CLINICAL REVIEW

Mechanisms of the training response in patients with peripheral arterial disease – a review

B Parr (MSc)[1]
Y Albertus-Kajee (PhD)[2]
E W Derman (MB ChB, PhD, FACSM, FFIMS)[2]

[1]Cape Peninsula University of Technology

[2]UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town and Sports Science Institute of South Africa

Abstract

Exercise training has proved to be a beneficial treatment for patients with peripheral arterial disease (PAD) suffering from the symptom of intermittent claudication. The mechanism by which symptomatic improvement occurs is unclear. The review summarises the mechanism of the training response in patients with PAD, focusing on improvements in bloodflow as well as biochemical, muscle recruitment and psychological adaptations. Possible areas of future research are suggested.

Introduction

Peripheral arterial disease (PAD) is characterised by the presence of atherosclerotic plaque in the peripheral arteries causing reduced blood flow to the peripheral limbs. Reduced blood flow results in ischaemia. The pain of intermittent claudication is felt, particularly during exercise.[1] The word 'claudicare' means to limp. Typically the patient with PAD will experience pain (either in the buttock, thigh or calf muscle) distal to the atherosclerotic obstruction. Studies have shown that exercise training is an important and effective therapy for patients with PAD. The effects of exercise training on PAD and intermittent claudication have been reviewed.[2]

Typically exercise programmes continue for 6 weeks to 6 months and vary in the mode of exercise training used. In a meta-analysis by Gardner *et al*.[18] of 21 studies on exercise training in patients with PAD, PFWD increased 179% and the MWD increased 122% following exercise training.[18] Despite the clear evidence of patients clinically benefiting from exercise training, the mechanism(s) of the training response remains unclear. Several mechanisms have been proposed and researched and these will be discussed in this paper.

CORRESPONDENCE:

Yumna Albertus
UCT/MRC Research Unit for Exercise Science and Sports Medicine
Sports Science Institute of South Africa
PO Box 115
Newlands, 7725
Phone: +27 21 650 4567
Fax: +27 21 686 7530
E-mail: Yumna.Albertus@uct.ac.za

Improvements in blood flow – increased collateral circulation and increased endothelium-dependent dilation

Skinner and Strandness[3] claimed that exercise training increased collateral circulation to the ischaemic muscle. They found a reduction in the post-exercise hyperaemic response with exercise training.[3] Post-exercise hyperaemia is when blood flow increases to the ischaemic muscle after exercise, and as a result blood flow decreases to the foot, causing a reduction in ankle pressure. The greater the reduction in ankle pressure, the greater the extent of the underlying peripheral arterial disease as blood is shunted to the ischaemic muscle.[19] Therefore the authors argued that because this post-exercise hyperaemic response was dampened by exercise training, exercise training must improve blood flow to the ischaemic limb and stated that this was through collateral growth (although they did not prove this).

In that same period, Alpert *et al*.[4] documented that exercise training increased absolute blood flow to the lower limbs (measured by the ^{133}Xe clearance method) and also attributed this to the development of a collateral circulation.[4]

Twenty years later a study by Carter *et al*.[5] also found that systolic ankle pressure recovery to normal levels following the post-exercise hyperaemic response was more rapid after a period of exercise training. Furthermore, an increase in walking tolerance was related to a decrease in the time of the ankle pressure to return to pre-exercise levels but not to any other haemodynamic variables (absolute ankle pressure and ABI),[5] and therefore the development of an increased collateral circulation and improved blood flow was unlikely. In support of this study, Jonason and Ringqvist[6] found that post-exercise ankle pressure (from minute 2 - 16) was higher after a period of exercise training. However, there was no change in calf blood flow at rest or post-ischaemic maximum blood flow measured by strain gauge plethysmography. They attributed this reduction in post-exercise hyperaemia to 'a more optimal distribution and utilization of available blood flow with exercise training'.[6]

Therefore neither Carter *et al*.[5] or Jonason and Ringqvist[6] could attribute increased walking tolerance following exercise training to increased blood flow to the lower limb through an increased collateral circulation. Subsequently two more studies have shown that blood flow to the lower limb as measured by strain gauge plethysmography increases with exercise training.[7,8] However, neither of the above

TABLE I. Review of the trials determining the mechanism of the training response in patients with PAD

Authors	Proposed mechanism of response	Effect of exercise training	Variable measured
Skinner and Strandness [3]	Increase in collateral circulation	The decrease in AP with exercise was less after training	Ankle pressure
Alpert *et al*.[4]	Increase in collateral circulation	Increased absolute blood flow to lower limb	Blood flow (^{133}Xe clearance method)
Carter *et al*. [5]	Redistribution of blood flow, increased capacity of skeletal muscles	Time for post-exercise ankle pressure to reach normal levels after exercise was less. No change in ABI or AP	Systolic AP recovery ABI AP absolute
Jonason and Ringqvist [6]	More optimal distrib and utilisation of available blood flow with exercise training	Post-exercise AP was higher 2-16 minutes after exercise	AP Blood flow (strain gauge plethysmography)
Hiatt *et al*. [7]	Increase in blood flow	Increase in blood flow	Blood flow (strain gauge plethysmography)
Gardner *et al*.[8]	Increase blood flow	Increase in blood flow	Blood flow (strain gauge plethysmography)
Brendle *et al*.[9]	Increase in endothelial-dependent dilation	60% improvement in flow mediated brachial artery diameter and resting artery diameter	Brachial artery diameter and flow velocity measured by an ultrasound system
Lundgren *et al*. [10]	Oxidative enzyme activity increases with physical activity	Cytochrome-c oxidase (Cyt-ox) activity increased with training	Biopsies of calf muscle tissue, Cyt-ox activity measured
Holm *et al*.[11]	Restricted oxygen supply during exercise increases oxidative enzymes	Activity mitochondrial succinic oxidase increases with training. Increased blood flow with training but not correlated to MWD	Biopsies of lateral vastus muscle and medial head of gastrocnemius muscle AP ABI
Sorlie and Myhre [12]	Increased oxygen extraction by skeletal muscles	Venous oxygen saturation was lower at exhaustion after training than before. Max lactate concentration lower after physical training	Catheter into distal femoral vein and brachial artery
Zetterquist [13]	Increased oxygen extraction by the skeletal muscles attributed to a regional redistribution of available blood flow towards active muscles	O_2 saturation of femoral venous blood was significantly lower after training at identical loads	Catheter into femoral vein of affected leg
Hiatt *et al*. [14]	Improved skeletal oxidative metabolism	Decrease in resting plasma short-chain acylcarnatine concentration	Blood samples taken and carnatine measured by radioenzymatic assay
Parr *et al*. [15]	Mechanism unclear	Venous lactate concentrations low at maximal exercise capacity and not correlated to walking distances	Blood samples from brachial artery
Ruell *et al*.[16]	Lower lactate concentrations after physical training	Venous lactate concentrations lower at submax and at exhaustion	Blood samples taken from brachial artery Walking distances
Pedrinelli *et al*. [17]	Central drive increases following a supervised walking programme	Raised initial MDF but not to normal values after the walking programme	Muscle fibre conduction velocity and median frequency of tibialis anterior muscle
Gardner *et al*. [18]	Improved pain tolerance through exposure to pain	Claudication pain end point used during training was the most important predictor of change in PFWD	Meta-analysis of controlled trials

AP = ankle pressure; ABI = ankle brachial index; Cyt-ox = Cytochrome-c oxidase; MDF = median frequency; MWD= mean walking distance; PFWD= pain-free walking distance.

studies proved that improvement in blood flow is due to an increased collateral circulation.

More recently a study in subjects with mild hypertension found that after 12 weeks of exercise training, forearm blood flow increased significantly in response to acetylcholine (an endothelium-dependent vasodilator) but not to isosorbide dinitrate (an endothelium-independent vasodilator) in the exercise group but not in the control group.[20] Studies using the elderly [21,22] or patients with coronary artery disease[23] and on animals with chronic coronary occlusion[24] have revealed that exercise training improves endothelium-dependent vasorelaxation through an increase in the release of nitric oxide.

Endothelial cells release nitric oxide, a lipid-soluble gas, in response to the stimulus of increased blood flow through the vessel lumen (as would happen during exercise).[25] Indeed, it is apparent that a depressed endothelial function is more likely to improve with exercise training than in patients with normal endothelial function (i.e. in the young and healthy).[26]

It has been shown in patients with PAD that endothelium-dependent dilation is impaired or depressed. This was shown by measuring maximum brachial artery diameter and flow after brachial artery occlusion (with a blood pressure cuff) in patients with PAD and controls.[27] Only one study has shown that exercise rehabilitation improves endothelial-dependent dilation in older patients with PAD.[9] This study found a 60% improvement in the flow-mediated brachial arterial diameter as well as in the resting arterial diameter. However, this study was not randomised or controlled.

It is perhaps the improved endothelial-dependent vasodilation that is responsible for improvements in walking tolerance and blood flow. It is possible that improved endothelial-dependent vasodilation in patients with PAD as a result of exercise training allows for a less pronounced and shorter duration post-exercise hyperaemic response and decrease in ankle pressure after a bout of exercise, which would explain the findings of the studies completed in the 1960s and 1980s.

Finally, it may not only be the endothelium that is responsible for vasodilation in patients with PAD. Further examination is also required of the ability of the smooth-muscle cells of the arteries to cause vasodilation in response to adenosine in patients with PAD. A study by Hambrecht *et al.*[23] found that coronary blood flow reserve (the ratio of the mean peak flow velocity to the resting velocity after adenosine infusion) increased significantly after 4 weeks of training in patients with coronary artery disease.[23] Future research should examine this response to exercise training in patients with PAD.

Biochemical adaptations in skeletal muscle in patients with PAD following exercise training

Because patients with PAD have reduced blood flow to the exercising limb(s), it has been suggested that anaerobic glycolysis resulting from ischaemia increases the lactate concentration in the skeletal muscles and blood, which leads to claudication pain.[27,10]

This was summarised in a review article by Tan *et al.*,[28] who stated, 'In patients with peripheral vascular disease, increasing the workload causes an inequality in the supply of and demand for oxygen. Aerobic generation of ATP becomes inadequate and anaerobic metabolism predominates. The result is an increase in lactic acid production, and a depletion of ATP and creatine phosphate, leading to pain.'

Support for this theory is found in studies that have shown that improvements in walking tolerance following exercise training in patients with PAD occur alongside increases in the number of oxidative enzymes found in the skeletal muscle,[11,10] improvements in oxygen extraction by the skeletal muscles[12,29] and a decrease in the concentration of acylcarnatines[16] (produced during skeletal muscle ischaemia). The theory is that these adaptations delay the onset of anaerobic glycolyis, lactate accumulation and pain.

This theory of walking intolerance in patients with PAD stems from the popular cardiovascular/anaerobic theory of fatigue which suggests that fatigue develops when the exercising skeletal muscles fail to get enough oxygen to them and as a result have to rely on anaerobic glycolysis to produce enough ATP to continue exercising.[30] A by-product of anaerobic glycolysis is lactate accumulation in the skeletal muscles and blood.

A recent study in this laboratory found that although venous lactate concentrations increased following a graded treadmill exercise test, the values were very low (2.08±1.6 to 3.28±1.39 mmol.l^{-1}) and furthermore did not correlate to PFWD or MWD in patients with PAD.[15] Others have found that venous and arterial lactate concentrations were higher in patients with PAD at maximal exercise capacity than in age-matched controls at maximal exercise capacity[29] and lower after surgical reconstruction or physical training in these patients.[29,16] However, concentrations of blood lactate never reached higher than 4 mmol.l^{-1} in these studies. Values in a normal population at maximal exercise capacity reach far greater values than this (7.59 mmol.l^{-1}) and the subjects never experience claudication.[31,32] In skeletal muscle, there was no significant difference in lactate concentration values between patients with PAD and controls at maximal exercise capacity.[16]

Therefore, the suggestion that accumulation of lactate in the skeletal muscles and blood leads to claudication pain, is unlikely. There has to be some other mechanism for the pain that patients with PAD experience.

Muscle recruitment response to claudication and exercise training

Recently it has been suggested that fatigue in the normal population develops when muscle recruitment is reduced by the motor cortex, causing exercise to terminate. This happens because inhibitory reflexes arise from the exercising muscles and feedback to the spinal cord and motor cortex, reducing skeletal muscle recruitment. This theory has been previously reviewed.[33,34]

The influence of the central nervous system on muscle recruitment is commonly measured using surface electromyography (EMG). EMG comprises of the sum of electrical contributions made by the active motor units which are detected by electrodes placed on the skin surface overlying the muscle.[35] Few studies have investigated muscle activity in patients with PAD after interventions including exercise training response and percutaneous transluminal angioplasty (PTA). The only published studies investigating EMG in these patients have studied changes in median frequency (MDF, the frequency value which divides the power density spectrum of EMG signal into two equal halves), nerve conduction velocity of peroneal and tibial nerves [36,37,33,17] and a recent case study investigating changes in EMG after angioplasty.[38] A study conducted by Pedrinelli *et al.*[17] examined muscle fibre conduction velocity (MFCV) and MDF of the tibialis anterior muscle during tetanic electrical stimulations in patients with PAD and controls. MFCV ranges did not differ significantly between patients and healthy controls. However, MDF of both the ischaemic and non-ischaemic legs were found to be significantly lower than the controls, as the healthy limb also showed a decrease in MDF. This finding suggests that chronic ischaemia was not the cause of lower MDF in patients with PAD. It is of interest to note that this study used a 3-week walking programme intervention, which resulted in improved exercise tolerance, raised initial MDF but not to normal values after the walking programme; and unchanged MFCV in patients with PAD. These findings suggest that central drive increases following a supervised walking programme and factors other than ischaemia and physical inactivity underlie the abnormal EMG signal in patients with PAD. A case study conducted by Albertus-Kajee *et al.*[38] on a patient with PAD came to similar conclusions, where muscle activity in the diseased leg was found to increase after angioplasty. They explain this increase in EMG as a possible increase in central drive to the lower limbs after angioplasty, which resulted in an increase in functional capacity. Interestingly, the blood lactate concentrations were low ranging between 2.00 and 1.75 mmol.l^{-1} before angioplasty and 1.75 - 1.50 mmol.l^{-1} after angioplasty.

The influence of muscle recruitment on the training response in these patients is therefore of special interest and needs to be further investigated. Although the use of EMG in the evaluation of this disease is still in early development, it provides a non-invasive assessment and understanding of the physiopathology of skeletal muscle involvement in patients with PAD.

Psychological adaptations to exercise training

Some of the improvement in exercise tolerance noted with exercise training in patients with intermittent claudication may be attributed to psychological factors. This was made apparent in a review where a number of important predictors of the outcome of an exercise programme were identified.[39] The best correlation with good outcome of the exercise programme was belief that the exercise would lead to an improvement in walking status. Moreover, patients can be influenced by the level of motivation they feel on the particular day of testing. This was made apparent in a study which noted: 'The psychology involved when walking with pain was highlighted by the two-thirds of patients who said they could walk no further but then immediately walked 15 - 45 m to the rest room'.[40]

Lastly it seems that as patients subject themselves to pain, their pain tolerance improves. Gardner *et al.*[18] found in a meta-analysis that claudication pain end-point used during an exercise training programme was the most important independently related predictor of the positive change in PFWD distance and MWD in patients with intermittent claudication.[18] The longer patients 'walked into' their pain during training, the more PFWD and MWD improved after training.

Therefore, factors including the belief that the exercise training will work, motivation to walk and improvements in pain tolerance can affect walking tolerance. If it is true that the motor cortex reduces muscle recruitment in response to pain then these psychological factors could perhaps act against central regulation, allowing for the patient to train longer and eliciting better functional results. This is an area of future research.

Conclusion

Early research attributed improvements in walking distances with exercise training to improvements in collateral circulation or peripheral adaptations in the exercising skeletal muscles. This review indicates that endothelium-dependent dilation improves with exercise training and should be researched further in controlled, randomised trials. Moreover, the possibility that the central governor causes exercise to terminate in patients with PAD should be investigated, especially in the light that factors including the belief that the exercise training will work, motivation to walk and improvements in pain tolerance affect walking distances in patients with PAD.

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