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**Breaking the tie: How to start rehabilitation in patients with severe limiting intermittent claudication****Authors**\*Bassem Zarif<sup>1,2</sup>, \*\* Akram Samir<sup>1,2</sup>, \*\* Safwat Elnahrawy<sup>1,2</sup>, \*\*\* Eman Gamal<sup>2</sup>**Affiliation**<sup>1</sup> National Heart Institute<sup>2</sup> Ministry of Health and Population**Last academic degree****\*Doctorate degree****\*\* Master Degree****\*\*\* Bachelor Degree****Corresponding Author****Bassem Zarif**

National Heart Intitute, Ministry of Health and Population, Postal code: 11311, Cairo, Egypt.

+201223950548, bassemzarif@gmail.com

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# Breaking the tie: How to start rehabilitation in patients with severe limiting intermittent claudication

Bassem Zarif, Akram Samir, Safwat Elnahrawy, Eman Gamal

## Abstract

Intermittent claudication (IC) is the most common symptom of peripheral artery disease (PAD). IC affects 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 cannot tolerate exercise 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

## Abbreviations

COT	Claudication Onset Time
MWD	Maximal Walking Distance
RT	Resistance Training
IC	Intermittent Claudication
PAD	Peripheral Artery Disease

## Introduction

### Peripheral Artery Disease

Around 200 million people around the world are living with PAD and the prevalence is rising strongly with elderly populations (Fowkes et al. 2013). PAD is a systemic vascular affection rather than the coronaries by atherosclerotic changes (Ugwu, Anyanwu, and Olamoyegun 2021), which occurs in more than one vascular bed, with increased atherothrombotic risk and the risk of microvascular disease (Olesen et al. 2021). As a final stage, it may be presented by chronic limb-threatening ischemia, which is characterized by ischemic rest pain and/or tissue necrosis (Peters et al. 2020).

### Intermittent Claudication and Exercise Intolerance

IC is an exertional leg pain that causes the patient to stop walking until pain resolves (Pescatello 2014; Treat-Jacobson et al. 2019). There are two types of intermittent claudication (IC) according to the underlying pathology, neurologic and vascular claudication, both produce activity-limiting symptoms in the legs, in neurogenic claudication narrowing of lumbar result in nerve compression directly or indirectly through vascular compression of nerve roots (Nadeau et

al. 2013). 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 (Hardman et al. 2014):

#### **i. 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.

#### **i.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, arterial brachial indices (ABI), and pulse volume recording to further classify the chronic limb ischemia. while acute limb ischemia was classified into viable, threatened, or irreversibly damaged.

#### **ii.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 was 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 (Hamburg and Balady 2011). 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 (Hamburg and Balady 2011).

### **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 (Swedish Council on Health Technology 2008). 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 (Swedish Council on Health Technology 2008). Cilostazol is a new phosphodiesterase III inhibitor, a potent inhibitor of platelet aggregation with vasodilatory, antithrombotic, antiproliferative, and positive lipid-altering effects (Samra et al. 2003). Pentoxifylline, another drug cause decreasing blood viscosity, improving red blood cells flexibility, and enhance microcirculatory flow and tissue oxygen concentration (Salhiyyah et al. 2015).

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 (Stewart et al. 2002; McDermott et al. 2009; Bronas et al. 2011; Hamburg and Balady 2011).

## **Exercise Therapy with IC**

Exercise training has the potential to reverse these pathologic events of IC and thereby interrupt the clinical course toward disability (Hamburg and Balady 2011). In the middle 60s, unsupervised walking was demonstrated to improve claudication onset time (COT) and maximal walking distance (MWD) (Larsen and Lassen 1966). Recently, supervised walking has been reported as the gold standard training modality in the management of IC (McDermott et al. 2009; Treat-Jacobson et al. 2019). Interval walking training is highly recommended with lower extremity PAD and intermittent claudication over 12-24 weeks (Table 1). Patients are supervised and instructed to walk till claudication onset then rest until the pain is resolved (Hiatt et al. 1994; Treat-Jacobson et al. 2019). Supervised treadmill walking has been shown to improve MWD and vascular function which in turn reduces cardiovascular risk (Hiatt et al. 1994; McDermott et al. 2009; Treat-Jacobson et al. 2019). Comprehensive exercise interventions with PAD have several benefits including but not limited to functional capacity, claudication symptoms, and quality of life. The physiologic mechanism behind exercise therapy in PAD is multifactorial, where exercise can reverse and suppress the inflammatory process of PAD and enhance physical capacity (McDermott et al. 2009; Hamburg and Balady 2011). 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 (Larsen and Lassen 1966; Stewart et al. 2002). 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 (Blomqvist and Saltin 1983; Haas et al. 2012). Thereby, enhanced muscle oxidative metabolism in response to exercise training can improve walking performance without change in muscle perfusion (Hiatt et al. 1990; Stewart et al. 2002). Furthermore, exercise training can contribute to the mitigation of claudication symptoms through reduced systemic inflammation, and improve endothelial function (Stewart et al. 2002). However, the association between the anti-inflammatory effect of exercise training with the improvement in walking capacity is unclear yet

(Stewart et al. 2002). 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 the ankle-brachial index (Walker et al. 2000; Treat-Jacobson et al. 2009; Bronas et al. 2011). Hence, improved general physical conditioning and aerobic capacity may contribute to the improved walking ability alongside metabolic adaptations (Bronas et al. 2011).

### **Neural Adaptation**

Peripheral neuropathy can be associated with PAD in the form of axonal and myelin damage that may cause muscle spasticity, muscle atrophy, and strength loss with more disability and claudication worsening (Dobson, McMillan, and Li 2014), another aspect that favors exercise as a part of the standard care for peripheral vascular disease, is the beneficial effect of exercise on peripheral nerves, as it was found that treadmill exercise improves nerve neurogenesis and nerves myelin repair (Cheng et al. 2020). Exercise can improve peripheral nerve sensory and motor function, reduce associated neuropathic pain and chronic neuro inflammation, and consequently may alter pain threshold in favor of improving claudication distance and exercise capacity (Dobson, McMillan, and Li 2014).

## **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 (Treat-Jacobson et al. 2019). Also, claudication symptom is a major barrier that impedes adherence to the walking training program (Abaraogu et al. 2018). In line with this, it has been reported that exercise training can reduce walking performance and mitochondrial capacity in some patients with advanced PAD (van Schaardenburgh et al. 2017). Additionally, patients with several comorbidities can have fewer improvements in walking distance after supervised exercise training (Dörenkamp et al. 2016). 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 (Treat-Jacobson et al. 2019). 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 (McDermott et al. 2004; Harwood et al. 2017). Resistance training (RT) can improve walking capacity and endurance (McGuigan et al. 2001; Ritti-Dias et al. 2010). 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 (McGuigan et al. 2001). 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 (Hiatt et al. 1994). In contrast, it has been shown that whole-body RT can improve walking capacity and claudication symptoms similar to walking training (McGuigan et al. 2001; Ritti-Dias et al. 2010; Parmenter et al. 2020). Few studies investigate the combined RT with aerobic training and found no additional improvement in maximal walking distance compared to isolated aerobic training (Hiatt et al. 1994; Machado et al. 2019). However, some patients reported less pain during RT compared to walking training (Ritti-Dias et al. 2010). Reduced pain during RT can be beneficial for claudicants with physical and social walking barriers, which can increase 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 (Askew et al. 2002). 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 (Sanderson et al. 2006). On the contrary side, Walker and colleagues have shown that arm and leg cycling can improve walking distance and mitigate claudication symptoms similarly (Walker et al. 2000). Different factors can contribute to this controversy. For instance, the modalities of exercise testing used for maximal walking distance 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 (Walker et al. 2000; Treat-Jacobson et al. 2009; Bronas et al. 2011). Furthermore, improved walking capacity was associated with peak cardiorespiratory fitness (Treat-Jacobson et al. 2009; Bronas et al. 2011). Arm cycling can be prescribed to patients with severe PAD and comorbidities to improve exercise tolerance with potential progression to leg cycling and walking.

## 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. For years a lot of 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 implementation of arm, leg cycling, and whole-body RT alongside walking in patients with markedly limiting IC is a. However further research is needed to ensure the effectiveness of this rehabilitation model.

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## Competing interests

None declared.

## Ethics approval

Not applicable.

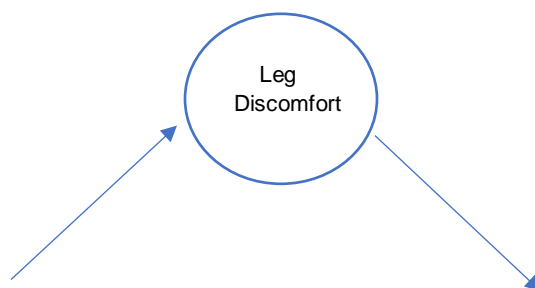
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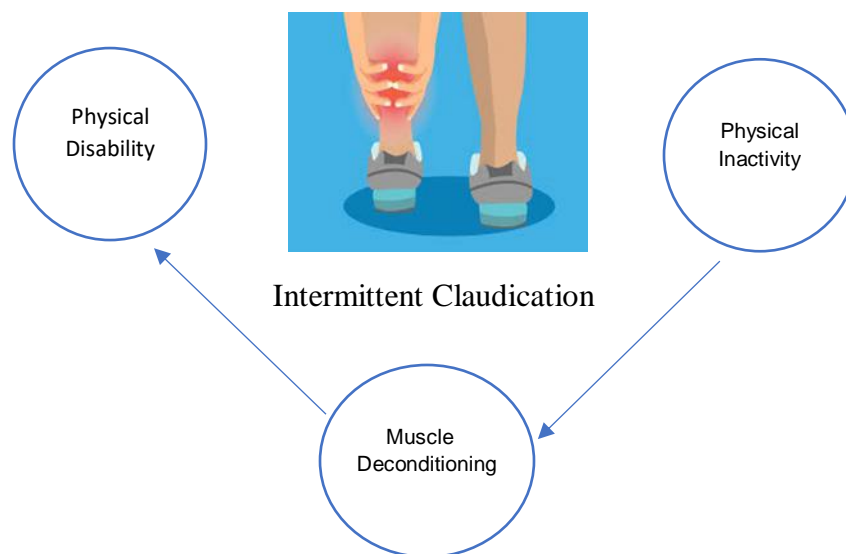
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**Figure 1**



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

**Table 1: Exercise prescription for patients with IC**

Type	Intensity	Duration	Work-to-rest Ratio	Frequency	Progression
<b>Interval walking (exercise-rest-exercise)</b> (Pescatello 2014; Treat-Jacobson et al. 2019; Ambrosetti et al. 2020)	<ul style="list-style-type: none"> <li>• 40-60% of max workload on a treadmill test</li> </ul> Or <ul style="list-style-type: none"> <li>• the workload that elicits claudication within 3-5 min on 6MWT</li> </ul> Or <ul style="list-style-type: none"> <li>• moderate to moderately severe claudication on the claudication scale</li> </ul>	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
<b>Interval arm or leg cycling</b> (Walker et al. 2000; Sanderson et al. 2006; Bronas et al. 2011)	80% VO <sub>2</sub> peak	20-40 min	2: 2 min	3 d/week	Progress to reach max workload after 6 weeks
<b>Resistance Training (Parmenter et al. 2013; Pescatello 2014; Ambrosetti et al. 2020)</b>	20-50% 1RM	30-60 min	-	2 d/week	Over 4 sessions to reach 30-80% 1RM

Table 1: 6MWT: six-minute- walk test, VO<sub>2</sub>peak: peak oxygen uptake, 1RM: one repetition maximum, max: maximal, min: minutes, d: days.