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A review of the potential local mechanisms by which exercise improves functional outcomes in intermittent claudication.

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Abstract: Intermittent claudication (IC) is a common condition which is associated with significant quality of life limitation. NICE guidelines recommend a group based supervised exercise programme as the primary treatment option for claudication, based on clinical and cost effectiveness. This review aims to assess the mechanisms by which exercise improves outcomes in patients with intermittent claudication

Methods: Medline, Embase and PubMed were searched using the search strategy 'claudication' [AND] 'exercise' [AND] 'mechanisms'. Searches were limited from 1947 to October 2014. Only full text articles published in the English language in adults (over 18 years of age) were eligible for the review. Any trial involving a non-supervised exercise programme was excluded. Abstracts identified by the database search were interrogated for relevance and citations from the shortlisted papers were hand searched for relevant references.

Results: The search yielded a total of 112 studies, of which 42 were duplicates. Forty seven of the remaining 70 were deemed appropriate for inclusion in the review. Exercise is the first line treatment for intermittent claudication. Supervised exercise programs improve walking distances; endothelial and mitochondrial function, muscle strength and endurance. Furthermore, it leads to a generalised improvement in cardiovascular fitness and overall quality of life.

Conclusion: The mechanism by which exercise improves outcome in claudicants are complicated and multifactorial. Further research is required in this area to fully elucidate the precise and predominant mechanisms and to assess whether targeted exercise programme modification maximises mechanism efficacy and patient outcome.

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Introduction

Intermittent claudication (IC), ischaemic muscle pain precipitated by exertion is the most common presenting symptom of peripheral arterial disease, affecting 5% of the population >50 years[1-3]. It was first described and defined by G.A Rose in 1962 with the following characteristics; (1) pain to include one or both calves, (2) provoked by hurrying or walking uphill, (3) never occur at rest, (4) must make the person stop, (5) disappear on a majority of occasions in 10 minutes or less, (6) and never disappear if walking continues [4]. Claudication is therefore, frequently associated with a substantial reduction in walking capacity[5, 6], significant deterioration in quality of life, balance impairment, and diminished physical function and activity levels[7-10]. A previous meta-analysis demonstrated that claudication distance varies between patients and between research trials, with ranges from 56m to 309m prior to starting an exercise treatment[11]. The data regarding patient recovery time is limited however it appears that on average patients require 3 minutes rest [12] to alleviate pain.

Initial treatment guidance for IC was to "go home and walk" later termed unsupervised exercise[13]. A Cochrane review[6] has demonstrated however, that unsupervised programmes have inferior outcomes in comparison to supervised programmes in terms of improvements in walking distance, claudication onset and adherence to treatment. Therefore NICE clinical guideline 147 recommends a group-based supervised exercise programme (SEP) as first line treatment for patients with IC[6, 14]. Consequently supervised exercise programmes for claudication have been demonstrated to improve walking distances, quality of life, physical function, balance and be cost effective[15]. There is however, no general consensus on what should be included in the exercise programmes resulting in significant variability between studies. There is a general consensus that exercise programmes should be supervised, comprise of intermittent walking to near maximal pain at least three times per week[16] for a

minimum of 12 weeks[17]. There is less agreement on the most effective intensity and modality of exercise in this scenario.

It is clear that supervised exercise improves functional outcomes in claudicants; however the underlying mechanisms precipitating this change remain unclear. There seems little evidence of major haemodynamic changes[18] therefore attention has shifted to the investigation of other potential mechanisms including skeletal muscle metabolism, cardiorespiratory function (resting heart rate, VO2 max, anaerobic threshold and endothelial (dys)function[19]. This review aims to examine the known evidence supporting the various potential mechanisms by which exercise improves outcome in patients with intermittent claudication.

Methods

Search strategy

All randomised and non-randomised trials were included of a supervised exercise regimen and a specific claudication mechanism.

Inclusion criteria

Trials involving patients with IC were included (diagnosed either clinically or by questionnaire). Any study involving patients who had prior endovascular intervention or undertaking an unsupervised exercise programme was excluded. Any intervention that included an exercise programme was included and the inclusion was not affected by the duration, length or time of the programme. This review will also consider any differences due to resistance versus aerobic exercise.

Data extraction

The main outcome measures are improvements in, blood flow, muscle strength, muscle power, muscle architecture, mitochondrial and muscular function and endothelial function.

Database search

Three databases; Medline, Embase, and PubMed were searched using the following search strategy: 'claudication' [AND], exercise [AND] mechanisms. Searches were limited to run from 1947 to 2014 using Ovid online in September 2014, with a second search conducted in October 2014 to ensure any new research was included. Only full text articles published in the English language in adults (over 18 years of age) were eligible for the review. Any trial involving a non-supervised exercise programme or home exercise programme was excluded [20-23]. Abstracts identified by the database search were interrogated for relevance by two independent reviewers. Citations from the shortlisted papers were hand searched for other relevant references.

Results

Search results

The search yielded a total of 112 studies, of which 42 were duplicates. Of the remaining 70, 47 were deemed appropriate for inclusion in the review. Of the specific exercise papers 40 used aerobic conditioning and seven studies included some form of resistance training (see figure one)

The aim of this review is to present a summary of the potential local mechanisms by which exercise is thought to improve functional outcome in patients with intermittent claudication, specifically in studies involving supervised exercise programmes only.

Neurohumoral Effect

The cardiovascular response to exercise includes an elevation in heart rate and increased sympathetic activation; this is known as the exercise pressor reflex. The afferent nerve fibres (group III, and IV)[24] are stimulated by mechanical and metabolic stimuli from the exercising muscles, and activate the sympathetic nervous system (increases heart rate, blood pressure, myocardial contractility, and peripheral vasoconstriction). In particular the blood pressure response is significantly exaggerated in patients with PAD[25], with values similar to that seen during resistance based exercise in age matched healthy controls. Systolic blood pressure was dramatically increased during exercise with some values even exceeding 300mmHg. This response has been associated with increasing disease severity as well as increased walking speed and duration of walking[26]. The exaggerated exercise pressor reflex and sympathetic overdrive may partially account for the excessive activation of these receptors, and thereby causing vasoconstriction and reduced blood flow, responsible for the reduction in walking distance and pain whilst walking, significantly contributing to symptoms.

Calf blood flow

It is well documented that a SEP for claudication improves walking distance, however analysis of associated lower limb hemodynamic measures produce somewhat conflicting results. Venous occlusion plethysmography and ankle-brachial pressure index are the two most common documented methods of measuring calf blood flow with the venous occlusion plethysmography appearing a more sensitive measure[27]. Whilst both have been found to correlate moderately with patients walking distance [20, 28], improvements in walking distances with SEP are not reflected in significant improvements in either ankle-brachial pressure index or calf blood flow[29]. Only ***two*** out of the 47 reviewed papers reported a significant improvement in ankle-brachial pressure index at six[16, 30] and 18 weeks after a SEP,

additionally a review conducted by Parmenter *et al* (2010) found no improvements in lower limb hemodynamic secondary to exercise in 33 trials. This suggests that whilst that ankle-brachial pressure index may be valuable in the diagnosis of claudication, it is not responsive to change in clinical symptoms with SEP, it may however be relevant for those patients undergoing angioplasty[31]. There is disputed evidence regarding calf muscle oxygen saturation[32] some studies show no improvement following an exercise programme, whereas others report significant change[33]. Given that the evidence is disputed it seems unlikely that improvement in calf blood flow has a significant role to play in the mechanism by which SEP improves outcome in patients with IC.

Angiogensis

Exercise is hypothesised to improve the collateral circulation and produce a "natural bypass" in claudicants. The growth factors implicated in formation of new vessels are vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGF). In vitro and in-vivo studies have demonstrated VEGF and FGF to promote angiogenesis, endothelial proliferation and increase vascular permeability[34]. Animal models of lower limb ischaemia (by femoral artery ligation) report; a 43% improved regional blood flow with exercise[35-37], an increase in the diameter of collateral blood vessels and up-regulation of VEGF[38]. Gene therapy to promote neovascularisation has restored blood flow in mouse models with ischaemic hind limbs [39]

In humans with lower limb ischaemia, exercise has not induced the same angiogenic response. Patients with PAD have reduced levels of VEGF-A, and its receptor VEGF-R1 and increased levels of anti-angiogenic factor VEGF165b[40]. Artificial supplementation of adenoviral vascular endothelial growth factor gene (AdVEGF121) has no effect on walking

ability or blood flow[41]. It is therefore unlikely that in humans with IC any significant angiogenesis occurs with supervised exercise.

Haemorheology.

Patients with PAD have significantly increased blood viscosity compared to controls[42]. Randomised controlled trials have shown a significant improvement in blood and plasma viscosity[43] back to that of age matched healthy controls, and red cell deformability[44] after a period of exercise training in patients with PAD. Pharmacological interventions to improve haemorrheology by haemodilution[45] or pentoxifylline[46] however, do not result in the same improvements in walking distance that are seen with SEP [47].

Endothelial Function

Flow mediated dilation is the gold standard assessment of endothelial function[48, 49]. The endothelium plays a crucial role in the regulation of vascular tone and blood flow via its production of nitric oxide (NO) by endothelial NO synthase. Physiologically stress from the viscous drag of blood flow is the most important stimulus for continuous formation of NO[50]. Released from endothelial cells, NO is rapidly transported to the neighbouring vascular smooth muscle cells, where it induces the production of cGMP as a second messenger. CGMP in turn increases calcium ion uptake into intracellular calcium stores, thereby inducing vascular smooth muscle cells relaxation and vasodilation. On its way to the vascular smooth muscle cells NO may be prematurely degraded by reactive oxygen species. The regulation of NO synthesis occurs at different levels: ENOS gene polymorphisms are related to eNOS expression & activity, mRNA expression is influenced by oestrogen status & shear stress, and enzyme activity is regulated by phosphorylation status. Flow mediated dilatation utilises reactive hyperaemia, the change in vessel diameter in response to a period of

ischemia as a surrogate marker for the endothelial function[51]. This change in vessel diameter is a predictor of overall cardiovascular mortality[48, 49]. Patients with IC have an impaired flow mediated dilatation[50] in comparison to age matched healthy controls, which significantly improves after an exercise programme from 4.81 to 7.97 ($p < 0.005$)[50, 52]. This is potentially related to the exercise associated bouts of increased laminar flow up regulating eNOS mRNA expression and phosphorylation and antioxidant protection[53]. Furthermore the exercise modality appears to have an impact on the degree of flow mediated dilatation improvement with aerobic being superior to resistance training[54]. However, given the lack of data within this specific patient population it is difficult to draw definitive conclusions as to whether this is a significant mechanism for the symptomatic improvement with exercise in claudicants. It does appear however, to be a strong candidate for a mechanism of change.

Mitochondrial and muscular function

Metabolites

Muscle ischemia secondary to PAD results in a higher muscle metabolic demand at rest, exercise results in an early accumulation of metabolic intermediates such as acylcarnitines in both the muscle and plasma. Human studies of muscle metabolism generally necessitate a muscle biopsy, and thus usually only contain a small number of participants due to the invasive nature of the procedure. However they have demonstrated claudicants to have a higher lactate and, acylcarnitine levels in comparison to controls[2]. The concentration of the metabolite acylcarnitine was also identified to be inversely proportional to maximum walking distance ($r=-0.75$, $p<0.05$)[2]. With a period of exercise training, both metabolites reduced in concentrations whilst walking distances improved[27, 55]. It appears that L-carnitine allows ischemic muscle to reach a higher level of energy expenditure before the pain of claudication develops[56]. The administration of L-carnitine to patients both orally and / or intravenously

demonstrates a moderate improvement in walking ability[56-58]. However more research is required to determine to optimal dose, duration and safety of supplementation and if it's supplementation is more beneficial than the current exercise programmes. Furthermore if exercise already lowers acylcarnitne and increases L-carnitine levels, it must be questioned whether having an additional supplementary dose is of any benefit to the PAD exercising population. However, it may be one alternative therapy to those who decline to participate in an exercise programme.

Mitochondria

Patients with PAD compensate for the higher metabolic demand on skeletal muscle via an increase in mitochondrial density and activity compared to healthy controls[59, 60]. Concurrently, the ischemia and inflammatory response, results in both morphological alterations [61-63] and DNA damage[64] to the mitochondria. One randomised control trial, which administered carbon monoxide to patients with PAD, resulted in a quicker onset of claudication, hypothesised to be secondary to impaired oxygen extraction and utilisation via the abnormal mitochondriae[65]. However, the effect of exercise on muscle metabolism at the cellular level remains uncertain at a higher exercising capacity [2, 66]. Surgical revascularisation results in a reversal of the elevated activity of the mitochondrial activity back to that of healthy controls[67], providing the bypass remains patent. Hypoxia is considered to be the mechanism driving mitochrondrial up-regulation and a randomised controlled trial demonstrated that administration of Pentoxifylline also improves mitochondrial function[68]. However, this improvement occurred without change in blood flow and therefore, is most likely due to a change in intrinsic mitochondrial oxidative activity.

Muscle architecture

Lower limb calf muscle architecture in claudicants comprises a higher fat percentage and a lower muscle cross sectional area compared to healthy controls[69, 70]. There is also a reduction in the proportion of Type 1 muscle fibres[69, 70] which have the greatest oxidative capacity and are, therefore important in aerobic endurance. In addition the number of capillaries per muscle fibre is reduced[71], apoptosis is increased[72], glucose uptake is impaired[73] and atrophy may occur[74]. In murine models of ischemia, exercise training was associated with improved muscle development, with associated improvements in peak oxygen uptake compared to sedentary controls[75]. Additionally human studies have demonstrated an improvement in mitochondrial content post-training as a contributing factor for training-induced performance improvements[76, 77]. Walking distances are not significantly affected by different exercise modalities, although resistance training produced greater improvement in muscle bulk and composition compared to aerobic exercise[78]. This occurs via an increase in type IIa fibres, capillary density and improvement in muscular function[22, 79]. The change in muscle architecture is perhaps one likely mechanism for improved walking distances in patients with IC.

Muscular Strength & Endurance

The current recommendations for IC include walking to a moderate-high level of pain [80], however exercise therapy guidelines vary amongst published literature. Consequently, much attention has been given to aerobic or treadmill walking in patients with IC, with few acknowledging how resistance training may be beneficial. Indeed only 15% [54, 79, 81-86] of all 47 exercise studies in this review had some form of resistance training. Crucially, some patients are unwilling and / or unable to undertake aerobic training[87]. A systematic review in 2014 showed that clinically relevant improvements are demonstrated with both aerobic,

resistance training and / or a mixture of both[87]. Further, there is a definitive lack of data regarding muscular strength and endurance in patients with PAD. One study showed that one repetition leg strength was significantly increased following a strength training programme, which in turn led to improvements in walking economy and walking performance[86]. There is also a potentially strong association between change in plantar flexor muscle strength and walking ability[54, 79, 84, 88]. Secondary to this resistance exercise does not promote the classic "walking to pain" and could potentially improve uptake and compliance to an exercise programme, although this is yet to be assessed, in comparison to classic treadmill and aerobic exercise[89]

Intra-Muscle Inflammatory Cascade

Evidence suggests that inflammatory cascade induced by exercising to pain may have a detrimental effect on both the endothelium[90, 91] and the muscle[92]. Ischemia – Reperfusion Injury is a possible consequence of exercise training in IC[93] characterised by an inflammatory cascade and increased microvascular permeability[94]. The increase in pro-inflammatory cytokines is one potential mechanism for the impairment in endothelial function after exercise in PAD patients[95]. Ischemic reperfusion injury causes a loss of calcium homeostasis leading to unregulated calcium activated enzymes, including the calpain system. Skeletal muscle exhibits u-calpain, m-calpain and calpain-3, which are activated following exercise[96]. These activated calpains can cause morphological damage to the skeletal muscle[96] and cell death[97]. Murine models support the pathway between calpain-induced muscle wasting and PAD, which was more severe in the exercising training model[98]. This suggests that classic aerobic training may prevent the maintenance of muscular mass in claudicants.

The importance of preserving muscle mass is well documented and is important in balance[74], functional daily activities and overall quality of life[99]. Treadmill-based exercise has been associated with an increase in calpain proteolytic activity and a relative reduction in the skeletal muscle size[92]. Although the study was small (*n*=35) it demonstrates that treadmill based aerobic exercise may be detrimental due to the increase in catabolic muscle wasting therefore reducing the skeletal muscle mass. It is clear that the prescription of an exercise programme must be focused on achieving the relevant clinical outcomes but awareness of the potential negative physiological consequence. However, studies have demonstrated that exercise training has no detrimental effects at 12 month follow-up[91]. There is some evidence suggesting that resistance training maintains muscle mass whilst achieving similar clinical benefits to aerobic exercise[87, 92, 100].

Conclusion

This review provides a summary of the potential mechanisms which by which exercise improves outcome in claudicants, highlighting areas of uncertainty. It would seem that the traditional beliefs that exercise in claudicants promote new blood vessel formation and improved blood flow is unlikely to be a major contributory mechanisms. Current evidence supports a multifactor aetiology, with the most likely mechanisms contributing to improvement including changes in cardio-respiratory physiology, endothelial function, mitochondrial number and activity and muscle conditioning. At present further research is required if we are to fully understand and maximise these mechanisms. In addition work is required to investigate how these mechanisms vary between different patient groups (e.g. responders & non responders) and between different training regimes (aerobic versus resistance)

Despite the mechanism of exercise improvements remaining poorly understood, the clinical benefit to patients is clearly supported by the available evidence. A recent review and meta-analysis in randomised controlled trials [101, 102] have demonstrated that patients compliant with a supervised exercise programme can expect maximum walking time and distance and pain-free walking time and distance to be significantly increased with an associated significant improvement in the walking impairment questionnaire[102] (specifically in aerobic training). In additional aerobic (walking) training improves the physical component of the SF36 but not the mental component. Importantly the benefit from a supervised exercise programme in claudicants seems to be sustained for up to two years[103].

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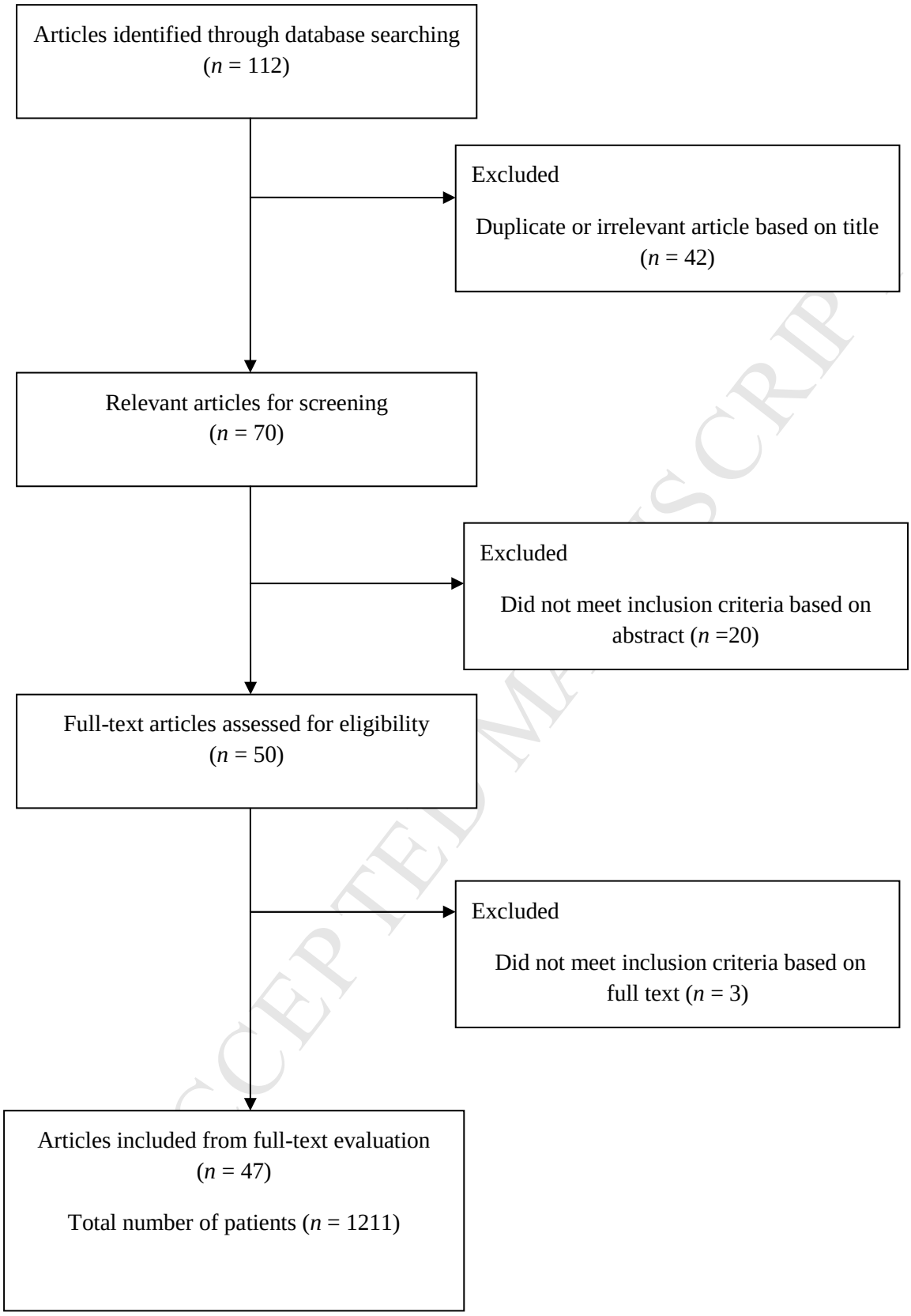

Figure one. Flow chart showing search strategy