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Review Article

Breaking the Tie: How to Start Rehabilitation in Patients with Severe Limiting Intermittent Claudication

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Abstract

Intermittent claudication (IC) is the most common symptom of peripheral artery disease (PAD). IC can worsen the quality of life and results in marked exercise intolerance and limitation to daily activities with increased risk of cardiovascular complications. Exercise training is the first line of conservative management in PAD. However, patients with IC may not tolerate weight-bearing exercises because of leg discomfort induced by physical effort. This review will address alternative rehabilitation strategies to reduce exercise limitations and improve exercise tolerance in patients with IC.

Keywords: Peripheral Artery Disease; Exercise Intolerance; Exercise Limitations; Intermittent Claudication; Exercise Training

Introduction

Around 200 million people around the world are living with peripheral artery disease (PAD) and the prevalence is rising strongly with elderly populations [9]. PAD is a systemic vascular affection rather than the coronaries by atherosclerotic changes [36], which occurs in more than one vascular bed, with increased atherothrombotic risk and the risk of microvascular disease [22]. As a final stage, it can present with chronic limb-threatening ischemia, which is characterized by ischemic rest pain and can progress to tissue necrosis [26]. Intermittent claudication (IC) is an exertional leg pain that causes the patient to stop walking until pain resolves [25]. There are two types of IC according to the underlying pathology, neurologic and vascular claudication, both produce activity-limiting symptoms in the legs. In neurogenic claudication, narrowing of lumbar spine results in nerve compression directly or indirectly through vascular compression of nerve roots [21]. While in vascular claudication, there is a narrowing of blood vessels results in a reduction of blood flow to extremities. This reduction in blood flow creates a mismatch between oxygen supply and metabolic demand (physical effort) causing ischemia in the legs, mainly the calf, thigh, or buttocks.

Classification of peripheral arterial disease

Many classifications were designed for PAD according to patient symptoms, angiographic findings, and incidence [12]:

Fontaine classification

This was the first classification for PAD depending on the patient symptoms only and classify the patient into four stages as follows, stage one is an organic disease without symptoms, stage

two patient starts to develop symptoms and divided into two subgroups according to walking distance when patients develop leg pain, either more or less than 200 meters, stage three patient develop pain during rest, while stage four necrosis or gangrenous changes occurs in the limbs.

Rutherford classification

Regarding the incidence of ischemia, Rutherford classified PAD into either acute or chronic. Then include the clinical data to other investigation results as doppler, ankle brachial indices (ABI), and pulse volume recording for further classification of chronic limb ischemia. Acute limb ischemia classified as viable, threatened, or irreversibly damaged.

Bollinger angiographic classification

According to the site and severity of atherosclerotic lesions (anatomy of the arterial affection) identified by catheter angiography, each arterial segment was given a score of four for severity degree: total occlusion, luminal stenosis more than 50%, stenosis 25 to 49% of the lumen, and plaques <25% of the lumen. Also, several lesions were included: single lesion, multiple lesions less than half of the diseased segment, or multiple lesions more than half of the diseased segment. This classification used to decide the treatment method (Surgical or catheter angioplasty).

Exercise limitations in PAD

Reduced blood flow to lower limbs exaggerates intermittent claudication and functional disability. IC is the major limitation of exercise training in PAD. Additionally, PAD can lead to reduced muscle mass and mitochondrial dysfunction leading to muscle deconditioning and disuse (Figure 1). These symptoms reduce walking and functional capacity leading to physical inactivity and increase the risk of cardiovascular events [11]. Inflammation may accelerate functional impairment in PAD by favoring plaque growth and inducing skeletal muscle injury. Furthermore, endothelial dysfunction and reduced nitric oxide bioavailability may blunt blood flow during exercise [11].

Management of peripheral arterial disease

There is no specific medication to cure this condition, as this a longstanding arterial affection by multiple risk factors for atherosclerosis, including hypertension, smoking, obesity, and redundancy [32]. Management of chronic limb ischemia includes aggressive control of all risk factors, physical training, and revascularization. Medical therapy includes adjunctive medications using a platelet inhibitor or vitamin K antagonist (warfarin) may help after revascularization therapy [32]. Cilostazol is a new phosphodiesterase III inhibitor, a potent inhibitor of platelet aggregation with vasodilatory, antithrombotic, antiproliferative, and positive lipid-altering effects [29]. Pentoxifylline, another drug cause decreasing blood viscosity, improving red blood cells flexibility, and enhance microcirculatory flow and tissue oxygen concentration [28].

Figure 1: Redundant lifestyle result in muscular malfunctioning and physical disability leading to lower limb pain which may causes more physical redundancy as a vicious circle.

Exercise is a very well-known adjuvant therapy besides medical and revascularization treatment. Exercise added to standard care, resulted in improvement of symptomatology, different outcomes, and quality of life [5,11,19,31].

Exercise therapy with intermittent claudication

Exercise training has the potential to reverse these pathologic events of IC and thereby interrupt the clinical course toward dis-

ability [11]. In the middle 60s, unsupervised walking was demonstrated to improve claudication onset time and maximal walking distance (MWD) [16]. Recently, supervised walking has been reported as the gold standard training modality in the management of IC [18,35]. Patients are supervised and instructed to walk till claudication onset then rest until the pain is resolved [14,35]. Supervised treadmill walking has been shown to improve MWD and vascular function which in turn reduces the cardiovascular risk [14,18,35]. Comprehensive exercise interventions with PAD have several benefits including but not limited to functional capacity, claudication symptoms, and quality of life. The physiological mechanism behind exercise therapy in PAD is multifactorial, where exercise can reverse and suppress the inflammatory process of PAD and enhance physical capacity [8,11]. The following physiological adaptations can summarize the potential benefits of exercise training with IC:

Vascular and metabolic adaptation

The evidence that exercise training improves calf muscle blood flow in claudication is scarce and inconsistent with the improvement in walking capacity [16,31]. It is known that exercise improves ischemia and consequently IC by different mechanisms, potentially through recruitment of collaterals and stimulation of angiogenesis. Merits of exercise in improving functional limitations may exceed recruiting new collaterals by improving muscle metabolism, mitochondrial function, microcirculation, and endothelial function [4,10]. Thereby, enhanced muscle oxidative metabolism in response to exercise training can improve walking performance without change in muscle perfusion [14,31]. Furthermore, exercise training can contribute to the mitigation of claudication symptoms through reduced systemic inflammation and improve endothelial function [31]. However, the association between the anti-inflammatory effect of exercise training with the improvement in walking capacity is unclear yet [31]. Further studies are required to assess the direct effect of exercise training on walking capacity and claudication symptoms mediated through vascular adaptations.

Cardiorespiratory adaptations

Cardiorespiratory fitness can defer the onset of claudication pain during walking in PAD and contributes to improved walking performance without changes in ABI [5,34,38]. Hence, improved general physical conditioning and aerobic capacity may contribute to the improved walking ability alongside metabolic adaptations [5].

Neural adaptation

Peripheral neuropathy can be associated with PAD in form of axonal and myelin damage that may cause muscle spasticity, muscle atrophy, and strength loss with further disability and claudication worsening [7]. Exercise training can enhance the sensory and motor function of peripheral nerves, and reduce associated neuropathic pain and chronic neuroinflammation. Consequently, these adaptations may alter the pain threshold in favor of improving claudication distance and exercise capacity [6,7].

Exercise prescription in PAD with severely limiting IC

In this section, we will focus on the dilemma between exertional leg symptoms induced by exercise, and how to tackle this cycle (Figure 1) to reduce physical inactivity and improve exercise tolerance in patients with severe claudication symptoms. In fact, some patients with advanced IC cannot tolerate walking because of persistent leg pain and severe muscular ischemia [35]. Also, claudication symptom is a major barrier that impedes adherence to the walking training program [1]. In line with this, it has been reported that exercise training can reduce walking performance and mitochondrial capacity in some patients with advanced PAD [37]. Additionally, patients with several comorbidities can have fewer improvements in walking distance after supervised exercise training [8]. Consequently, the role of exercise and healthcare professionals is to tailor alternative training strategies alongside walking to reduce the physical impact on lower arteries and improve exercise tolerance simultaneously. Several exercise interventions can be beneficial for all patients with IC despite the severity of the condition [35]. Examples of these alternative modalities that can be prescribed for patients with severe IC are summarized in table 1 including:

Resistance training

Patients with IC can have less muscle mass and lower strength [13,19]. Resistance training (RT) can improve walking capacity and endurance [20,27]. RT increases muscle fiber area and capillarization to muscle, which in turn improves oxygen delivery and promotes walking endurance in symptomatic patients with PAD after long-term (24 weeks) resistance training [20]. In the middle of the 90s, Hiatt and colleagues reported the superiority of treadmill walking to resistance training in terms of walking performance and tolerance [15]. In contrast, it has been shown that whole-body RT can improve walking capacity and claudication symptoms similar to walking training [20,24,27]. Few studies investigate the

combined RT with aerobic training and found no additional improvement in MWD compared to isolated aerobic training [15,17]. However, some patients reported less pain during RT compared to walking training [27]. Reduced pain during RT can be beneficial for claudicants with physical and social walking barriers, which can increase their engagement to regular physical activity with similar training adaptations to walking.

Cycling

Leg cycling has been shown to elicit similar cardiovascular and metabolic strain to treadmill walking in patients with IC [3]. However, the prescription of cycling as an alternative mode to walking has little evidence yet, and there are controversial findings in the literature. In the previous decay, Sanderson and colleagues reported that treadmill walking is more effective than cycling for the improvement of walking endurance and tolerance [30]. On the contrary side, Walker and colleagues have shown that arm and leg cycling can improve walking distance and mitigate claudication symptoms similarly [38]. Different factors can contribute to this controversy. For instance, the modalities of exercise testing used for MWD were different among the aforementioned trials (graded treadmill walking vs incremental shuttle test). Further clinical trials are required to validate the accuracy and reliability of exercises test used with PAD patients. Surprisingly, arm cycling can improve walking distance in patients with IC, this finding was attributed to systemic adaptations of cardiorespiratory fitness [5,34,38]. Furthermore, improved walking capacity was associated with peak cardiorespiratory fitness [5,34]. Arm cycling can be prescribed to patients with severe PAD and comorbidities to improve exercise tolerance with potential progression to leg cycling and walking.

Table 1: Exercise prescription for patients with IC.

Type	Intensity	Duration	Work-to-rest Ratio	Frequency	Progression
Interval walking (exercise-rest-exercise) [2, 25, 35]	• 40-60% of max workload on a treadmill test Or • The workload that elicits claudication within 3-5 min on 6MWT Or • Moderate to moderately severe claudication on the claudication scale	30-60 min	5-10: 2-5 min	3-5 d/week	Every 1-2 weeks duration increases (5 min/day) to reach 60 min
Interval arm or leg cycling [5,30,38]	80% VO_2peak	20-40 min	2: 2 min	3 d/week	Progress to reach max workload after 6 weeks
Resistance Training [2,24,25]	20-50% 1RM	30-60 min	NA	2 d/week	Over 4 sessions to reach 30-80% 1RM

6MWT: six-minute-walk test, VO_2 peak: peak oxygen uptake, 1RM: one repetition maximum, Max: maximal, Min: minutes, d: days , NA: not available.

Conclusion

Exercise therapy consists of multiple interventions that need to be personalized and tailored to meet the patient's condition and tolerance. In context with IC in PAD, walking is a gold standard training of IC management, and feasible in most patients. Several research studies looked for other alternative exercise modes to be implemented for those who cannot tolerate walking, and for those who cannot attain sufficient physiological adaptations because of severe limiting IC. One of the most promising lines of those rehabilitation modalities is the implementation of arm, leg cycling, and whole-body RT alongside walking in patients with markedly limiting IC, however, further research is needed to ensure the effectiveness of this rehabilitation model.

Conflict of Interest

None declared.

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