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Review article

# Peripheral arterial disease: A small and large vessel problem

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ABSTRACT

Peripheral arterial disease (PAD) is one clinical manifestation of systemic atherosclerosis and is very common. Despite its prevalence, PAD remains underdiagnosed, undertreated, and understudied. The most common symptom in patients with PAD is intermittent claudication (IC), or pain in the lower extremities with walking or exertion, which is relieved after a short period of rest. Many patients with confirmed PAD are asymptomatic or have symptoms other than IC. Regardless of symptoms, patients with PAD have poor cardiovascular outcomes. PAD has largely been viewed a disease of large vessel atherosclerosis but what is becoming clear is that arterial plaques and occlusions are only one piece of the puzzle. Recent work has shown that abnormalities in the microvasculature contribute to the outcome of patients with PAD. From the perspective of the leg, limitation in blood flow is not the only problem as patients have a myriad of other problems, including muscle fibrosis, neuropathic changes, changes in the cellular respiration machinery and dysfunction of the small vessels that perfuse skeletal muscle and the supporting structures. Supervised exercise training remains one of the most effective tool to treat patients with PAD, however, the mechanisms behind its effectiveness are still being elucidated and use of structured exercise programs is not widespread. Medical therapy to treat systemic atherosclerosis is underutilized in patients with PAD. Invasive therapies are used only when patients with PAD have reached an advanced stage. While invasive strategies are effective in some patients with PAD, these strategies are costly, carry risk, and many patients are not amenable to invasive therapy. Appreciating the complex pathophysiology of PAD will hopefully spur new research and development of effective therapies for PAD.

## 1. Peripheral arterial disease: scope of the problem

Peripheral arterial disease (PAD) is a complication of systemic atherosclerosis and is defined by the presence of a reduced ankle-brachial blood pressure index (ABI). Though less studied than coronary artery or cerebrovascular disease, PAD is a disease where atherosclerotic occlusions develop in one or more locations from the distal aorta, external iliac, superficial femoral artery and popliteal artery and its major branches. These occlusions limit blood flow to one or both lower extremities causing ischemia with exertion or even at rest. Ischemia from PAD may cause pain or cramping in the buttocks or calf during walking, which resolves after a short period of rest; a clinical syndrome called intermittent claudication (IC) [1]. IC limits walking distances and patients may begin to restrict activity to avoid symptoms. The majority of subjects with PAD defined by their ABI have atypical or totally lack symptoms. In others, the disease may remain clinically silent until lack of blood flow has led to, or imminently threatens, tissue loss in the lower extremities. This is called chronic limb-threatening ischemia (CLTI) and develops when persistent hypo-perfusion causes rest pain and/or tissue loss in the form of non-healing ulcers or frank gangrene [2]. Patients with IC can also progress to CLTI. Every year, it is estimated that 1–2 % of patients with IC will progress to CLTI for each limb involved [3]. CLTI can be a devastating development as it often leads to major adverse limb events (MALE), such as amputation. CLTI also carries a grave prognosis. Untreated CLTI is associated with a 22 % mortality rate and a 22 % amputation rate at 1 year following the diagnosis [4] both of which may be higher in those with the most severe disease [5]. Indeed, PAD is the number one cause for amputation in adults in the US [6].

It is estimated that 8–12 million Americans have PAD [7]. The dominant risk factors for the development of PAD include advancing age, smoking, and diabetes. While the prevalence of coronary artery disease (CAD) and cerebrovascular disease is declining [8], that is not the case for PAD [9]. The risk of PAD increases rapidly with age, such that approximately 5 % of individuals aged 40 or greater have PAD, while approximately 12 % of individuals over age 70 have the disease

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[10]. PAD disproportionately affects ethnic minorities [11], who may also be less likely to have the disease diagnosed and receive guideline-directed therapies [12]. Indeed, after controlling for major demographic risk factors, food insecurity (a marker for health disparities) was associated with the diagnosis of PAD [13].

PAD is associated with many adverse outcomes that are not limited to the leg. The presence of PAD is associated with higher risk of disease in other vascular beds, such as the coronary and cerebral arteries [14–18]. Another possible explanation for acceleration of atherosclerotic disease in other vascular beds is the extent to which the ischemic limb is a source for increased levels of circulating inflammatory cytokines. PAD is also associated with lower quality of life, as afflicted patients may be unable to carry out usual daily activities, including employment.

PAD has historically been viewed diagnostically and therapeutically as a disease of large vessel atherosclerosis. If so, surgical and percutaneous interventions, which target localized atherosclerotic disease, would be expected to largely eliminate complications. This has not been borne out in studies. In patients with claudication, successful percutaneous revascularization of the inflow vessel does not necessarily correct impaired muscle perfusion as assessed by magnetic resonance imaging [19]. In CLTI, even after successful large vessel revascularization, patients can still proceed to have adverse clinical events including progressive loss of ambulation and death [20]. Here, PAD has a corollary to coronary disease: Osborne et al. showed that patients having no epicardial disease, but signs of coronary microvascular dysfunction as measured by positron emission tomography myocardial perfusion imaging, still experienced a high rate of coronary events [21]. PAD clearly effects both large and smaller vessels. In this review, the effects of PAD on both small and large vessel will be explored.

## 2. Atherosclerosis of the conduit arteries

How does PAD begin in patients? The presence of atherosclerotic plaque, defined as localized thickening of the arterial wall >1.2 mm in the common femoral artery has been identified in about 2/3rd of individuals aged 54–77 years [22]. This is much higher than the reported number of individuals with symptomatic PAD and while no hemodynamic testing was performed in this study, it suggests that the substrate for developing PAD is quite common. The progression of disease in the peripheral arteries is thought to proceed similarly to disease in the coronary and cerebrovascular beds. As a first step in this process, endothelial cells, which line the arteries, are exposed to excess low-density lipoprotein (LDL) in the circulation [23]. LDL particles can permeate into the subendothelial layer and undergo chemical changes that make the LDL particle proinflammatory. This is associated with activation and dysfunction of the endothelial cells lining the artery. LDL particles incite an inflammatory response involving monocytes, neutrophils, natural killer cells, and others. Monocytes differentiate into macrophages in the intimal wall, take up LDL and turn into foam cells. Foam cells in turn release cytokines that encourage the migration and growth of smooth muscle cells into the intimal layer. By these processes, a plaque is formed in the vessel wall. Foam cells may also undergo apoptosis and in that process, release additional substances such as metalloproteinases that can weaken the vessel wall [23]. A weakened wall would make a plaque more likely to rupture, which would expose the contents of the plaque to the circulating blood. This incites an inflammatory and thrombotic response which could acutely block the vessel and cause acute limb ischemia which is not common. In most cases of PAD leads to a further narrowing over time in a process called inward remodeling [24], restricting blood flow distally. This limits oxygen and nutrient delivery to the tissues downstream.

## 3. Diagnosing PAD: the ABI and symptoms

The easiest and most widely available method to diagnose PAD is to obtain measurements of blood pressures at the ankles and comparing it with the highest blood pressure in either arm. These measures are called the ankle-branchial index (ABI). An ABI less than or equal to 0.9 defines the presence of PAD, though in a minority of patients the ABI can be normal at rest and is only detected as low based on a post-exercise ABI. Additionally, patients with PAD may have an elevated ABI (>1.40), which is generally accepted as an indication of incompressible arteries [25]. Some [26], but not all [27] studies have suggested that these patients are at similar risk for cardiovascular events and mortality as those with low ABI [28,29]. The toe-brachial index (TBI) compares pressures at the toes to the pressures in the upper extremities which avoids the pitfalls of the ABI in measuring heavily calcified vessels [30]. Many patients diagnosed with PAD via the ABI are asymptomatic or report symptoms other than classic IC. For example, in the Study of Osteoporotic Fractures, only 18 % of community dwelling women 65 years of age or older with an ABI < 0.90 reported classical claudication symptoms [31]. Similarly, the Cardiovascular Health Study found an abnormal ABI in 12 % of participants, while only 2 % reported IC [14]. Even when PAD has progressed to more severe stages, the ABI may fail to detect its presence. A retrospective review of ABI testing performed in a single, accredited vascular lab showed that 40 % of patients with known limb-threatening ischemia had a normal resting ABI [32]. Sukul et al. examined patients with CTLI undergoing endovascular or surgical intervention and found that up to 25 % of these patients had a normal ABI [33]. The authors also found that those with CTLI and a normal ABI were more likely to have vascular disease distal to the knees. The ABI detects changes in the hemodynamic pressures driving blood flow into the leg. Abnormal ABIs are highly correlated to disease in other vascular beds [14,15,17,18], suggesting that the ABI is well suited to detect disease in large arteries, but may miss disease in smaller, distal arteries. The ABI certainly does not measure perfusion. Therefore, the disconnect between the ABI and symptomatology may lie in the inability of the ABI to fully measure all pathophysiologic abnormalities caused by PAD.

## 4. PAD and muscle perfusion

Perfusion describes blood and other nutrient material reaching target organs and the ability of the organ to expel toxins. Perfusion occurs at the levels of the terminal arterioles and capillaries in the muscle tissue and is the primary problem at the crux of PAD. Poor muscle perfusion has been linked directly with shorter walking distances [34] and more significant symptoms [35] in patients with PAD. It has been shown that patients with PAD have decreased capillary density in the muscles of the affected limb [36]. Decreased capillary density has been correlated with time to onset of claudication symptoms, peak oxygen consumption [36], and lower oxygen consumption at peak exercise [37]. Arteriolar rarefaction is a term describing decreased density of arterioles supplying an organ. In a model of PAD, arteriolar rarefaction was shown to increase resistance to blood flow [38]. Thus, even if flow in the conduit arteries was restored, rarefaction of the vascular network supplying the muscle tissue did not allow for a proportionate increase in muscle perfusion [38]. In addition to the symptoms associated with poor perfusion described above, ischemic skeletal muscles in patients with PAD show higher fat content [39] and fibrotic changes [40] than control muscle in the less affected extremity of the same person. Such changes may not be reversible even if perfusion is improved.

Restoring perfusion should be the sine qua non of PAD treatment. The human body has a remarkable but variable ability to adapt to reduced blood flow, especially in the skeletal muscles of the leg in comparison to the heart or brain. When flow-limiting lesions develop, blood flow can be diverted around the blockage through the development of pre-existing or the formation of new vascular channels. Angiogenesis describes the formation of new capillary vessels from existing capillaries typically involving endothelial cell migration under the influence of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) [41].

Arteriogenesis describes enlargement of existing collateral vessels due to increased shear stress that is due in turn to higher blood flow through these areas [41,42]. Vasculogenesis is yet another adaptive process by which angiogenic precursor cells from the bone marrow enter circulation and augment angiogenic processes by secreting growth factors and chemokines that may home vascular precursor cells to areas of ischemia [41]. There were multiple trials of therapeutic angiogenesis which attempted to harness these natural adaptations for the treatment of PAD. Usually, this involved administration of growth factors directly into the affected limbs of patients with PAD. While non-blinded or small studies of these therapies showed some promise, when the larger trials were conducted, they were largely unsuccessful [43]. There are multiple theories on why these trials failed [41]. One of these gets back to the concept of arteriolar rarefaction and the unique interplay of large and small vessel dysfunction in PAD. The new vessels that form are of smaller diameter than the blocked conduit vessel and therefore, are of higher resistance. Many smaller vessels of higher resistance cannot fully compensate for the loss of a larger vessel [44]. Additionally, these new vessels may not function as well as healthy capillaries and arterioles and ultimately, will not improve perfusion (Fig. 1). That increased numbers of blood vessels may not translate into improved perfusion was demonstrated in the early work on therapeutic angiogenesis. When $VEGF_{165}$ was administered to the affected limbs of PAD patients via adenoviral transfection, there was a significant increase in the number of new collateral vessels formed, but no differences in MALE, wound healing, or rest pain [45]. The RAVE trial, which used a different isoform of VEGF, $VEGF_{121}$, showed significantly more edema in the treated limb compared to those receiving an empty transfection vector [46]. This was attributed to the possibility of the growth factor inducing additional, but more permeable, capillary vessels [46].

## 5. PAD: the impact of microvascular disease

Regardless of vessel size, endothelial cells (EC) line the walls of blood vessels and abnormal function of EC remains at the core of PAD and other cardiovascular disease. Over the years, it has become understood that endothelial cells have paracrine functions that effect circulating blood cells as well as the cells residing in the sub-endothelial layer. One of the key mediators of this is nitric oxide (NO). NO is produced by endothelial cells through the consumption of L-arginine using a unique nitrogen oxygen synthase, eNOS [47]. NO modulates vascular tone, enhances the barrier function of the endothelial cell, and inhibits thrombosis. This has been shown in animal models. Specifically, murine models deficient in eNOS are hypertensive [48], demonstrate increased propensity for adhesions of leukocytes to the endothelial cell surface [49], and increased platelet activation and aggregation [50]. When

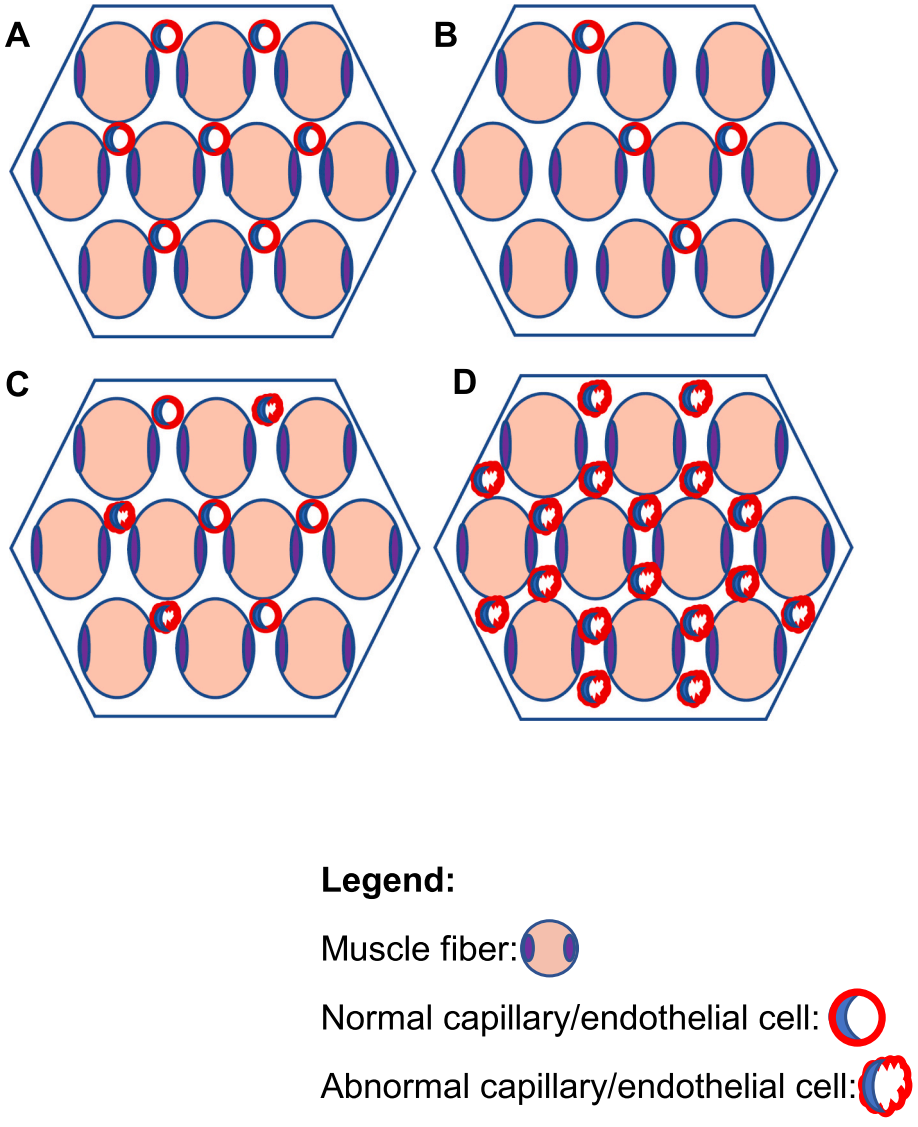


**Fig. 1.** Perfusion in muscle cells. Separate of inflow, the number of endothelial cells (EC, lining capillaries) per muscle fiber effects muscle cell perfusion. In A, there are 10 muscle fibers and 7 normal EC. If each normal EC has a perfusion unit of 1, then in A perfusion = 7/10. In B, a patient with PAD could have vascular rarefaction and even if all of the EC were normal, perfusion to that unit of muscle would be 4/10. Patients with PAD do not have entirely normal EC and in C, even though the total number of EC is equal to A, perfusion would be lower. If abnormal EC are assigned a perfusion unit of 0.33 then perfusion would be 5/10. Finally, in D, a patient with PAD and most or all abnormal EC, could have more EC/area but lower muscle perfusion. In this example, perfusion is still 5/10.

subjected to surgical hind-limb ischemia in these preclinical models, tissue loss is common and therapeutic approaches limited [51].

Endothelial dysfunction has been observed as poor vasodilation in the larger conduit arteries. In areas where plaque has formed, endothelial cells demonstrate a paradoxical response to vasodilatory signals. Pathological vasoconstriction was observed in diseased coronary vessels after exposure to acetylcholine, a substance that normally causes vasodilation [52]. These abnormalities are present even in endothelial cells downstream of the lesion, thus, endothelial dysfunction is part of the pathophysiology of PAD. Endothelial dysfunction is not only a local event, it too is a systemic problem [53], with manifestations in conduit and resistance vessels [53]. Resistance vessels are small arterioles that distribute blood into capillaries, where exchange of oxygen and nutrients to cells occur [54]. Resistance vessels are the division of the vasculature tree that produces the vascular resistance to maintain mean arterial pressure [54]. In PAD, resistance vessels are not able to dilate maximally in response to exercise [55]. Further, in patients with CLTI, these vessels become adapted to chronic hypoperfusion, causing decreased wall thickness, cross sectional area, and wall-to-lumen ratio [56]. These adaptations make the vessel less able to withstand increases with hydrostatic pressure and contribute to edema formation, especially after revascularization procedures, which suddenly increase blood flow to a distal extremity [42]. In CLTI patients, edema may contribute to poor wound healing after revascularization procedures and ultimately hasten the need for amputation [42].

A number of secondary and tertiary problems can develop in PAD. The pathological vasoconstriction induced by endothelial dysfunction can worsen muscle ischemia during exercise. The repeated cycles of muscle hypoperfusion during exercise with normalization during rest induces the generation of damaging reactive oxygen species, inflammation, muscle fiber apoptosis, muscle fiber type switching, and overall atrophy of the fibers [57,58]. A motor neuropathy develops, further decreasing muscle strength, though it is unclear if this is from arterial insufficiency or from the atrophy that ensues from lack of exercise [59]. In patients with PAD versus controls there is often associated mitochondrial dysfunction that can negatively affect muscle energy metabolism [60]. Additionally, there are other alterations in muscle fiber innervation [61] and inflammatory changes [62] that also likely correlate with symptom severity. There are no established pre-clinical models of recurrent ischemia in animals, which makes it difficult to study these phenomena.

There is evidence that microvascular disease (MVD) in PAD is an independent risk factor for adverse limb events such as amputation. Beckman et al. followed a large sample of mostly male Veterans (n = 125,674) in the Veterans Aging Cohort study who had no amputation at the study initiation date of April 1, 2003 [63]. These patients were followed until death, amputation, or the date of December 31st, 2014. For the purposes of this study, microvascular disease was defined as the presence of retinopathy, peripheral neuropathy, and/or nephropathy (proteinuria). PAD was defined by a novel algorithm using administrative data (not by ABI); however, this study found that the presence of both PAD and MVD conferred a 15.9-fold risk of having an amputation compared to having neither diagnosis [63]. Similarly, in the coronary and cerebral vascular beds, MVD has been associated with higher mortality. MVD is now being viewed as a critical component of systemic atherosclerotic disease, affecting multiple organ systems and contributing to excess risk of poor health outcomes [64].

## 6. How treatment of PAD impacts small and large vessel disease

### 6.1. Medications and lifestyle changes

Lifestyle changes, including smoking cessation and blood sugar control are modifiable risk factors at the individual patient level. Additionally, antihypertensive medications to control blood pressure along with antiplatelet and statin medications are also recommended [65]. In patients with PAD and CAD there is an emerging role for anticoagulants, such as direct oral anticoagulants, as shown in the VOYAGER trial [66]. The VOYAGER trial showed that in patients with symptomatic PAD undergoing revascularization, addition of low-dose Xarelto to aspirin reduced acute limb ischemia and major amputation up to 3 years after randomization. This benefit was at least partially offset by significant increases in symptomatic bleeding. This study included both patients with IC and CLTI, the analyses presented did not further stratify them. Otherwise, there are few PAD-specific medications that have been shown to provide benefit except for cilostazol and pentoxifylline. Cilostazol, a phosphodiesterase-3 inhibitor, interferes with platelet aggregation and may act as a vasodilator [67]. One study showed that Cilostazol reduced restenosis and 1-year amputation rates [68]. However, cilostazol is contraindicated in the presence of left ventricular systolic dysfunction [69], a prevalent comorbid condition in PAD patients [70,71]. Pentoxifylline weakly inhibits fibrinogen and may increase the flexibility of red blood cells to transverse the capillaries [72]. Both medications have been shown to significantly increase walking distance [73,74]. In spite of these therapies, PAD may still progress to needing an invasive intervention to restore blood flow. Percutaneous and surgical interventions target lesions of the conduit arteries but are usually limited to those who fail treatment with conservative measures or have manifestations of CTLI.

### 6.2. Exercise and PAD

Supervised exercise remains the main non-invasive treatment for PAD. Exercise has limited side effects and has been consistently shown to improve walking distance, but implementation of effective exercise programs is not widespread. There is a large body of literature on supervised or structured exercise programs. Almost 30 years ago, Gardener and Poehlman performed a meta-analysis of published studies on exercise programs for patients with IC [75]. They found the key characteristics of a successful program included walking, as opposed to other forms of exercise, to near-maximal levels of discomfort, for 30 min at time at least 3 times weekly for a total of 6 months [75]. Programs following this paradigm were able to increase the distance before onset of pain 179 %, from 126 m to 351 m, and the maximum walking distance 122 %, from 326 m to 723 m [75]. A limitation of this meta-analysis was the inclusion of non-randomized studies [75], thus, there remained some uncertainty about exactly what constitutes a successful exercise program for PAD. The issue was revisited in 2012 in a meta-analysis by Fakhry et al., including 25 randomized control trials with an intervention group receiving some sort of exercise training [76]. For all but one of these studies, the program including walking, or walking in addition to another exercise (e.g. heel lifts). This meta-analysis found that a supervised walking program was associated with greater walking distances post-intervention compared to no intervention. However, walking to near-maximal pain, use of a treadmill, or length of the program was not independently associated with these improvements [76]. Additionally, it has been shown that intensive programs such as that described by Gardener and Poehlman have been associated with high rates of drop-out, approximately 40 % in one Danish study [77].

Structured or supervised programs are required to achieve success in patients with PAD, therefore, some studies have explored strategies for improving access. A Danish study [77] included an intervention group that performed exercise out in the communities where patients lived, as opposed to traveling to a clinic. This was found to be as effective in increasing walking distance with similar rates of discontinuation, when compared to historical controls that participated in structured exercise programs in larger medical centers. Offering such programs closer to where people work and live may increase compliance, however, patient involvement in such programs remains low. There may be other underlying reasons for poor participation in exercise programs such as cost, lack of transportation and inconvenience [78]. Although often cited as a reason for poor participation, cost may not be the primary factor.

Divakaran et al. demonstrated that only 1.3 % of Medicare patients with IC participated in exercise programs, which have been reimbursable by Medicare since 2017 [79,80].

### 6.3. How does exercise specifically improve circulation in PAD?

During exercise, healthy individuals can increase blood flow to the legs up to 20-fold, while patients with PAD have only a modest ability to increase flow, up to 2-fold [81]. Exercise has also been shown to increase femoral artery diameter, decrease intimal-media thickness (IMT) and decrease the IMT to lumen ratio in sedentary men, but these men did not have known PAD [82]. Therefore, it is likely that exercise does not correct large vessel occlusion to any significant degree. One of ways exercise improves perfusion is by reversing endothelial dysfunction in distal muscle. After a 4-week exercise program, Hambrecht et al. showed less vasoconstrictive response to acetylcholine in conduit and resistance vessels of the coronary vascular bed in men with symptomatic CAD compared to a control group treated with medications only [83].

Exercise increases cardiac output in both healthy patients and those with PAD [84]. This increase in output may increase blood flow velocity and increase shear stress and potentially activate arteriogenesis in PAD patients. There have been numerous studies in large and small animal models demonstrating the positive effects of exercise on arteriogenesis [85]. Despite all the strong data in animal models, it remains unclear if exercise improves collateral blood flow in humans with PAD [86]. This may be due to the challenges inherent to accurately measuring blood flow to the lower extremity in humans, however, the precise reasons are likely to be very complex [85].

Exercise has been shown to upregulate inflammatory cytokines which could stimulate angiogenesis [87]. Specifically, VEGF levels were increased in the interstitial fluid around muscles of PAD patients after active and passive exercise [88]. Exercise may also directly improve muscle perfusion. Duscha et al. showed that in a sample of patients with IC that completed an exercise program, there was an increase in capillary density in the muscles that was followed by an increase in oxygen utilization by the muscles [89]. Other studies have shown that sera from patients involved in both structured and home-based exercise programs reduced endothelial cell apoptosis in vitro [90].

### 6.4. Percutaneous transluminal angioplasty (PTA) and surgery for treatment of PAD

In spite of optimal medical management with lifestyle changes, medications and exercise, PAD may still progress and necessitate an invasive intervention to restore blood flow. Percutaneous and surgical interventions target lesions of the conduit arteries but are usually limited to those who fail treatment with conservative measures or have manifestations of CTLI. Endovascular therapy via PTA is an option for patients who have failed conservative therapy and have suitable anatomy. Generally, short lesions that are not around a bi-or trifurcation point are suitable for endovascular treatment. More complex lesions are generally best suited for open surgical revascularization. Endovascular treatments and surgery are an immediate remedy to blockages of large vessels that restore arterial inflow.

Open surgery may have a slight edge over percutaneous revascularization in diabetic patients with foot ulcers [91]. In the very recently published BEST-CLI trial, patients with symptomatic PAD due to infrainguinal disease suitable for either endovascular or open repair were randomized to surgery or endovascular intervention [92]. The groups randomized to surgery were further divided based on the availability of a native saphenous vein segment to serve as a conduit. It was found that the group randomized to surgery with a native saphenous vein graft had significantly fewer individuals reaching the primary outcome of a MALE (major amputation, repeat intervention or death) compared to the endovascular group or the surgical group that needed an alternative conduit. This study did not stratify patients by disease severity.

Studies have shown that stenting improves resting ABI [19,93,94]. Further, endovascular treatments have been shown by some to improve markers of microvascular dysfunction such as flow-mediated dilation as measured in the arm [95,96] and pulse transit time [97]. There is also data to suggest that endovascular and surgical treatments do improve perfusion [98,99]; however, they may not be as efficacious in improving perfusion than structured exercise programs. Measures of changes in flow may not reflect changes in the microvasculature.

Other studies have shown no effect of PTA on flow measures [100] or even a worsening of perfusion [101]. Data on the effect of surgical revascularization on microvascular disease is more sparse, but is probably similar to endovascular therapy, notwithstanding the other potential deleterious effects of surgery.

For patients with IC, it has been shown that PTA alone did not significantly improve walking distance or quality of life at 2 years compared to exercise [102]. The CLEVER study was an NIH-sponsored multi-center study that randomized patients with (primarily or exclusively) aorto-iliac PAD and moderate to severe intermittent claudication to revascularization versus exercise [103]. Patients with CTLI were excluded. The patients were randomized to three treatment arms: optimal medical treatment (OMT), structured exercise and stenting. OMT consisted of an antiplatelet agent and an anticlaudication drug, such as cilostazol, with advice on maintaining a healthy diet and exercise at home. The structured exercise program involved thrice weekly, 1-hour sessions for 26 weeks in total. The other intervention arm was the stenting arm in which flow-limiting stenosis (>50 %) were treated with PTA and stenting. The primary endpoint was peak walking time, there were multiple secondary endpoints, including quality of life (QoL) and claudication onset time. The randomized groups were overall well-matched at baseline, the presence of stroke was more common in the structured exercise group. After 18 months, peak walking time improved by approximately 5 min in the exercise group, 3 min in the stented group and less than 1 min in the OMT group. Similarly, claudication onset time increased by approximately 3 min in the exercise group and stented groups and increased less than 1 min in the OMT group. There was a significant improvement of the ABI in the stented group compared to both the exercise and the OMT groups. Based on SF-12 scores, stenting and exercise showed greater improvement in physical functioning over the OMT group. There were also improvements in pain and walking distance in the stented and exercise groups compared to OMT, but no differences between each other. Therefore, there was no benefit to undergoing a procedure over completing the exercise program. Interestingly, the questionnaire scores regarding symptoms, treatment satisfaction, and QoL all favored stenting over exercise [103]. The extent of the response in the stented group suggests that microvascular dysfunction is present in this population and may not be resolved with an endovascular intervention. In more recent meta-analyses of strategies for treatment of IC, it was found that the combination of PTA and structured exercise provided the most benefit in maximum walking distance [104,105].

Clearly, there is a role for invasive therapies in the treatment of PAD, but the findings above beg the question: are these therapies able to overcome abnormalities in the microvasculature? Beyond the endothelium, many of the deleterious changes to the muscle tissue will already have occurred by the time of a surgery or intervention and may not be reversible. More research is desperately needed on all modalities of therapy for PAD. An important limitation in research is measuring flow (or hemodynamics) versus true perfusion. In fact, many of the available techniques for measuring flow, including ABI, duplex ultrasound, venous plethysmography, and angiography are fraught with limitations [106]. Magnetic resonance angiography (MRA) gives very detailed anatomical pictures but is often limited by artifacts [106]. X-ray angiography, often considered the “gold-standard”, can only image the lumen of the vessel (not the vessel walls) and also cannot measure perfusion [106]. More sophisticated techniques to measure perfusion have been developed [106] but they may be expensive and cumbersome

and are therefore currently limited to research applications. This will be an important challenge to overcome in future studies of treatment of PAD.

## 7. Concluding remarks

In summary, PAD is a common disease affecting limbs and life. While known as a condition of large vessel atherosclerosis, the microvasculature clearly and directly contributes to the symptoms and outcomes in patients with PAD. Despite its prevalence, PAD receives less attention compared to other manifestations of atherosclerosis, and this may contribute to slow progress in treatment. Surgical and endovascular interventions target atherosclerotic disease in large vessels not small vessels. Medications and exercise may help mitigate microvascular dysfunction when used, but they have not been reliably shown to improve QoL in patients with symptomatic PAD. No treatment has emerged as superior in terms of restoring muscle perfusion in the long term; therefore, the optimal treatment for PAD remains unclear. The evolution in conceptualizing PAD as not merely a distinct lesion in a large artery but a systemic disease with effects on large and small blood vessels as well as dysfunction of the target organ will hopefully open doors to other potential therapeutic targets and improve the lives of the many patients afflicted with this disease.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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