogenesis and Reduced Microcirculatory Flow

Chronic limb ischemia initiates several vascular structural adaptations. Insufficient blood supply produced by arterial ischemia induces a complex program of vascular growth.63 Multiple factors have been identified that regulate angiogenesis in animal models, including vascular endothelial growth factor (VEGF), fibroblast growth factor, hepatocyte...
growth factor, and hypoxia-inducible factor 1-α.64-66 In addition, specific bone marrow-derived cells may target regions of ischemia and promote vessel regeneration.67-69 Genetic regulators, including microRNA, are also important for angiogenesis.70 MicroRNA93 shows lower expression in animals genetically predisposed to severe clinical phenotypes such as hindlimb ischemia.71 In animal models, there is abundant evidence that therapies stimulating angiogenesis increase skeletal muscle perfusion and restore functional status.

In patients with PAD, inadequate angiogenesis and collateral formation may potentiate limb ischemia and serve as a mechanism driving functional impairment. One study found that lower capillary density in PAD patients, as assessed by skeletal muscle biopsy, was associated with reduced functional measures including peak walking time.72 Similarly, imaging studies using MRI or contrast-enhanced ultrasound have demonstrated lower microvascular flow in the calf musculature in PAD patients.73,74 Exercise blood flow measured by contrast ultrasound was related to claudication time in a treadmill test.75 Also, reduced skeletal muscle blood flow as measured by MR during exercise was associated with impaired 6-minute walking time.43 Taken together, evidence from clinical investigations supports the concept that microcirculatory dysfunction affects limb function in patients with PAD, and that enhanced calf blood flow may be a therapeutic avenue. Thus, proangiogenic therapy approaches to treating PAD have been used in many studies of growth factor and cell-based therapies. As reviewed recently, these clinical trials have failed to convincingly demonstrate a reduction in limb symptoms, including pain and wound healing.80 There are a number of potential explanations for the disappointment with pro-angiogenic interventions in patients with PAD. Translational studies emphasize the relevance of systemic disease and risk factors to impaired angiogenesis in clinical PAD. Paradoxically, patients with PAD have higher levels of VEGF-A, a key promoter of angiogenesis.75,76 A recent study found evidence that an anti-angiogenic isoform of VEGF, VEGF-165b, is upregulated in both preclinical models and patients with PAD.77 The enhanced expression of anti-angiogenic VEGF is driven by the pro-inflammatory Wnt5a/JNK pathway, which is activated by obesity. Thus, metabolic dysfunction may mediate inadequate angiogenesis in PAD by generating anti-angiogenic factors and complicate the responses to therapies aimed to stimulate angiogenesis. Resolvin D2, an anti-inflammatory regulator of tissue reparative responses, is important in both hindlimb ischemia models and patients with PAD.78 Resolvin D2 treatment enhances arteriogenesis and reduces inflammation, including in diabetic animals. Thus, the next generation of pro-angiogenic therapies may require evaluation in animal models with metabolic dysfunction and target both inflammation and vascular growth.

Skeletal Muscle Alterations and Mitochondrial Dysfunction

Repeated episodes of ischemia have deleterious effects on the limb skeletal musculature.79 Altered skeletal muscle structural and metabolic properties magnify ischemia-induced functional impairment.80,81 Imaging studies with CT demonstrate that patients with PAD have a reduced calf muscle area that is not fully explained by inactivity.82 Further, the skeletal muscle displays lower density and higher fat content, which may limit muscle function.82 On muscle biopsy, there is greater muscle cell apoptosis and reduced type I fiber content, which may interfere with performance.83,84 Ischemia also damages peripheral nerve function, with evidence of poor nerve conduction in patients with severe PAD.85,86 Mitochondrial dysfunction contributes to impaired skeletal muscle metabolism in PAD. Both the circulating and muscle levels of intermediates of oxidative phosphorylation, including acylcarnitines, are higher in PAD, suggesting reduced mitochondrial metabolism.87 In the muscle tissue, mitochondrial mass is higher; however, there is lower activity of several mitochondrial complexes impeding ATP generation and enhancing reactive oxygen species production.88-91 Altered mitochondrial function restricts oxygen utilization and may also promote endothelial dysfunction as mitochondrial-derived oxidants reduce nitric oxide bioactivity.92-94 Muscle fiber degeneration is associated with evidence of oxidative stress, including carbonyl groups and 4-hydroxy-2-nonenal adducts, protein modifications produced by reactive oxygen species.95 Mitochondrial function is also important in angiogenesis, consistent with the notion of coupling of vascular and muscular parameters. In hindlimb ischemia models, peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α), a key regulator of mitochondrial biogenesis, promotes vascular regeneration.96

Altered muscle metabolism also reflects reduced nutrient uptake related to systemic metabolic disturbances in PAD patients. Patients with PAD display insulin resistance and insulin resistance predicts a higher risk of developing clinical PAD.96,97 By evaluating skeletal muscle glucose uptake with PET, it has been shown that PAD patients with intermittent claudication have calf muscle insulin resistance.98 Additional studies are required to link muscle insulin resistance to functional parameters in PAD and to determine whether interventions to promote insulin sensitivity will reduce limb symptoms.

Skeletal muscle dysfunction, including mitochondrial abnormalities, affects walking ability in PAD.80 Both decreased calf muscle content and altered fiber type relate to reduced functional parameters.82,84 Importantly, mitochondrial dysfunction assessed by MR spectroscopy to evaluate phosphocreatine recovery is associated with lower treadmill walking time.43 PAD patients with greater amounts of muscle acylcarnitine accumulation have greater degrees of exercise limitation.87 Evidence of myofiber damage is associated with both reduced walking distance and muscle strength in patients with claudication.99 Further, altered regulation of a cytoskeletal protein, desmin, is associated with reduced mitochondrial respiratory function and functional capacity in PAD.100 There is evidence of inadequate mitochondrial clearance through autophagy in the skeletal muscle in PAD that associates with walking parameters, consistent with increased mitochondrial damage.100 Greater levels of daily activity is associated with healthy calf muscle parameters. Several aspects of skeletal muscle phenotype, including increased calf muscle fat and decreased muscle density, predicted 2-year functional decline in a longitudinal study.102 Evidence of reduced mitochondrial biogenesis is associated with higher overall mortality, which is potentially mediated through reduced physical activity.103

Systemic and Local Inflammation

Inflammatory activation participates in the development of atherosclerosis and may play a part in the generation of limb symptoms. Circulating biomarkers of systemic
inflammation, including C-reactive protein (CRP) and soluble intracellular adhesion molecule-1 (sICAM-1), predict a higher risk of developing clinical PAD. In patients with established PAD, higher levels of inflammatory biomarker are associated with both progression of lower extremity arterial obstruction and the risk of cardiovascular events. Skeletal muscle ischemia may drive local inflammation, exacerbating symptoms and altering muscle metabolism. In imaging studies, lower calf muscle area and higher calf muscle fat content were associated with systemic inflammation. Vascular inflammation also impairs dynamic responses by reducing nitric oxide bioactivity, which leads to decreased endothelium-mediated vasodilation.

Inflammation has been associated with reduced walking capacity in PAD. Markers of vascular inflammation relate to lower functional measures in PAD patients. Higher peripheral monocyte expression of tumor necrosis factor α is associated with lower treadmill walking time in patients with intermittent claudication. In a similar fashion, higher peripheral mononuclear expression of the pro-inflammatory mediator, Wnt5a, is associated with lower ABI. In patients with PAD, a greater degree of daily physical activity is associated with lower levels of CRP, IL-6, fibrinogen, sICAM-1, and sVCAM-1. In prospective studies, functional decline is less in PAD patients with lower levels of CRP.

Treateme

Treatment of Limb Symptoms in PAD

Reduction of limb morbidity is a key component of the comprehensive care for PAD patients. Several studies have emphasized the high rate of limb complications in patients with symptomatic PAD. In the REACH registry, 18.2% of patients with symptomatic PAD underwent peripheral revascularization and 3.8% had an amputation at 4-year follow-up. Similarly, recent clinical trials that included patients with symptomatic PAD demonstrated that 1 in 5 patients with PAD undergo revascularization at 3 years. As discussed before, patients with obstructive PAD, regardless of limb symptom characteristics, have functional impairment. As shown in the Table, available medical treatment modalities to improve limb function and outcome include exercise therapy and antiplatelet therapy. Revascularization remains an option for persistent symptoms despite optimal medical therapy.

Robust evidence supports the utility of exercise training programs to improve walking function in patients with PAD. In patients with claudication, exercise is the most effective noninterventional approach to reducing leg symptoms. Based on numerous clinical trials, supervised exercise programs are recommended as initial therapy for claudication. Controlled studies and systematic reviews indicate that supervised exercise training improves both walking time and walking distance by clinically relevant amounts. Increases in treadmill walking confer improved physical functioning, as exercise rehabilitation augments accelerometer-based daily activity levels and quality of life measures. Patients with PAD without claudication also derive benefit from supervised exercise. In a trial of 156 PAD patients of whom over 80% had atypical symptoms or were asymptomatic, treadmill exercise intervention increased the 6-minute walk distance.

Though less beneficial than structured exercise treatment, home-based exercise programs have demonstrated improvements in functional parameters. Randomized trials show that home-based walking exercise programs that include measures to enhance adherence increase the 6-minute walk distance as well as quality of life measures. As shown in the Table, the updated ACCF/AHA practice guidelines support the use of home-based walking and alternate approaches to exercise to enhance walking ability in patients with claudication. Ongoing studies are evaluating the use of mobile technology-based activity monitors to deliver exercise training at home and potentially expand access to exercise interventions.

The benefits of exercise therapy in PAD have not been convincingly linked to gains in peripheral blood flow. In animal models of hindlimb ischemia, restoration of blood flow in the ischemic limb depends on vascular growth and collateral enlargement. In contrast, studies in patients with PAD do not consistently show changes in blood flow following exercise training. Measurements of hyperemic blood flow, a dynamic response that depends on arterial supply and vasodilation, increased in some but not all studies of exercise training. Further, the change in calf blood flow is not associated with the improvements in walking ability following exercise, indicating a divergence between arterial flow and functional measures. It is possible that more advanced assessment of microvascular flow in the calf will be necessary to evaluate the effects of exercise. However, evaluation of randomized trials of exercise training showed no effect on the resting ABI, suggesting that hemodynamic changes are not the major determinant of the exercise-induced reduction in limb symptoms.

Exercise induces important vascular and skeletal muscle adaptations that may account for the improvements in functional status. Interventional studies show an improvement in flow-mediated dilation, a measure of conduit artery endothelium-dependent vasodilation, with exercise training in PAD patients. Exercise training also has a favorable effect on skeletal muscle, with restoration of carnitine metabolism that is associated with improved treadmill walking time. Further studies are needed to evaluate whether exercise training improves mitochondrial function or calf muscle phenotype in PAD. Chronic exercise training may also suppress inflammatory activation. Supervised exercise intervention reduced neutrophil activation in a small study of PAD patients with claudication.

The available trial evidence indicates that exercise training and revascularization are complementary approaches to treating limb symptoms. In patients with claudication, exercise training and lower extremity bypass surgery had similar effects on walking distance. The randomized CLEVER study compared exercise training to endovascular therapy or optimal medical therapy for aorto-iliac disease in 111 patients with claudication. Overall, supervised exercise training induced the most robust increase in treadmill walking time at 6 months, without causing a concomitant change in ABI. Endovascular therapy also increased treadmill walking time, which was accompanied by a greater improvement in patient-reported quality of life metrics. The combination of supervised exercise training with endovascular revascularization for claudication was evaluated in the ERASE trial. Compared with supervised exercise alone, the combined therapy had a greater effect on treadmill walking distance at 1, 6 and 12 months. Thus, the choice of therapeutic approach is optimally applied in a patient-centered fashion with the option of multimodality treatments to maximize functional improvement.
Summary and Conclusions

Patients with PAD have both increased cardiovascular risk and decreased functional ability because of their limb symptoms. The recently updated ACC/AHA guidelines emphasize the importance of risk factor modification with antplatelet therapy, statins, antihypertensive agents, and smoking cessation in patients with PAD. The mechanisms that lead to intermittent claudication in PAD are complex and include reduced limb perfusion, systemic inflammation, vascular dysfunction, impaired angiogenesis, reduced microcirculatory flow, and skeletal muscle dysfunction. An enhanced understanding of the pathophysiology of leg symptoms in PAD is critical for the development of novel therapeutic approaches. Exercise therapy improves walking ability in PAD through multiple beneficial effects on both vascular and skeletal muscle function. A patient-centered approach combining medical treatment, exercise intervention and selective use of revascularization is warranted to reduce limb symptoms and improve the quality of life in PAD.

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Limb Symptoms in PAD


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Limb Symptoms in PAD

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