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TESI DI LAUREA

EFFECT OF CARDIO-PHA TRAINING ON PERIPHERAL ARTERY DESEASE

A case report of the applicability and safety of Cardio-PHA in a patient with lower extremities arterial disease (LEAD)

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ABSTRACT

Background - Lower Extremity Artery Disease (LEAD) is a degenerative atherosclerotic condition that causes progressive partial or complete blockage of blood vessels in the lower limbs, resulting in circulatory deficits. Physical exercise in patients with LEAD can reduce cardiovascular risk factors, improve quality of life and walking ability. Exercise training recommended for LEAD patients involves treadmill walking phases lasting 8-10 minutes each, aiming to achieve at least moderate pain intensity, followed by recovery phases lasting at least 5 minutes or until symptoms completely regress. Peripheral Heart Action (PHA) is a total body circuit training protocol which involves alternating upper and lower body exercises without pauses between stations, to 'pump', through the skeletal muscle pump, the blood flow redistributing it to all the districts located at the different body extremities. A variant of PHA is Cardio-PHA, which integrates aerobic stations into the circuit, in addition to strength exercises, using equipment such as treadmills or the cycle ergometer for a duration of several minutes.

Study objective - The aim of the thesis was to study the applicability and the safety of Cardio-PHA training in a subject with LEAD, as an alternative to the recommended treadmill standard work.

Materials and methods The exercise training program included a run-in period of 150 minutes/week of aerobic exercise at an intensity set on pain sensation, strength training with 2-3 sets for 12-15 repetitions per muscle group at 60 to 75 % of 1 RM., and a progression phase with the introduction of Cardio-PHA with same volume and intensity. – The case-study was on a 70-year-old man with LEAD in the right lower extremity that voluntarily participated in two sessions per week for four weeks of Cardio-PHA. 6 senior fitness test (6SFT), handgrip, isokinetic and isometric strength, the level of physical activity and the quality of life were assessed at the beginning and end of the intervention.

Results – After eight Cardio-PHA sessions maximal walking distance, all test outcome but ankle plantar flexor, knee flexor and extensor, and Back scratch improved. Moreover, also and quality of life increased.

Conclusions - This case report demonstrates that eight Cardio-PHA training sessions could be a safe and effective strategy to improve walking ability, general strength, fitness level and quality of life in people with LEAD. However, these results need to be confirmed with further studies.

INTRODUCTION

PERIPHERAL ARTERIOPATHY

Lower extremity artery disease (LEAD) is an atherosclerotic-based degenerative condition that results in the progressive occlusion, partial or complete, of the lumen of vessels leading to circulatory deficits in the lower limbs. Reduced blood flow then creates a mismatch between tissue oxygen availability and demand, causing ischemia. Most patients with LEAD are initially asymptomatic, but as the condition worsens, the main symptom is claudication intermittent, a pain or cramp in the lower limb during walking caused by progressive ischemia of the tissues downstream of the occlusion. The pain disappears within a few minutes with rest, allowing walking to resume, only to reappear with the same dynamic. Aquino et al.[2] studied the natural progression of the disease and found a decrease of about 8-9 metres per year in the maximum distance the patient can walk in the absence of symptoms. Other symptoms of LEAD are cold, numb, weak, aching at rest, tired and heavy legs. If the feet have wounds, peripheral arteriopathy prevents them from healing due to limited blood flow. The possible evolution of the pathology is critical ischemia and subsequent amputation of the limb. Furthermore, subjects with LEAD, due to claudication intermittent, will become increasingly sedentary, predisposing them to have a lower functional capacity and aerobic fitness and to be sarcopenic. Indeed, in the study by Addison et al.[1] men with LEAD showed a high prevalence of sarcopenia. Diagnosing PAD even in patients who are still asymptomatic has a major clinical impact as the condition is a marker of systemic atherosclerosis and carries a high cardiovascular risk. Studies have determined the extent of the risk for these patients. Subjects with peripheral arteriopathy have a cardiovascular risk equivalent to that of patients with previous myocardial infarction. Fowkes et al.[4] showed that an ABI of less than 0.9 is associated with a more than doubled risk of having a cardiovascular event in the next 10 years. Aboyans et al.[3] estimated that, over a period of about 5 years, 20% of patients symptomatic for claudication have a myocardial infarction or stroke, with a mortality of 10-15%. Management of the disease varies depending on the severity and status of symptoms. Treatment options include lifestyle changes through the reduction of cardiovascular risk factors, drug therapy, endovascular intervention and surgery.

ETIOLOGY
Peripheral artery disease is generally caused by arteriosclerosis. LEAD and CVD therefore share the same risk factors (Simon et al.[11]) such as:

- smoking habit
- alterations in lipid profile
- diabetes mellitus
- arterial hypertension
- obesity
- Age, especially after 50 years old
- A family history of peripheral artery disease, heart disease, or stroke
- High levels of homocysteine, a protein component that helps build and maintain tissues

EPIDEMIOLOGY
Peripheral artery disease is the third leading cause of arteriosclerosis after Coronary artery disease (CAD) and stroke (Criqui et al.[12]). Fowkes et al.[13] estimated a prevalence of PAD of about 5% between the ages of 40 and 44, and about 12% between the ages of 70 and 74 in both men and women in high-income countries. The prevalence of PAD in women in low- and middle-income countries was similar to that in high-income countries, while for men the prevalence was 2% and 8% respectively. Between 2000 and 2010, the number of people with PAD increased by 13.1% in high-income countries and by 28.7% in low- and middle-income countries.
More specifically, LEAD affects more than 230 people worldwide, particularly only 8 million in the United States, where it is estimated that every 20 Americans over the age of 50, one is affected by PAD. The prevalence of the disease has been increasing since 1990, with a rise in cases every year. However, despite its prevalence and clinical importance, PAD has historically been under-diagnosed and its severity underestimated. For this reason, the disease should be studied more and recognized as a global problem.

EVALUATION AND DIAGNOSIS OF LOWER EXTREMITIES ARTERIAL DISEASE

The Ankle- Brachial Index (ABI) is the primary non-invasive means of diagnosing Peripheral artery disease, and is the ratio of ankle systolic pressure to brachial systolic pressure. An ABI below 0.90 indicates the presence of PAD and a 2 to 3-fold correlated risk for total and cardiovascular death. The ABI is an inexpensive and fast diagnostic tool that requires an operator trained in its use (Aboyans et al.[4]). Dachun et al.[14] reported a high level of specificity, of 83.3-99%, and sensitivity, of 72.1-89.2%, for an ABI less than 0.90 in detecting stenosis greater than 50%.

The ABI measurement is done with the patient in a supine position with the cuff positioned just above the ankle. After resting for approximately 5-10 minutes, the systolic pressure is measured with a Doppler probe on the posterior and anterior tibial arteries of each foot and the brachial artery of each arm. The ABI of each leg is then calculated by dividing the highest systolic pressure of the ankle by the highest systolic pressure of the arm. The severity of the pad is defined according to the ABI value:

Table 1. Ankle-brachial index (ABI) interpretation

RATIO	**INTERPRETATION**
> 0,9	Normal
0,6 - 0,9	Moderate
0,3 – 0,6	Moderate Severe
< 0,3	Critical ischaemia

Classification of PAD according to ABI value

Another tool for identifying the severity of PAD is the Fontaine classification: I = asymptomatic; IIa = moderate claudication (after 200 metres); IIb = moderate-severe claudication (before 200 metres); III = pain at rest; IV = tissue damage. Other diagnostic means for PAD are angiography, computed tomography angiography and magnetic resonance angiography.

• Angiography is the gold standard for vascular imaging. Due to its invasiveness and risk of complications, it has been replaced by other less invasive diagnostic means. It can be used in the event of a discrepancy between other non-invasive diagnostic tools.

• Computed tomography angiography is a method that offers rapid non-invasive acquisition with wide availability and high resolution. The disadvantages are the lack of functional and haemodynamic data and the exposure of the patient to radiation or contrast medium in the case of chronic renal failure.

• Magnetic resonance angiography may be the alternative for subjects with mild and moderate chronic renal failure. The limitations of the instrument are the presence of motion artefacts and the fact that it cannot be used in patients with pacemakers and ICDs.

PHARMACOLOGICAL AND SURGICAL MANAGEMENT AND TREATMENT

Management strategies for Peripheral Artery Disease are to achieve two distinct goals: reducing cardiovascular risk and improving walking ability. All patients with PAD, asymptomatic and with symptoms, have an increased risk of stroke, myocardial infarction and thrombosis (Aboyans et al.[3]). All patients with PAD should undertake lifestyle changes such as quitting smoking, lowering cholesterol, controlling diabetes and hypertension to reduce their cardiovascular risk. Specific pharmacotherapy for claudication intermittens caused by PAD, in addition to that for reducing cardiovascular risk, includes the use of Cilostazol and Pentoxifylline. Cilostazol is an antiplatelet drug that promotes vasodilation and suppresses the proliferation of vascular smooth muscle cells. Brown et al.[16] demonstrated that the use of Cilostazol improved walking distance in subjects with cludicatio intermittens. Pentoxifylline, on the other hand, improves oxygen supply by increasing red blood cell flexibility. According to Salhiyyah et al.[15] the benefit of Pentoxifylline for patients with claudication intermittens remains uncertain despite the fact that it is generally well tolerated. Surgical therapy involves balloon angioplasty or placement of a stent in cases where the patient does not respond to medical therapy and exercise. Another surgical option for PAD is bypass grafting to divert flow around the obstruction.

EXERCISE IN ARTERIOPATHIC PATIENT

Lane et al.[5] proved that exercise in the arteriopathic patient not only reduces cardiovascular risk factors, but also improves quality of life and improves walking ability. According to Hamburg et al.[18] the positive mechanisms produced by rehabilitative exercise are numerous and still being studied. Some of these are: improvement of macrocirculation and microcirculation, improvement of muscle metabolism, improvement of endothelial function, reduction of inflammation mechanisms and modification of pain perception. As reported in the 2016 AHA/ACC guidelines by Gerhard-Herman et al.[17] , exercise has strong evidence of efficacy and safety in individuals with PAD. The 11th edition of the ACSM Functional Assessment and Exercise Prescription Guidelines[19] proposes the following program:

Table 2: exercise prescription in LEAD

	AEROBIC	STRENGTH	FLESSIBILITY
Frequency	At least 3 times a week; preferably up to 5 days a week	At least 2 days a week on non-consecutive days	≥2-3 days per week; each day is most effective
Intensity	Moderate (40-59% of VO_2R) at the point of moderate pain (3 out of 4 on the claudication pain scale) or 50% to 80% of maximum walking speed)	60%-80% of 1RM	Stretch to the point of tension or slight discomfort.
Time	30-45 minutes per day (excluding rest time) for a minimum of 12 weeks; progress to 60 minutes per day	2-3 sets of 8-12 repetitions; 6-8 exercises for larger muscle groups	Hold 10-30 seconds for static stretching; 2-4 repetitions for each exercise
Type	Free walking or treadmill walking, interspersed with recovery breaks when the pain is moderate. Resume exercise when the pain disappears.	Total body. If time is limited give priority to the lower limb	Static, dynamic and/or PNF

The rehabilitation training recommended by the European Society of Cardiology for patients with LEAD, described by Mazzolai et al.[31], consists of walking phases, with the goal of achieving moderate-to-high pain intensity, followed by recovery phases until complete regression of symptoms. Subjects should exercise at least 3 times a week for at least 30 minutes per training session. Many subjects will initially be able to accumulate as little as 15 total minutes of daily aerobic activity, which should then be gradually increased. In this situation, the duration of exercise should be increased 5 minutes per week until the patient reaches 30 minutes of autonomy in the single training session. The duration of the rehabilitation program should be at least 12 weeks. Bulmer et al.[20] showed that improvement in PAD with physical rehabilitation may be most evident in the first 2-3 months of therapy. In contrast, physiological benefits are optimized after about 20 weeks of training. The review and meta-analysis by Parmenter et al.[30], on the other hand, suggests that at least 24 weeks of vigorous exercise might be optimal and that exercise at mild pain intensities might produce better results than moderate or maximal pain intensity modalities. According to Castellani et al.[21] a cold environment could exacerbate the symptoms of claudication intermittens so it is recommended to start training with a longer warm-up.

Patients with 45-60 minutes of walking autonomy should also be encouraged to perform other types of exercise, considered secondary to walking exercise, to improve cardiorespiratory fitness and muscle strength. Biking may be useful as a warm-up, but it should not be the main type of activity. Bulmer et al.[20] demonstrated that exercise without a load, such as using a cycle ergometer, can provide additional benefits. Workout progressions occur by increasing the speed or incline of the mat when exercise tolerance improves. Other alternative training protocols involve walking below the pain threshold, either in the absence of pain (Manfredini et al.[38]) or at 60-70% of the total walking capacity assessed at the initial test. They allow a clinical benefit to be achieved, although often to a lesser extent. Once rehabilitation has been completed, Carlon and Morlino et al.[10] recommend interval training in the same manner. However, this training modality may be poorly tolerated by the patient from a psychological and pain perspective. The better-tolerated alternative seems to be aerobic training, of about 45 minutes session time, at the treadmill with a walking speed slightly below the ischaemic threshold. Parmenter et al.[30] argue that exercise prescription should consider treadmill exercise as much as lower-limb exercise, always at a moderate pain intensity.

Walking training, which is usually proposed to subjects with LEAD, has as its main objective the reduction of the symptom, while the other components such as aerobic fitness and general strength of the subject are trained less specifically, as they are considered as secondary objectives. According to Harwood et al.[6] circuit training could be a practical way to combine aerobic exercise and resistance training to improve both strength and cardiorespiratory fitness, both of which are related to the reduction of cardiovascular and all-cause death. According to Gerhard-Herman et al.[17] unsupervised training can be just as beneficial, although it is not as well established as supervised training.

ARM ERGOMETER TRAINING IN THE LEAD SUBJECT

The review by Parmenter et al.[30] argues that exercise prescription should consider exercise with the arm ergometer as much as exercise with the lower limbs, always at moderate pain intensity. Some studies in the previous review with meta-analysis suggest that aerobic upper limb training with an arm ergometer may increase maximum walking distance in subjects with LEAD. Tew et al.[22] studied the effects of aerobic exercise with a arm ergometer on lower limb oxygen transport. The research group studied 51 subjects with claudication intermittens randomised into an intervention group and a control group. The intervention group trained twice a week for 12 weeks. At the end of the protocol, the intervention group increased the maximum walking distance (from 496 + - 250 to 661 + - 324 metres) the VO_2 peak (from 17.2 ± 2.7 to 18.2 ± 3.4 ml · kg−1 · min−1). There was also an increase in the time required to reach minimum StO2 (from 268 ± 305 s to 410 ± 366 s), an acceleration of VO_2 kinetics (from 44.7 ± 10.4 to 413 ± 14.4 s) and a statistically significant increase in submaximal StO2 during treadmill walking. Zwierska et al.[23] and Bronas et al.[24] compared the effects of arm ergometer exercise and treadmill training.

Zwierska et al.[23] studied 104 patients with PAD randomised into a group with upper-limb training, a group with lower-limb training and a control group. The patients exercised twice a week for 24 weeks. Claudicating distance and maximum walking distance increased with clinically significant manner in both the group with treadmill training and the group with armoergometer training. After 24 weeks, the claudicating distance improved by 51% in the ergometer group and by 57% in the treadmill group. The maximum walking distance increased by 29% in the ergometer group and 31% in the treadmill group. Furthermore, in both intervention groups there was a clinically significant increase in VO_2 peak in the leg cranking test. The VO_2 peak in the arm cranking test increased with statistical significance only in the group that trained with the armoergometer.

Bronas et al.[24] studied a sample of 28 subjects randomised into an arm ergometer training group, a treadmill group and a control group. The intervention groups trained 3 hours per week for 12 weeks. At the end of the protocol, both intervention groups achieved similar statistically significant improvements in sub-maximal double product, maximum walking distance, ventilatory threshold, VO_2 at onset of claudication and VO_2 peak. The control group remained unchanged.

The results obtained from these studies suggest that aerobic exercise with an arm ergometer is safe and useful for improving walking ability in patients with LEAD. The studies hypothesise that the results obtained on increased walking distance can be partly attributed to improved oxygen transport to the lower limbs.

STRENGTH TRAINING IN THE SUBJECT WITH LEAD

The meta-analysis by Blears et al.[26] examined the effectiveness of strength training as an alternative on walking ability and whether it resulted in vascular and skeletal adaptations in subjects with PAD. The authors compared the studies with strength training, aerobic training and drug treatment alone. Strength training, compared to drug treatment alone, increased walking ability and muscle strength of the below- and above-knee muscle groups. Strength training, when compared to aerobic walking training, is less effective in improving walking ability. The review showed that resistance training is effective in prolonging walking in subjects with PAD, but less so than aerobic training. Strength training may therefore be an effective alternative for all those patients with ulcers and amputations who feel unsafe walking on the treadmill. Due to the limited number of studies, it is still unclear whether the increase in functional capacity produced by strength training is caused by an increase in oxygen supply or an increase in muscle strength. Although the evidence is growing, strength training is still to be considered as a single therapy in international guidelines. Strength training should be recommended as complementary, to increase strength or reduce the risk of falls, but never substituted for walking exercise as it has a greater impact on walking ability. (Harwood et al.[6]).

WATER TRAINING IN THE SUBJECTS WITH LEAD

Park et al.[27] studied the effect of a 12-week water walking protocol. 72 subjects with PAD were recruited and randomised into a group with water walking at waist height, and a control group. At the end of 12 weeks, the intervention group achieved a statistically significant decrease in heart rate and leg pulse wave velocity while VO_2max, the six minute walking test and muscle strength increased significantly compared to the control group. In another study Park et al.[28] compared the effects of warm water training and treadmill training. 53 subjects with PAD were recruited for 12 weeks and randomised into a group with hot water walking and a group with treadmill walking. Both groups significantly reduced leg pulse wage velocity, blood pressure and fat mass percentage with lower results in the warm water group. Both groups improved significantly in the six minute walking test, claudication onset time and basal metabolism with higher results in the hot water group. These results from these two studies suggest that walking exercise is an effective therapy for reducing arterial stiffness and improving cardio respiratory capacity, muscle strength and walking ability in subjects with PAD. Furthermore, walking exercise in warm water may lead to better results in subjects with PAD than walking on land.

INTERVAL TRAINING WITH ACTIVE RECOVERY IN SUBJECT WITH LEAD

The study by Villemur et al.[29] investigated the effect of treadmill interval training followed by active recovery with low-intensity exercise. Sub-maximal interval training with active recovery, which is often used with athletes, produces superior improvements in VO_2max in both healthy sedentary subjects and subjects with metabolic syndrome, subjects undergoing coronary artery bypass surgery, and subjects with heart failure. Eleven subjects with stage II PAD were enrolled for 2 weeks of rehabilitation that included: gymnasium exercises, exercises below the level of occlusion (standing on tiptoes, toe bending exercises), exercises above the level of occlusion (including cycle ergometer), and 11 treadmill training. The treadmill training consisted of two 30-minute sessions per day with increasing intensity. Each session comprised five six-minute cycles consisting of three minutes of active walking and three minutes of active recovery. The intensity of the active phase was set at 70 per cent of the previously assessed maximum walking speed. In the phase during active recovery the intensity was at 40% of the maximum walking speed. During the first week, the speed was increased by 0.1 per session. In the second week, the intensity was increased by including a 0.5 per cent gradient only in the active phase. At the end of the rehabilitation all patients increased their maximum walking distance significantly. Although the study proved to be effective and safe for patients with stage II PAD, it needs to be validated by a clinical trial.

CIRCUIT TRAINING IN THE SUBJECT WITH LEAD

The study by Lanéelle et al.[32] is the only one that tested mixed aerobic and strength circuit training on subjects with LEAD. The aim of the study was to evaluate the effect of this type of training on cardiorespiratory fitness and perioperative risk in these patients. 106 patients (77% male) and 155 healthy participants without PAD were enrolled in the study. The patients underwent two training sessions per week for 10 weeks. Subsequently, 52 patients completed 12 weeks of customised, unsupervised home exercises. Supervised circuit training significantly increased PWD (+44±81m, p=<0.001), MWD (+44±71m, p=<0.001) and $\dot{V}O_2PEAK$ (+1.01±1.63ml/kg/min, p=<0.001) and reduced perioperative risk (91% to 85%, p=<0.001). Improvements in PWD were maintained over the 12 weeks of unsupervised exercise (+11±91m vs supervised exercise, p=0.572);however, MWD and $\dot{V}O_2PEAK$ decreased (-15±48m, p=0.030 and -0.34±1.11ml/kg/min, p=0.030, respectively) and perioperative risk increased (+3%, p=<0.001). These results demonstrate that a supervised circuit exercise protocol of mixed aerobic and strength training improves walking ability and cardiorespiratory fitness and reduces perioperative risk in PAD patients with claudication intermittens.

PERIPHERAL HEART ACTION AND CARDIO-PHA

PHA is a total body circuit training protocol, devised in 1940 by Dr. Steinhaus, which involves alternating upper and lower body exercises without pauses between stations, so as to 'pump', through the skeletal muscle pump, the blood flow redistributing it to all the districts located at the different body extremities; the aim of PHA is to improve strength and aerobic fitness in a single circuit training session. Piras et al.[7] found, after 3 months of using PHA, an increase in muscular strength and an increase in VO_2max (+8%) using loads of 55-60% of 1-RM. Strength exercises at this intensity and with short recovery periods between sets (30s), studied by Okamoto et al.[8] produced improvements in vascular function, a decrease in arterial stiffness and an increase in arterial diameter at rest. Furthermore, active pauses between stations had more significant effects than static pauses. This training technique has little monotony because the exercises are changed at each station. Moreover, the structure of the protocol allows for greater strength development in all sets, compared to classic strength training. This phenomenon would appear to be caused by a 'distraction of the nervous system'. A variant of Peripheral Heart Action is Cardio-PHA, which integrates aerobic stations into the circuit, in addition to strength exercises, using equipment such as treadmills or the cycle ergometer for a duration of several minutes. Cardio-PHA, the aim of which is slimming, is designed for a female clientele, especially with circulatory problems or oedematous-fibro-sclerotic panniculopathy. Peripheral Heart Action has been used in only a few studies, while Cardio-PHA is absent from the literature.

APPLICATION OF CARDIO-PHA IN THE LEAD PATIENT

The recommended training for the patient with PAD consists of walking phases until moderate pain intensities are reached, followed by recovery phases until complete regression of the symptoms. This modality may prove to be very time-consuming but with a low final volume. Villemur et al.[29] studied the effect of interval training at the treadmill followed by active recovery with low-intensity exercises also at the treadmill. Although the study demonstrated efficacy and safety for patients with stage II PAD, it needs to be validated by a clinical trial. Cardio-PHA shares with the previous study the active pauses with the advantage of engaging, during these, muscle groups distant from the occlusion. A parallel effect of active pauses with exercises of the upper body, or muscle groups above the vessel obstruction, could be the production of a higher blood flow, through the skeletal muscle pump generated by these, to the oxygen-deficient tissues allowing for faster recovery. In addition, active pauses could produce the following effects at cardiac level: 1) The increased venous return pushed by the muscles will positively influence systolic output; 2) The heart rate will not decrease significantly as it does in passive recovery in interval training; 3) the higher systolic output and heart rate will then produce a higher cardiac output which will result in greater oxygen transport to the muscles, particularly those in oxygen deficit downstream of the obstruction. Cardio-PHA, in addition to training aerobic fitness, utilises active breaks to train global strength, which is equally important for subjects with LEAD, achieving the recommended ACSM guidelines[19]. According to Harwood et al.[6], circuit training, such as Cardio-PHA, in subjects with LEAD can be a practical way to combine aerobic exercise and resistance training to improve both strength and cardio respiratory fitness, both of which correlate with reduced cardiovascular and all-cause death. Cardio-PHA, due to its characteristics, could therefore produce cardiovascular, strength and symptomatic adaptations. The strength exercises of the protocol, being of low intensity (approx. 55-60% of 1-RM) and with short recovery periods between high and low, could decrease arterial stiffness and improve vascular function by increasing the diameter of arteries at rest (Okamoto et al.[8]), especially where occlusion is present. Furthermore, aerobic lower limb stations could produce muscular adaptations such as increased enzymes and oxidative potential, increased local myoglobin concentration and increased number and size of mitochondria. At the cardiovascular level, together with the alternating effect of circuit strength exercises, it causes adaptations such as: optimisation of cardiac output distribution and increased peripheral blood flow and to the active muscles (Mcardle, Katch; Exercise Physiology: Nutrition, Energy, and Human Performance[25]). The results of Cardio-PHA in clinical and scientific settings are limited due to the few studies in the literature. Piras et al.[7] found after 3 months of PHA an increase in global maximum strength and an increase in VO_2max of 8%. Nabilpour and Mayhew[9], one of the few studies that used PHA in a clinical setting, achieved an increase in muscle strength, an improvement in general fitness, and a reduction in systolic blood pressure by 2.2 per cent and diastolic blood pressure by 3.2 per cent in a group of hypertensive women. The latter results could suggest that a lowering of the chronic pressure state in subjects with PAD, caused by training, could improve the initial ABI value. Hypotheses not supported by the literature, but suggested by the particular structure of the Cardio-PHA could suggest that alternating strength and aerobic stations could keep blood sugar more controlled in diabetic subjects with peripheral arterial disease. Furthermore, Cardio-PHA, being a total body workout, could prevent and limit the progression of other atherosclerotic processes in other body districts by increasing capillary and collateral vessels and reducing arterial stiffness and vascular resistance. Another possible effect of Cardio-PHA, compared to classic interval aerobic training, is to train the subject's general endurance in various tasks. With regard to the safety of Cardio-PHA, the exercises should be well tolerated by the patient, even in the area where the obstruction is present, as the load is low intensity for a limited time. Lower limb aerobic stations, in order to be safe, could be run as in standard aerobic training for arteriopathic patients, that is at a walking speed slightly below the ischaemic threshold. Lower limb aerobic stations being spaced by 3 to 5 strength stations, 2/3 for the upper body or core and 1/2 for the lower, could allow sufficient recovery time comparable to that of aerobic interval training. In addition, at the end of a station, the oxygen consumption of the trained muscle will decrease, as it remains active, and it will have the opportunity to restore its energy substrates and prepare for the next series where it will be recruited. However, the application of Cardio-PHA in subjects with LEAD could have some disadvantages. The intensity of the circuit and the individual stations may be too high, thus ineffective if the subject is very deconditioned and has little endurance, not allowing an immediate transition to the next station. It is therefore important to adapt the intensity of each station to the subject through strength and aerobic tests, to allow for the correct progression of the session. If claudication intermittens occurs, it is important to monitor the symptom and its evolution during training. As recommended by the standard training protocol, it is important that the pain is always less than 3 or 4 on a scale structured from 0, absence of pain, to 5, unbearable pain that forces one to stop. If the subject reaches a high intensity of pain, possible strategies could be used: if the intense pain appears in a lower body exercise, stop that station and go directly to the next upper body exercise, monitoring the symptom during execution; if the pain persists, the session should be interrupted with a passive pause until the symptomatology disappears. One of the possible disadvantages of Cardio-PHA in subjects with LEAD could theoretically be an aspect of the principle on which it is based: by alternating lower and upper body exercises, the muscles recruited during the station could limit and 'steal' oxygen from the tissues downstream of the obstruction, slowing their recovery or causing claudication to appear. A further limitation is DOMS, caused by the strength exercises in the protocol, which could adversely affect the performance of the next session. In conclusion, at the end of a medium to long training protocol with Cardio-PHA in patients with LEAD, the expected results could be the following: increase in maximum walking distance, reduction in symptoms, increase in VO_2max or VO_2 peak, increase in specific and global strength measured with hangrip and/or 1RM, decrease in cardiovascular risk, decrease in chronic pressure status, increase in ABI, increase in autonomy, improvement in quality of life.

METHODS

ETHICAL APPROVAL

The patient read and signed the informed consent about the rationale and the purpose of this case study, and how the data collected would be processed were described.

PATIENT

The patient is a 70-year-old man with lower extremity arteriopathy disease with predominant right lower extremity involvement due to occlusion of the superficial femoral artery about 6 cm from the bifurcation. He also has bilateral carotid vasculopathy; dyslipidemia (total cholesterol 133 mg/dl, HDL 59 mg/dl, triglycerides 51 mg/dl, LDL 66 mg/dl (target < 55 mg/dl); impaired fasting blood glucose (110 mg/dl), with HbA1c in the normal range (38 mmol/mol). The patient was an occasional smoker (termination for about a year) and had osteo-articular pain such as chronic low back pain and diffuse arthralgia due to sedentary.

The patient takes the following medications: Statin, Anticholesterolemic, Pantoprazole, tamsulosin, Antiplatelet drug, NOAC and low dose benzodiazepine.

The patient started the exercise training program on 11/07/23 and the functional starting point was setted at 1 km of flat walking. At the evaluation on 12/04/2024, he was walking up to 3 km because from the exercise prescription he was committed in walking every day finding a huge benefit. He also expressed his willingness to treat mobility and musculoskeletal function as he feels stiff and sore.

EXERCISE INTERVENTION

The patient, after evaluation on 16/04/24, was initially prescribed an 8-week mesocycle of two workouts per week. The exercise training program included the use of Cardio Fitness training, a training methodology that combines both cardiovascular and resistance training exercises for all body districts.

The prescribed weekly aerobic volume was 150 minutes at an intensity set on pain. Aerobic exercises could be performed continuously or interspersed. The patient could split the daily sessions into 15-minute sessions.

Strength training was structured as a circuit of 2-3 sets with 12-15 repetitions for each muscle group. The prescribed intensity in strength exercises was 60 to 75 % of 1 RM.

The training form was structured in the following scheme:

Table 3: proposal for the "run-in" training program

TYPE	EXERCISE	INTENSITY	VOLUME
ACTIVATION In standing position 10 x 1	- Toes/heels + arm elevation up and opening thoracic - Anterior/ retroversion of pelvis with hands on hips - Lateral tilts of the torso alternating with respirations - Forward and backward shoulder circulations in walking - Add-abd of the shoulder blades with arms extended to shoulder height - Head mobility (flexion-extension + lateral rotations) - Shoulder-to-wall flexion-extensions with softball (emphasizing the extension) - Walking back and forth on theraband pads	light	10' (10 reps x exercise)
AEROBIC	Treadmill	according to threshold of pain (get up to 3 out of 4)	30'
STRETCHING AT THE WALL BAR	-Knee flexion-extension -Static calf stretching - Mezieres with knee flexion-extension	11 RPE	30-45''PER EX.
STRENGTH	Squat box		15x2
	Dynamic alternating backward lunges		20 (10+10) x 2
	Chest press with stroops	medium	15x2
	Tight elbow pulley with stroops (with shoulder blade activation)	medium	15x2
STRETCHING To the mat 10x1	- Anterior/ retroversion of the pelvis from supine - Gluteal bridge with supine unwinding Forward/backward thrusts of the shoulder blades	11RPE	10' (10 reps x ex.)

	from supine with the arms outstretched at shoulder height - "Angel" movement with arms on the ground - Anterior/ retroversion of the pelvis in quadrupedal motion - Forward/backward thrusts of the shoulder blades in quadrupedal position - Cat-camel		

CARDIO-PHA TRAINING PROTOCOL

On 04/23/24, the patient's programming was modified and converted to Cardio-PHA. The new training program maintained most of the exercise type, volume and intensity of the previous programming. In the cool down phase, postural exercises were replaced by static calf and quadriceps femoris stretching. Only the aerobic and strength part followed the structure of Cardio-PHA. From 4/23/24 to 5/21/24, the patient performed eight Cardio-PHA workouts.

The training form was structured in the following scheme:

Table 4: proposal for the “run-in” training program

TYPE	EXERCISE	INTENSITY	VOLUME
ACTIVATION In standing position 10 x 1	- Toes/heels + arm elevation up and opening thoracic -Anterior/retroversion of pelvis with hands on hips - Lateral tilts of the torso alternating with respirations - Forward and backward shoulder circulations in walking - Add-abd of the shoulder blades with arms extended to shoulder height - Head mobility (flexion- extension + lateral rotations) - Shoulder-to-wall flexion-extensions with softball (emphasizing the extension) - Walking back and forth on theraband pads	light	10 reps x exercise)

Cardio-PHA Circuit: 2 times	Treadmill	according to threshold of pain (get up to 3 out of 4)	10’
	Chest press with stroops	Medium	15 repetitions
	Squat box		15 repetitions
	Arm ergometer	5’	11-13 Borg
	Dynamic alternating backward lunges		20 (10+10)
	Tight elbow pulley with stroops (with shoulder blade activation)	Medium	15 repetitions
STRETCHING	- Calf stretching Quadriceps stretching		2x30’

PROGRESSIONS

During the eight training sessions, progressions were applied on treadmill walking and strength exercises. The progression on the treadmill was the increase in walking slope, speed, and time based always on the intensity of pain reported by the subject. The walking slope increased progressively in the sessions from 2.5% to 6% while the speed increased from 4 km/h to 5.5 km/h. Aerobic volume increased by 6 minutes, increasing the two walking sets by 2 minutes each and the armoergometer sets by 1 minute each. In the strength exercises, on the other hand, the loads and resistance of the elastic bands are increased . In the chest press and tight elbow pulls, the stiffness of the stroops was increased from medium to strong. In squat box, initially done free-body, two 3 kg dumbbells were used at the end of the eight sessions.

PHYSICAL PERFORMACE EVALUATION

WALKING PERFORMANCE

The maximum walking distance was assessed through the 6-minute walking test (6MWT). During the test, at each minute of walking, the intensity of pain was assessed using the claudication training pain scale. The test was administered at the beginning of the 8 Cardio-PHA sessions and at the end of them.

MUSCULAR FUNCTION

In July 2023, at the beginning and end of the 8-week intervention period, overall strength was measured by means of a Handgrip. Three tests, of approximately 5 seconds each, were done for both the dominant and nondominant limbs. At the end of the trials, the results were averaged. More specific strength tests were done before the start of the 8 Cardio-PHA sessions. The strength of both ankle flexor and extensor muscles and knee flexor and extensor muscles were evaluated through an isokinetic force test with a flexion-extension velocity of 90°/s. Two 5-repetition tests were performed for both ankle and knee. Data collected were peak mean, peak torque, peak power, total work and the ratio of extensors to flexors. In addition, the knee extensor muscles were tested through with an isometric force test with leg constrained at 15° of extension. Mean torque, maximum torque and work data were collected from the test. The tests were performed after a warm-up of the muscles involved. Next, the performance of the test was explained to the patient and the machine was set up according to the anthropometry of the subject. Two tests were performed in each test, separated by 2 minutes of recovery time.

SIX SENIOR FITNESS TEST

The six senior fitness test (6sft) was administered at the beginning and end of the intervention. The patient was administered: the six minute walking test, thirty second chair test, timed up and go test, arm curl, sit and reach test and back scratch.

BLOOD PRESSURE

In each session systolic and diastolic pressure was measured at the beginning and at the end of training with an oscillometric validated device. Each measurement was taken after a few minutes of rest and in a sitting position and standard environmental conditions.

PHYSICAL ACTIVITY LEVEL AND QUALITY OF LIFE

The amount of physical activity was measured using the Italian version of the International Physical Activity Questionnaire (IPAQ). The patient's quality of life was assessed using the SF-36 questionnaire. Both questionnaires were administered at the beginning of physical debilitation and at the end of the 8 Cardio-PHA sessions. In addition, during the initial and final counselling the patient was also asked about their motivation for change using Diclemente and Prochaska's Transtheoretical model.

STATISTICAL ANALYSIS

The collected data were entered on Excel and organized into tables for study. Averages, variations between the initial and final data, and the percentage increase between them were calculated. Some graphs were constructed to have a graphic representation of the results.

RESULTS

WALKING PERFORMANCE

The maximum distance walked in the 6-minute walking test increased by 18.5 percent, from 480 meters to 569 meters, after 8 Cardio-PHA workouts. The trend of pain during the two tests is depicted in the graph below:

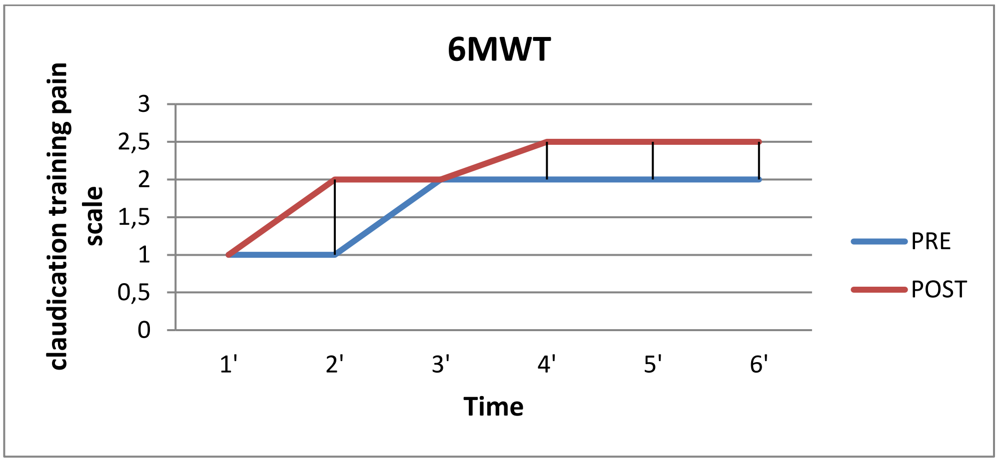

Figure 1: Pain trend during the 6MWT

The pain during the test after the intervention was earlier and slightly more intense. Despite this, the patient was able to walk 89 metres further.

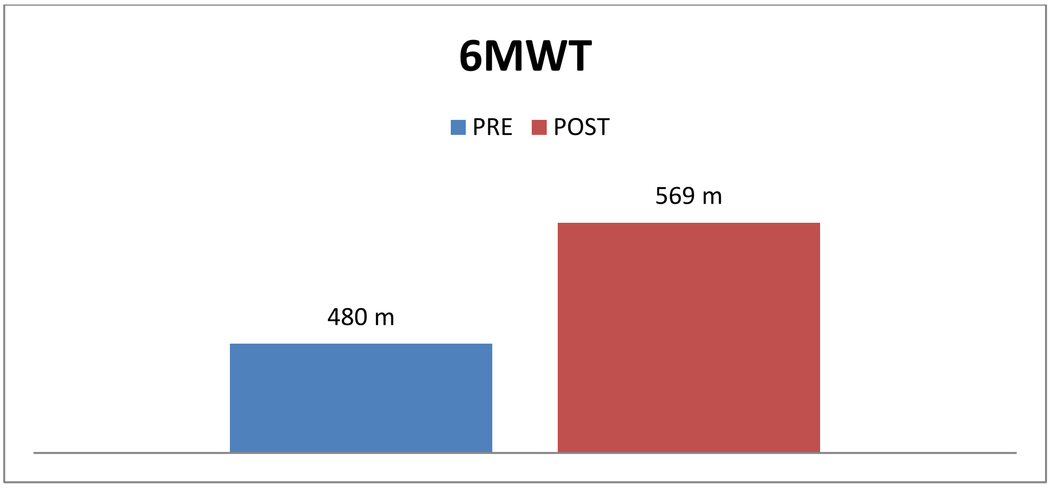

Figure 2: Maximal walking distance in 6MWT

MUSCULAR FUNCTION

The graph below shows the strength results in the three handgrip evaluations:

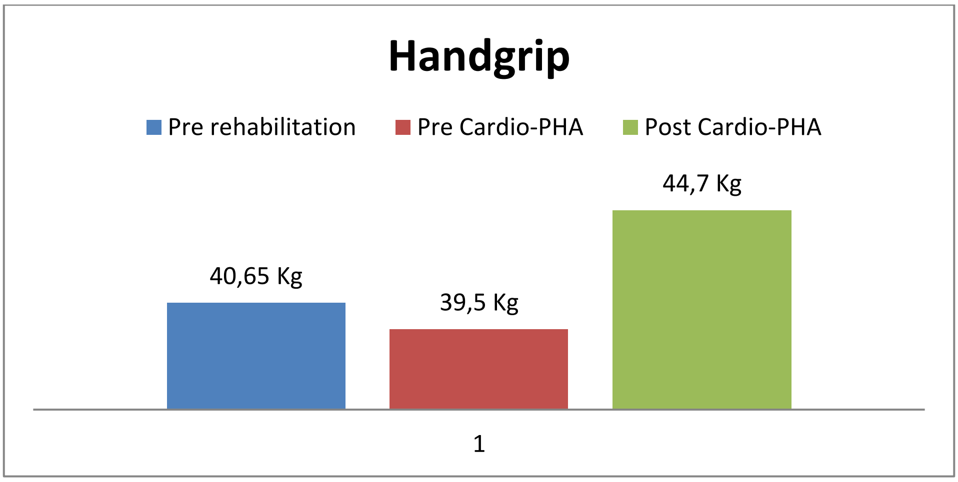

Figure 3: handgrip test results before rehabilitation, before and after the intervention protocol

From the beginning of the rehabilitation to the start of the intervention protocol, the patient lost 2.8% grip strength. From the start of the 8 Cardio-PHA training sessions to the end of these, the patient had a 13.2% increase in strength. Between the first and the last evaluation, the increase in strength was 10%.

The results of the isokinetic test of the ankle muscles are shown in the tables below:

Table 5: Isokinetic test of left dorsal flexor

	Pre	Post	Δ	% gain
Peak Mean (N/m)	22,5	35,5	13	57,77778
Peak Torque (N/m)	26	37,5	11,5	44,23077
Peak Power (W)	27,5	42,5	15	54,54545
Total Work (J)	8	87	79	987,5
Extensors/Flexors Ratio	91	36,5	-54,5	-59,8901

Table 6: Isokinetic test of left plantar flexor

	Pre	Post	Δ	% gain
Peak Mean (N/m)	17,5	10,5	-7	-40

Peak Torque (N/m)	23,5	14	-9,5	-40,4255
Peak Power (W)	32,5	18	-14,5	-44,6154
Total Work (J)	12,5	0	-12,5	-100
Extensors/Flexors Ratio	91	36,5	-54,5	-59,8901

Table 7: Isokinetic test of right dorsal flexor

	Pre	**Post**	**Δ**	**% gain**
Peak Mean (N/m)	22	28	6	27,27273
Peak Torque (N/m)	24,5	30,5	6	24,4898
Peak Power (W)	26	34,5	8,5	32,69231
Total Work (J)	5,5	51,5	46	836,3636
Extensors/Flexors Ratio	77	50,5	-26,5	-34,4156

Table 8: Isokinetic test of right plantar flexor

	Pre	**Post**	**Δ**	**% gain**
Peak Mean (N/m)	14	11,5	-2,5	-17,8571
Peak Torque (N/m)	19	15,5	-3,5	-18,4211
Peak Power (W)	23	19,5	-3,5	-15,2174
Total Work (J)	4	0	-4	-100
Extensors/Flexors Ratio	77	50,5	-26,5	-34,4156

In both limbs, the ankle dorsal flexor muscles improved in all outcomes measured during the isokinetic test. The ankle flexor plantar muscles, on the other hand, deteriorated in all measured parameters.

The results of isokinetic and isometric testing of the knee muscles are shown in the tables below:

Table 9: Isokinetic test of knee extensor

	Pre	Post	Δ	% gain
Peak Mean (N/m)	168	124	-44	-26,1905
Peak Torque (N/m)	184,5	146,5	-38	-20,5962
Peak Power (W)	304	236	-68	-22,3684
Total Work (J)	915,5	633	-282,5	-30,8575
Extensors/Flexors Ratio	40,5	44	3,5	8,641975

Table 10: Isokinetic test of knee flexor

	Pre	Post	Δ	% gain
Peak Mean (N/m)	68	52,5	-15,5	-22,7941
Peak Torque (N/m)	76	65	-11	-14,4737
Peak Power (W)	307	238	-69	-22,4756
Total Work (J)	61	47	-14	-22,9508
Extensors/Flexors Ratio	40,5	44	3,5	8,641975

Table 11: Isometric test of knee extensor

	Pre	Post	Δ	% gain
Max Tourque (N/m)	286	234	-52	-18,1818
Peak Mean (N/m)	260	208	-52	-20
Work (J)	1312,5	1050	-262,5	-20

In both the isokinetic test and the isometric test, the knee muscles worsened in all outcomes measured. The only improvement achieved was the Extensors/Flexors Ratio with an increase of 8.6%.

SIX SENIOR FITNESS TEST

At the end of the protocol, the patient improved in all six senior fitness tests except the Back scratch. The results of the individual tests are shown in the table below:

Table 12: results of the six senior fitness test

	Pre	Post	Δ	% gain
Six minute walk (m)	480	569	89	18,54167
30" chair stand (n)	11	16	5	45,45455
Time up and go (s)	5,5	4,73	-0,77	-14
Arm curl (n)	14	21	7	50
Sit and reach (cm)	-3	3,5	6,5	-216,667
Back scratch (cm)	-4,5	-7,5	-3	66,66667

In the 6MWT the patient went from the 10th to the 35th percentile. In the 30' chair stand the patient went from the 20th percentile to the 65th percentile. In the Time up and go the patient went from the 45th to the 65th percentile. In the Arm curl he went from the 25th percentile to the 75th percentile. In the Sit and reach, the patient went from the fair class to the average class. In the Back scratch he went from the 50th percentile to the 25th percentile.

BLOOD PRESSURE

The blood pressure decreased at the end of the training compared to the start by approximately 14 ± 2.3 mmHg. The diastolic pressure remained unchanged (-0.1 ± 1.4 mmHg)

PHYSICAL ACTIVITY AND QUALITY OF LIFE

From the beginning to the end of the exercise training program course, both quality of life and physical activity increased. Total METs increased significantly from 310 to 3910. Much of this increase is due to the improvement in the patient's walking ability. Before the exercise program the patient was doing 150 METs per week of slow walking, while at the end of the course he is doing 1080 METs of moderate walking per week (60 minutes per day, 6 days per week). In addition, the patient devotes a lot of time per week to vigorous activities, from daily home activities to gym workouts (10 to 360 minutes per day on some days). Sedentary time during the weekend has also improved from 8 hours to 2 hours per day.

The SF-36 scores in the various life domains are shown in the table below:

Table 13 : SF-36 scores in the various life domains

	Pre	Post	Δ
Physical functioning	80	95	18
Role limitations due to physical health	75	75	0
Role limitations due to emotional problems	100	100	0
Energy/fatigue	70	90	20
Emotional well-being	80	96	16
Social functioning	100	100	0
Pain	80	80	0
General health	85	80	-5

Quality of life remained unchanged in the domains Role limitations due to physical health, Role limitations due to emotional problems, Social functioning and Pain. The SF-36 scores increased in the scales Energy/fatigue and Emotional well-being. The only area where the score decreased slightly was General health.

The patient's motivation to change, according to Diclemente and Prochaska's Transtheoretical model, increased from the action phase to the maintenance phase.

DISCUSSION

The aim of this project was to study the applicability and the safety of Cardio- PHA training in a subject with LEAD, as an alternative to the recommended treadmill mode. The treatment and preventive measures of patients with LEAD should receive more attention as they are more underestimated than patients with CAD (Aboyans et al.[34]). Even after revascularisation, patients with LEAD do not reduce their risk of death compared to patients with CAD. In fact, according to Takahara et al.[35], patients with PAD have a 2.9 times higher risk of death than revascularised patients with CAD. Finding effective strategies, such as rehabilitation and adapted exercise, for patients with PAD is crucial. Cardio-PHA, the training protocol used, could be a more compliant alternative for LEAD patients of all severity. The use of the armoergometer, included in the protocol proposed to the studied subject, may be a strategy for all those patients who are limited and unable to walk (Peñín-Grandes et al.[37], Parmenter et al.[30]). Furthermore, Cardio-PHA, as circuit training, has been shown to be a practical way for the patient to combine aerobic exercise and resistance training to improve both strength and cardiorespiratory fitness, both of which correlate with reduced cardiovascular and all-cause death (Harwood et al.[6]). According to Lanéelle et al.[32] a supervised circuit exercise protocol of mixed aerobic and strength training improves walking ability and cardiorespiratory fitness and reduces perioperative risk in PAD patients with claudication intermittens. Results about physical performance tests show that this type of training had a positive effect. The patient increased his maximal walking distance by approximately 90 metres, reporting results congruent with the study by Lanéelle et al.[32] who used circuit training. Improvements in the 6MWT can be attributed to a lower risk of mortality. According to McDermott et al.[36], PAD patients with declining functional performance in the 6MWT are at increased risk of loss of mobility and mortality. Strength values measured with handgrip also increased, suggesting a possible reduction in the risk of death. In fact, according to Leong et al.[33], handgrip force values are inversely correlated with the risk of death from all causes, cancer and cardiovascular causes. Although the prehension strength improved, strength values of the sura triceps and quadriceps femoris, as measured by isokinetic and isometric tests, decreased. The reduction in strength in the plantar flexor muscles could be justified by the fact that the patient did not performed muscle-specific strength exercises, but aerobic exercises such as walking. In contrast, the dorsi flexor muscles in both limbs improved. The strength of the extensor and flexor hamstrings only worsened in the isometric and isokinetic tests possibly due to too much specificity and unfamiliarity of the tests for the subject. This worsening is not justified by the load progressions in the lower limb exercises that the patient had during the sessions and the positive results in the 30’ chair stand test. The lower limb strength exercises, squat boxes and lunges, were not changed to maintain both continuity with the previous training programme and because they were more functional for the subject's life.

Compared to previous studies using PHA, the subject achieved similar improvements in general strength. However, the studies are not comparable due to a longer study period, different exercises modalities and different evaluation methods. Furthermore, these two studies did not perform aerobic exercises in the intervention phase. Piras et al.[7] compared 30 PHA workouts to HIIT training and obtained cardiovascular and strength adaptations. Nabilpour et al.[9] studied the safety and effect on blood pressure of 36 PHA workouts in hypertensive women with positive results. During the proposed patient protocol, the effect of the training on blood pressure was not studied due to a lack of blood pressure values prior to the start of the intervention. Despite this, it was possible to observe the decrease in pressure values at the end of the training session compared to those at the beginning. As described by Carpio-Riveraet al.[39], at the end of an exercise session, whether aerobic or resistance or mixed, and in the following hours, blood pressure decreases. In particular, interval exercise results in a greater extent of post-exercise hypotension than continuous exercise (Perrier-Melo et al.[40]).

The patient liked the exercise training program and was motivated in increasing the intensity during the weeks. Indeed, the subject, at the end of the protocol, expressed the desire to continue at home the exercises performed in the gym during the 8 sessions by asking me for a list of them. The special structure of the Cardio-PHA enabled the patient to increase the intensity of the exercises, especially the walking, compared to the previous training programme. After the first training sessions, where the subject's starting point and training capacity and tolerance were observed, the incline and walking speed on the treadmill increased. The two walking series of ten minutes each, up to pain 3 out of 4, may have increased the intensity of treadmill walking more than a 20-minute series. In addition, the patient reported in the next treadmill series that he had recovered his calf pain, despite doing strength exercises for both upper and lower limbs between the two series. The intensity of the strength exercises also increased with the sessions and were well tolerated by the patient, who reported no Doms on the following days. The overall intensity of the training, assessed using the Borg scale, was perceived by the subject as moderate (12/20 RPE). The proposed type of training never affected and limited the subject's daily habits, in particular daily walks, during the protocol weeks.

LIMITATIONS

Some of the results obtained may have been biased by the subject's state of health during the week of the final tests. In fact, the day before the tests he reported having an ear infection for a few days. In addition, the day before the tests, the patient performed the last workout of the protocol, not allowing the subject an adequate recovery.

FUTURE PERSPECTIVES

The aim of the study is to find new adapted training strategies for subjects with LEAD considering the limitations of the pathology. In the next few months, an RCT will be started at the University of Padua to study the effect of a Cardio-PHA training protocol on patients with LEAD compared to standard walking training. A possible further future study could be to investigate the effect of training on saturation downstream of occlusion using the Moxy Monitor, a device already used by Olympic and world champions around the world to improve training. In LEAD patients, it could be a new tool to be used in training as an alternative to the claudication training pain scale.

CONCLUSION

This case report demonstrates that eight Cardio-PHA training could be a safe and effective strategy to improve walking ability, general strength, fitness level, quality of life and mortality risk in subjects with LEAD. However, these results need to be confirmed by more studies.

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